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PART A. NATURAL SCIENCES

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Daugavpils Universitātē docētāju un studējošo zinātniskās konferences notiek kopš 1958. gada. Konferencēm ir starpdisciplinārs raksturs un tajās piedalās gan studējošie, gan docētāji, gan arī ievērojami zinātnieki no dažādām pasaules valstīm. Daugavpils Universitātes 59. starptautiskās zinātniskās konferences pētījumu tematika bija ļoti plaša – eksaktās, humanitārās, izglītības, mākslas un sociālo zinātņu jomās.

Zinātnisko rakstu krājumā ***Daugavpils Universitātes 59. starptautiskās zinātniskās konferences rakstu krājums = Proceedings of the 59th International Scientific Conference of Daugavpils University*** apkopoti 2017. gada 6.–7. aprīlī konferencē prezentētie materiāli.

Daugavpils Universitātes 59. starptautiskās zinātniskās konferences rakstu krājums tiek publicēts 3 daļās: A. daļa. *Dabaszinātnes*; B. daļa. *Sociālās zinātnes*; C. daļa. *Humanitārās zinātnes*.

The annual scientific conferences at Daugavpils University have been organized since 1958. The themes of research presented at the conferences cover all spheres of life. Due to the facts that the conference was of interdisciplinary character and that its participants were students and outstanding scientists from different countries, the subjects of scientific investigations were very varied – in the domains of exact sciences, the humanities, education, art and social sciences.

The results of scientific investigations presented during the conference are collected in the collection of scientific articles ***Proceedings of the 59th International Scientific Conference of Daugavpils University.***

Proceedings of the 59th International Scientific Conference of Daugavpils University are published in three parts: part A. *Natural sciences*; part B. *Social Sciences*; part C. *Humanities.*

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VIDES ZINĀTNES / ENVIRONMENTAL SCIENCES

THE RESEARCH OF ODOUR CONCENTRATION AND ANALYSIS OF AIR POLLUTANTS IN RIGA

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Abstract
Kew words: *gas analysis, odours, Riga neighbourhoods*
As the standard of living and quality of life increase, more and more people start thinking of their health, well-being and environmental cleanliness, thus, recently adverse effects of different odour nuisances on human well-being has become a pressing environmental issue. Nowadays this issue becomes increasingly important. Odour emission sources are the odours caused by both business activities and the activity or inactivity of physical persons. The studies carried out in Riga in 2016 and 2017 show that the highest number of complaints was received from the following Riga neighbourhoods: Bolderaja, Sarkandaugava, Kundzinsala, Mangalsala, Milgravis and Vecmilgravis, respectively, from the areas with the highest number of companies. The odour concentration studies carried out so far by a field olfactometer show that the odour concentration in Riga neighbourhoods may be as high as 7 odour units. The studies carried out by the gas analyzer indicate the presence of oil products and fuel gases in air.

Kopsavilkums
Atslēgvārdi: *gāzu analīze, smakas, Rīgas mikrorajoni*
Līdz ar dzīves līmeņa un kvalitātes celšanos, aizvien vairāk cilvēki sāk domāt par veselību, labsajūtu un vides tīrību, tādējādi pēdējos gados aktuāla vides problēma ir dažādu traucējošu smaku negatīva ietekme uz cilvēku labsajūtu. Mūsdienās šim jautājumam tiek pievērsta aizvien lielāka uzmanība. Smaku emisijas avoti ir gan uzņēmumu saimnieciskās darbības rezultātā radītās smakas, gan arī fizisku peronu darbības vai bezdarbības rezultātā radītās smakas. 2016. un 2017. gadā Rīgā veiktie pētījumi norāda, ka visvairāk iedzīvotāju sūdzības ir saņemtas no sekojošiem Rīgas mikrorajoniem: Bolderāja, Sarkandaugava, Kundziņsala, Mangaļsala, Milgrāvjis un Vecmīlgrāvis, respektīvi teritorijās, kurās ir koncentrējies vislielākais uzņēmumu skaits. Līdz šīm veiktie smaku koncentrācijas pētījumi ar lauku olfaktometru, ļauj secināt, ka Rīgas mikrorajonos smaku koncentrācija var sasniegt 7 smaku vienības. Veiktie pētījumi ar gāzu analizatoru norāda uz naftas produktu un dūmgāzu klātbūtni gaisā.

Introduction

The quality of life is a relatively new concept which is actively used since 1960-ties to describe living conditions of society (Wolfensberg 1994). The quality of life is a set of objective and subjective factors including material well-being, health, productivity, intimacy, safety, well being of community and emotional well-being (Cummins 1996). One of the indicators of the quality of life is human health and well-being. As higher the level of life is, as more attention is paid to ensure well-being. Some of the factors that can affect both human well-being and health, thus, also the quality of life, are emissions of different odours and air pollution. These issues are more pressing in the densely populated administrative territories of the cities where economic activities are carried out.

Increasing attention is being paid to the odour studies not only in Latvia (Kāla et al. 2015), but also elsewhere in the world (Bokowa 2010; Brattoli et al. 2011; Dravnieks 2012; Sironia 2014; Zarra 2012) indicating the urgency of the problem and the necessity to carry out studies to identify easier the odour emission source, perform more effective control and eliminate faster nuisances

caused by odours. Therefore since 2016 the odour concentration and air pollutant analyses have been carried out in Riga administrative territory. The main goal of the research was to determine the probability of nuisance caused by odours in Riga beyond the business operation territories, as well as to identify the presence of odour nuisance and the source of odour emission.

Mostly, odour perception for each human is subjective, perception depends also on the cause of the odour, its frequency, intensity, duration, hedonic tone (unpleasantness) and the nature of the location. It is stated in the Regulation of the Cabinet No. 724 "Regulations Regarding the Methods for Determination of the Odours Caused by Polluting Activity, as well as the Procedures for Restricting the Spread of such Odours" adopted on 25.11.2014 (Republic of Latvia, Cabinet Regulation No. 724, 2014) that the odour threshold is such concentration of a malodorous substance, if at least half of the participants of the odour evaluation panel confirm the presence of an odour and if it is 1 ou_E/m^3, while odour nuisance is such odour, which causes negative effect on human well-being.

Nowadays more and more advanced technologies such as electrochemical, metal oxide and photo ionization detectors or "electronic noses" are used to measure the odour concentration. By help of these detectors it is possible to make indicative odour concentration measurements on an ongoing basis, however, these devices are stationary and are set for recording a specific parameter (chemical substance). So far the best odour indicator still is a human nose. Thus, within the framework of the studies, the analysis of odours and complaints received by the competent state institutions in cases of accidents were carried out, the objects (companies) performing polluting activities resulting in odour emission were identified, an analysis of the odour emission limit projects developed by the companies was carried out, sites where odour nuisance emission is possible were identified and inspected, the odour concentration and air pollutants were determined.

During research it was found out that odour emission sources can be both diffuse sources and point sources. Odour emission sources may be pollution caused by the operation of such companies as oil product terminals, chemical plants, waste storage and composting sites, wastewater treatment plants, etc. However, odours can be caused also by physical persons which do not perform economic activities, for example, by discharging poorly treated or even untreated domestic wastewaters in the environment. During the heating season there is a smell of smoke in the air coming from the private houses, especially when coal is used as fuel.

Material and methods

To analyse the odour concentration and airborne pollutants both field survey and desk-based research methods were applied. Desk-based research methods included the following: processing of data (complaints) received from the State Environmental Service and the State Fire and Rescue Service and their analysis, analysis of cartographic materials, identification of the air polluting sites

and objects (analysing permits issued to the companies for polluting activities of category A and B), and analysis of the odour emission limit projects.

Field survey methods included determination of the odour concentration by the Scentroid SM100 field olfactometer, determination of the presence and concentration of the volatile substances in the air by using the Gasmet DX-4030 gas analyzer, as well as determination of the co-ordinates of the study sites by GPS or a satellite navigation device TRIMBLE JUNO SB was performed. This GPS device is equipped with the 35 TerraSync software, allowing to enter data and attributes, as well as to edit them in the field. The accuracy of positioning using the TRIMBLE JUNO SB GPS device is 2 – 5 m.

Scentroid SM100 field olfactometer

The Scentroid SM100 field olfactometer (Fig. 1) is designed for measuring the odour concentration from the direct emission sources and for measuring the odour background level (not in the direct emission source), as well as it can be used for collecting source samples for further analysis in the laboratory (Scentroid Model 110C, 2012). The operation of the equipped field olfactometer is based on dilution of the odour sample (until the operator feels the odour) by high pressure odourless gas from a high pressure carbon fibre tank, respectively, the odour sample is drawn by help of vacuum generated by the diluted compressed air flow. The dilution ratio of fresh to ambient air is controlled through the patented Scentroid flow regulator valve. The panel list of the Scentroid SM100 field olfactometer offers 15 discreet dilution levels, the minimum dilution is 2 odour units, and the maximum – 30000, respectively it is possible to determine the odour concentration from 2 to 30000 odour units (OU_E / m^3) by the Scentroid SM100 field olfactometer (Scentroid Model 110C, 2013).

The studies carried out so far (Bokowa 2012) indicate that the results obtained by the Scentroid SM100 field olfactometer in the field and at the stationary laboratory match satisfactory both for the point sources and diffuse sources.

Fig. 1. **Field measurements by the Scentroid SM100 field olfactometer**

Fig. 2. **Field measurements using the Gasmet DX-4030 gas analyzer**

Gasmet DX-4030 gas analyzer

The portable gas analyzer Gasmet DX-4030 can be used for determining air temperature, humidity and 23 inorganic and organic gases such as carbon monoxide, carbon dioxide, methane, benzene, acids, aldehydes and other volatile vapours (DX-4030 FTIR Gas Analyser Instruction and Operating Manual 2009).

The Gasmet DX-4030 analyzer incorporates a Fourier Transform Infrared (FTIR) spectrometer, Rhodium-Gold coated sample cell and signal processing electronics (DX-4030 FTIR Gas Analyser Instruction and Operating Manual 2009). The sample gas is extracted via a probe with a built-in particle filter, thus no sample preparation and preliminary collection is needed. Calcmet-Lite software which runs on the Windows Mobile platform is used to control the operation of the the Gasmet DX-4030 gas analyzer. Data are transmitted from the Gasmet DX-4030 gas analyzer to Calcmet-Lite software by help of Bluetooth (DX-4030 FTIR Gas Analyser Instruction and Operating Manual, 2009). Researcher can freely move around and make measurements at different locations using the Gasmet DX-4030 gas analyzer (Fig. 2), the results are displayed by Calcmet-Lite softweare immediately after the measurements, afterwards they are stored and transferred on the computer.

Result and discussion

Appendix No. 1 to the Law “On Pollution” (The Saeima law “On Pollution” 2011) specifies polluting activities of category A such as in energy industries – combustion installations with a rated thermal input exceeding 50 MW, production and processing of metals, production of mineral products, chemical industry, production of cellulose from wood or other fibres, wastewater treatment plants, waste management, etc. In Latvia, as of the beginning of 2017, there were in total 100 permits for the polluting activities of category A issued (A, B permit 2017). Polluting activities of category B have less capacity in comparison with polluting activities of category A, and they are specified in Annex 1 to the Cabinet Regulation No. 1082 “Procedures by which Polluting Activities of Category A, B and C shall be Registered and Permits for the Performance of Category A and B Polluting Activities shall be Issued” of 30.11.2010 (Republic of Latvia, Cabinet Regulation No. 1082, 2010). In Latvia, there are in total 2,549 companies which perform polluting activities of category B (A, B permit 2017).

Not all economic activities cause odour nuisance, it depends on the type of activity, technological specification and emission sources existing in the company. There are eight companies of category A and 286 companies of category B in Riga administrative territory which due to their operation discharge air pollutants such as dust, volatile organic compounds and inorganic compounds. Economic activities to a much lesser extent are carried out in the Centre district – there are 3 companies of category B which emit air pollutants. There are 40 companies in

Kurzeme suburban district of which two companies are of category A and 38 companies are of category B. There are 42 companies in Latgale suburban district, two of them are performers of polluting activities of category A and 40 of them are performers of polluting activities of category B (Fig. 3). There are 57 companies of category B located in Zemgale suburban district, while Zemgale suburban district has 52 companies of category B and two companies of category A. The highest number of companies emitting air pollutants are located in the Northern district in comparison with other suburban districts, respectively, 100 companies of which 98 companies are performers of polluting activities of category B and two companies are performers of polluting activities of category A (Fig. 3).

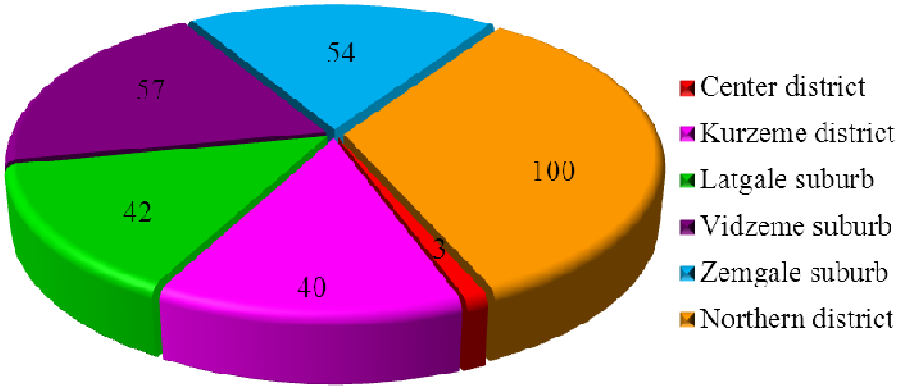

Fig. 3. **The number of companies performing polluting activities of category A and B in Riga regions as of beginning of 2017**

Analysis of the odour emission projects developed by the companies of category A and B allowed to find it was found that the results of odour dispersion modelling show that the maximum odour concentration caused by the companies is not significant, i.e., from 0.0011 to 3.58 ou_E/m^3, complying with the odour guideline value which is determined for a period of an hour and is 5 odour units (ou_E/m^3) according to that stated in Paragraph 8 of the Cabinet Regulations No. 724 "Regulations Regarding the Methods for Determination of the Odours Caused by Polluting Activity, as well as the Procedures for Restricting the Spread of such Odours" of 25.11.2014. (Republic of Latvia, Cabinet Regulation No. 724, 2014).

Analysing complaints of inhabitant received by the public authorities (the State Environmental Service and the State Fire and Rescue Service) regarding odour nuisance, it was found that odour nuisance problem in Latvia and Riga is urgent pressing, respectively, in 2012 the State Fire and Rescue Service received 94 complaints regarding odours and possible leakage of chemical substances, in 2013 – 50 calls were received, while in 2014 and 2015 similarly – 35 and 34 calls were received. In 2016, the State Fire and Rescue Service in Latvia received in total 1,087 complaints on phone regarding odour nuisance and unpleasant odours of which 384 complaints were received in Riga administrative territory.

Analysing complaints regarding odour nuisance within the interval of 24 hours, it was found out that the highest number of complaints in percentage was received during the period of time from 16:00 to 24:00 (Fig. 4), it means that people were affected by odour nuisance mostly directly at their homes.

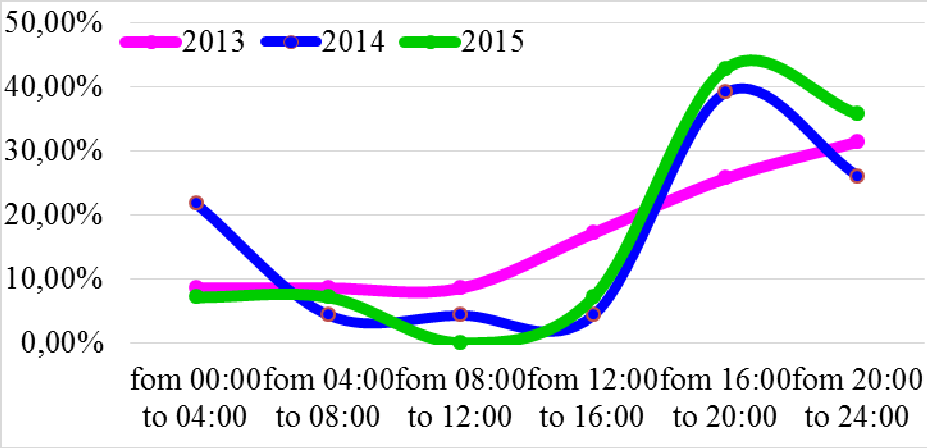

Fig. 4. **Complaints within the interval of 24 hours in 2013, 2014 and 2015**
(data source: the State Fire and Rescue Service)

Analysing complaints on odour nuisance within the monthly interval, it can be concluded that in 2012 the highest number of complaints were received exactly during the summer months, while in 2013, 2014 and 2015 there were no significant differences observed within the interval of months. It means that the number of the odour nuisance cases is equal in all seasons. (Fig. 5).

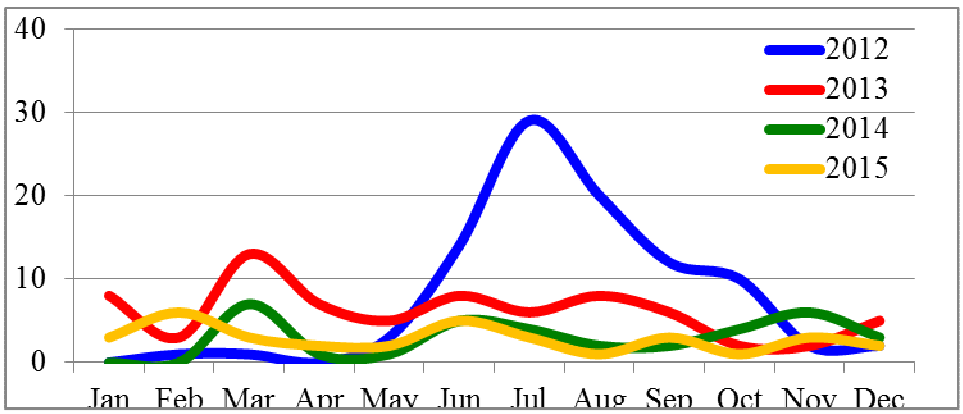

Fig. 5. **Complaints at the monthly interval from 2012 to 2015**
(data source**:** the State Fire and Rescue Service)

Upon analysing complaints, it was found that out of 384 complaints received within Riga territory 272 complaints were from the inhabitants of seven neighbourhoods, respectively, Bolderaja, Sarkandaugava, Kundzinsala, Mangalsala, Milgravis, Vecmilgravis and Petersala-Andrejsala (Fig. 6). The highest number of complaints was received from the inhabitants of

Sarkandaugava, i.e., 74 complaints, while 57 complaints were received from those living in Bolderaja, 53 complaints were recorded in Milgravis, 37 – in Vecmilgravis, 14 – in Mangalsala, 19 – in Kundzinsala, and 18 complaints were recorded in Petersala-Andrejsala.

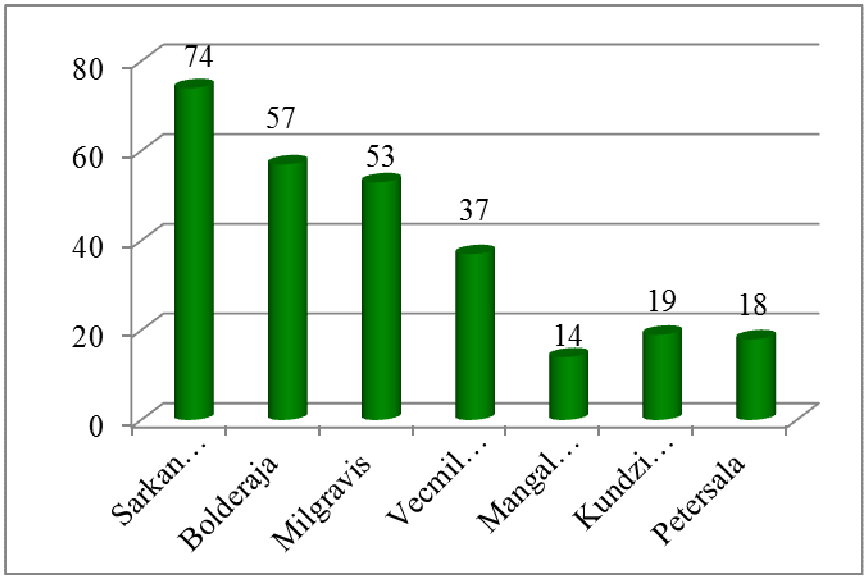

Fig. 6. **Proportion of complaints by neighbourhoods of Riga in 2016**

Upon analysing the data provided by the inhabitants on the odour quality, i.e., what kind of odours people can perceive, it was found out that the highest number of complaints was received on oil product odours, i.e., 147 complaints or 38 % of the total number of complaints were received in 2016 (Fig. 7). A relatively large proportion of complaints is about smoke odours, respectively, 26 %, i.e., in 2016, 98 phone calls were received on unpleasant smoke odour nuisance.

A relatively large number of complaints was received on sewerage odour nuisance, i.e., 39 complaints or 10 % of the total number of complaints. The reason for unpleasant sewerage odours is inadequately maintained treatment plants or overflowing wells – the filling level of the wells is not checked.

In 2016, there were 36 complaints (or 10 %) on chemical odours and 11 complaints (or 9 %) on paint and lacquer odours (Fig. 7). The emission sources of chemical substances and lacquers (often also adhesives) are such companies as various production facilities, wood impregnation companies, service stations, etc. Likewise, inhabitants often mention chemical odour, although, the oil product odour is felt in the air.

Inhabitants relatively often – 37 times (or 10 %) – provided information on other odours (Fig. 7) such as odours of waste, food odours from cafes and fast food restaurants, rubber odours from vehicle racing sites, odours from street repairs, etc. Similarly, inhabitants have complained on plastic odour and odour nuisance caused by metal processing.

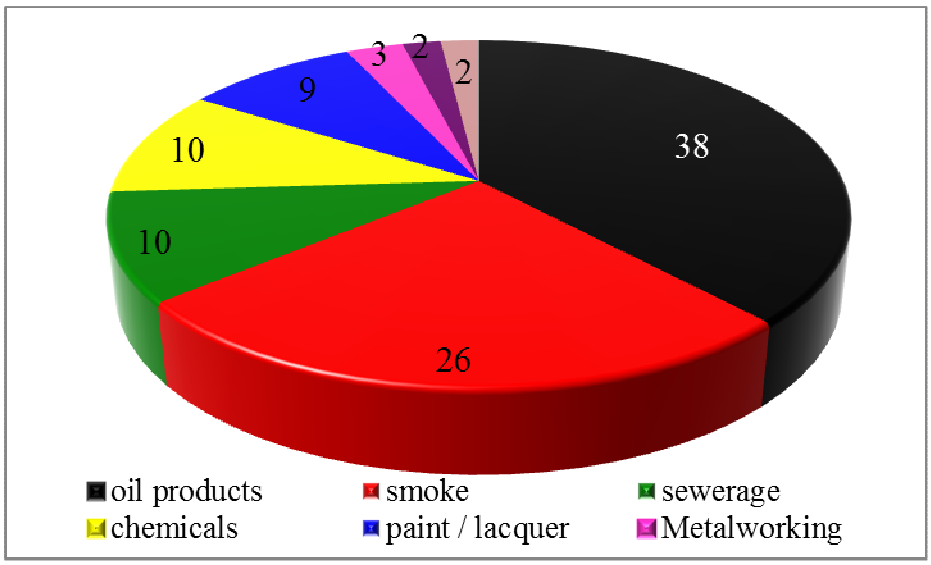

Fig.7. **Proportion of the number of complaints by the type of odour nuisance in 2016**

Within the framework of the research, the odour concentration and airborne substances were examined using the Scentroid SM100 field olfactometer and Gasmet DX-4030 gas analyzer in the neighborhoods of Riga where the highest number of complaints on odour nuisance was received**.** Smoke, wood, sewerage and oil product odours were detected during the studies. The odour concentration ranged from 2 to 7 odour units (ou_E/m^3), respectively, during the inspection of the territory oil product odour nuisance in amount of 6 – 7 odour units (ou_E/m^3) was detected in Sarkandaugava and Kundzinsala.

The measurements of the airborne substances with the Gasmet DX-4030 gas analyzer in Sarkandaugava recorded a high concentration of carbon dioxide, respectively, from 462 to 690 ppm.

Comparison of the results of measurements made on 29.01.2017 and 21.04.2017 (Fig. 8) in the same neighbourhood at Ezera Street 20, Riga, allow to conclude, that the air pollutant concentration does not differ significantly although the odour concentration on 29.01.2017 was below 2 odour units, while on 21.04.2017 the odour concentration was 6 odour units (ou_E/m^3). It can be explained by the fact that odour intensity changes very quickly depending on the wind direction and speed. Measurements made on 29.01.2017 and 21.04.2017 were carried out close to the oil product terminals, thus the following substances were identified in air: benzol, toluol, methane, nitromethan (Fig. 8), as well as carbon dioxide, nitric oxides, chloroform, etc.

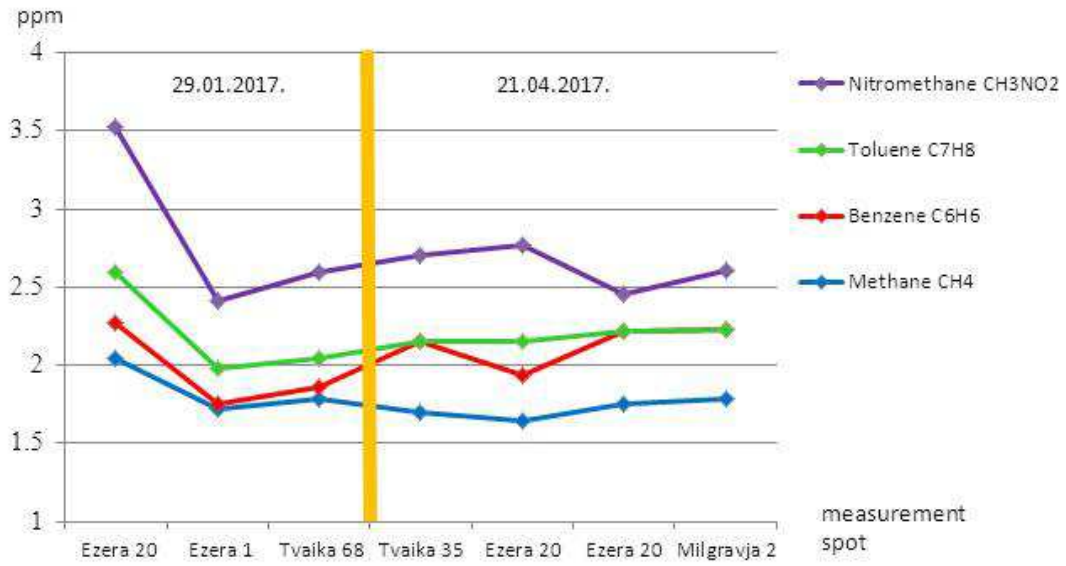

Fig. 8. **Mutual comparison of the air pollutant concentration (measurements made on 29.01.2017 and on 21.04.2017) at the area of Tvaika and Ezera Streets, Riga**

Conclusions

Studies carried out up to now show that the companies operating in compliance with the requirements of the conditions stated in the permits of category A and B do not cause odour nuisance, respectively, their emissions are below 4 odour units (ou_E/m^3). However, taking into account the fact that during the research also 6 - 7 odour units (ou_E/m^3) were detected, it can be concluded that nuisance odours result from the operation of a number of companies, i.e., one territory is affected by the operation of a number of companies. Within a monthly interval, people are exposed to odour nuisance in equal amounts, while in the 24-hour interval odours most often are perceived in the evenings, it means that people are affected by odours at their places of residence. Mostly, inhabitants of Riga perceive oil product odours, thus the largest number of complaints was received from Bolderaja, Sarkandaugava, Kundzinsala, Mangalsala, Milgravis, Vecmilgravis and Petersala-Andrejsala.

Correlation of the results on air pollutant concentrations and odours allow to conclude that odour intensity can not always be described by identifying 23 possible substances, likewise meteorological conditions are very significant for obtaining results. It is necessary to carry out additional studies regarding the odour and air pollutant concentrations to describe the air quality, odour nuisance frequency, intensity and type in Riga administrative territory.

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CONSTRUCTED WETLANDS AS ENVIRONMENTALLY FRIENDLY DRAINAGE SYSTEM ELEMENT

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Abstract

Constructed wetlands as environmentally friendly drainage system element

Key words: *constructed wetlands, nutrient retention, construction, principles of design*

Eutrophication is the state with high nutrient concentration, which can cause plant growth including algae blooms. Nutrients drain into the Baltic Sea from agricultural lands and drainage systems, from weak or insufficient wastewater treatment, from contaminated industrial waste water, and even from the rain water, if it contains dust, unburnt oil from the roads and parking areas or other pollutants washed from hard coverings or accumulated in the air. High nutrient level into the natural waters affects the human economic activity. An inexpensive way to reduce nutrient load to water objects from agricultural lands is formation of constructed wetlands or restoration of natural wetlands. The main tasks of this study were to describe the processes in constructed wetlands, the conditions of construction and to analyze the capacity of constructed wetlands to reduce nutrients and suspended particles inflow to open waters. Another task was to determine nutrient retention efficiency in the Mežacīruļi constructed wetland in Latvia by the descriptive methods of mathematical statistics and Wilcoxon T test method and to compare the obtained results with ones from Bergaholm constructed wetland in Sweden. In the end of this article, the evaluation of efficient theoretical design parameters for constructed wetlands in Latvia is made. The research results indicate that the Mežacīruļi constructed wetland does not provide the sufficient nutrient retention. To improve the nutrient retention efficiency, it would be necessary to develop it, e.g., to increase the amount of vegetation, such as planting *Typha spp.* or to make a small constructed wetland extension to a depth of 0.3 m for *Carex spp*. to stabilize the sediments.

Kopsavilkums

Mākslīgās mitrzemes kā videi draudzīgs meliorācijas sistēmas elements

Atslēgvārdi: *mākslīgās mitrzemes, barības vielu aizture, konstrukcija, projektēšanas principi*

Eitrofikācija ir process, kad, pieaugot biogēno vielu saturam ūdenstilpēs, paātrinās bioloģiskie procesi, kas izraisa ūdensaugu pastiprinātu augšanu, tai skaitā aļģu ziedēšanu un organisko vielu uzkrāšanos. Viens no galvenajiem biogēno elementu avotiem vaļējās ūdenskrātuvēs ir lauksaimniecības zemes, no kurām ar meliorācijas sistēmu palīdzību notiek šo vielu izskalošanās no augsnes. Mākslīgā mitrzeme ir viens no variantiem, kā samazināt biogēno elementu un suspendēto daļiņu slodzi uz vaļējām ūdenskrātuvēm. Darba mērķis bija izpētīt mitrzemes darbības principu un biogēno elementu aiztures efektivitāti atkarībā no izmēra un konstrukcijas. Galvenie darba uzdevumi bija izvērtēt mākslīgās mitrzemes "Mežacīruļi" Latvijā barības vielu aiztures efektivitāti, pielietojot aprakstošās matemātiskās statistikas metodi un Vilkoksona T-kritērija metodi, rezultātus salīdzināt ar mākslīgo mitrzemi "Bergaholm" Zviedrijā. Nobeigumā sniegt teorētiskas mākslīgās mitrzemes efektīvas konstrukcijas parametrus Latvijā. Pētījuma rezultāti liecināja to, ka mākslīgā mitrzeme "Mežacīruļi" neveic biogēno elementu pilnvērtīgu aizturi. Lai uzlabotu mākslīgās mitrzemes "Mežacīruļi" biogēno elementu aiztures efektivitāti, būtu nepieciešams to pilnveidot, t.i., palielināt veģetācijas daudzumu, piemēram, stādot vilkvālītes *Typha spp*., un pie iespējas veikt nelielu mākslīgās mitrzemes paplašinājumu ar dziļumu 0.3m, sedimentu stabilizēšanai stādīt grīšļus *Carex spp*.

Introduction

Eutrophication is one of the most important environmental problems facing the Baltic Sea today. Only 5 % of total nitrogen (N) directly drains into the Baltic Sea, the remaining 95 % of the nitrogen compounds are discharged from river catchments (HELCOM 2015). Phosphorus (P) losses also contribute strongly to eutrophication. Phosphorus is the limiting factor in many lakes and coastal areas (Andersson 2012). In the Baltic Sea, about 92 % of P is discharged from river catchments (HELCOM 2015). Nutrients drain into the Baltic Sea from agricultural lands and drainage systems, they are delivered by polluted or insufficiently treated wastewaters, and even by

the rain, because it contains dust and unburnt oil from roads and parking areas. Therefore, the mitigation of eutrophication is important from many perspectives.

High phosphorus and nitrogen levels in natural waters are affected mainly by human economic activity. Measures directed to decrease transferring of nutrients to the aquatic environment must be combined with measures directed to increase retention efficiency of nutrients at catchments. There is not one single solution to mitigate eutrophication, but rather a complex of different solutions. One of the easiest and relatively inexpensive ways to reduce nitrogen and phosphorus load into the water from agricultural lands are establishment or restoration of wetlands. Wetlands have an important economic, scientific, cultural and recreational value. They regulate water treatment, help to reduce flooding, perform water treatment and can increase the biodiversity. Wetlands are also important for climate change mitigation, because they attract a significant amount (up to 40%) of the world's terrestrial carbon stocks (Ramsar Convention 1971). In Latvia, constructed wetlands have not been widely implemented and there is a lack of knowledge on wetlands of such type.

The main objectives of this study were to describe the processes in the constructed wetlands, the conditions of construction and analyze the cappacity of constructed wetlands to reduce nutrients and suspended particle inflow to open waters. Another objective was to determine the nutrient retention efficiency in the Mežacīruļi constructed wetland in Latvia (from here on referred to as “Mežacīruļi”) as well as to compare its size and design with the Bergaholm constructed wetland in Sweden (from here on referred to as “Bergaholm”). Finally, an evaluation of efficient design parameters for constructed wetlands in Latvia is made.

Background

Retention processes

In wetlands, several nutrient retention processes take place. The main phosphorus retention process is physical sedimentation (Kynkäänniemi 2014), but phosphorus retention in wetlands also happen through chemical binding and biological uptake by plants (Grinberga & Jansons 2012). Wetlands have a positive effect on reduced nitrogen transport to aquatic environments. Some retention processes are the same for N and P (Figure 1), like biological uptake by plants and accumulation of organic N in the sediment. In wetlands, nitrates are reduced to gaseous end products, nitrous gas and dinitrogen gas, through the bacterial process which is called denitrification (Bastviken 2006) and it is the main N retention process.

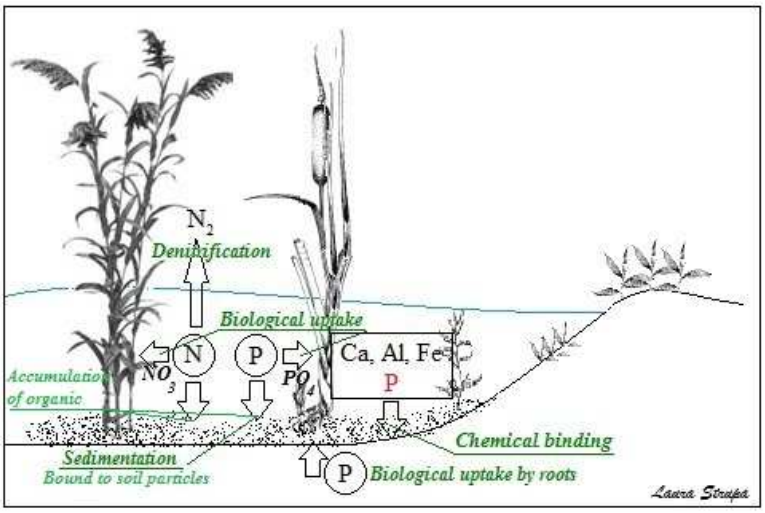


Figure 1. **Nutrient retention processes in constructed wetlands** (Fig. by L. Strupa)

Description of the constructed wetlands

The catchment of Mežacīruļi is located in the Jelgava district and Tērvete district within the Zemgale region, situated in the central part of Latvia (Figure 2). The total catchment area is 74.7 ha. 90 % of the catchment area consists of arable land (Grinberga 2013). The soil type in the area is dominated by rendzina. The aim of constructing Mežacīruļi was to decrease the pollution of nutrients and to treat waste water. The construction is located within the ditch and consists of a deep part and the water level has been regulated by a triangular spillway. Vegetation was established naturally (Grinberga 2013).

Figure 2. **The placement of constructed wetlands** (Karšu izdevniecība…)

The catchment of Bergaholm is located in the Södermanland county in Sweden (Figure 2). 43 % of the catchment area is arable land, 12 % is paddocks and 46 % is forests (Kynkäänniemi 2014). In the catchment area dominate soil with clay content about 30 %. The aim of constructing Bergaholm was to reduce the leaching of phosphorus to lake Bornsjön. The construction is long and narrow, for the increasing of residence time peninsulas was built. The inlet is located at the drainage pipe and the constructed wetland consists of a deep and a shallow part. Great pond-sedge and yellow Iris were planted there (Kynkäänniemi 2014).

Material and methods

Two types of methods were used in this study: Data Processing and Comparative Analysis. Data Processing includes the descriptive method of mathematical statistics and Wilcoxon T test

method. The descriptive method of mathematical statistics was used to calculate the average nutrient values and standard errors in the Mežacīruļi outlet and inlet. Whereas, Wilcoxon t-test method was used to determine if major and important differences existed between the measured results of the nutrient concentrations in the inlet and outlet of the Mežacīruļi constructed wetland. Wilcoxon t-test methods hypothesis were defined as:

H0: there is no statistically significant difference between outlet and inlet parameters indication in the Mežacīruļi;

H1: difference between outlet and inlet parameters indication in the Mežacīruļi is statistically significant.

The actual T value was calculated by using formula 1.:

$$T = \min(|R_+|, |R_-|), \quad (1)$$

where R_+ - sum of the positive rank;

R_- - sum of the negative rank (Arhipova & Bāliņa 2006).

Critical T value depends on the number of degrees of freedom (n-k, where n is the number of pairs, k - the number of pairs for which difference is 0) and the one-sided level of significance (α). In the study was established that if α = 0.05 and n-k = 26, then $T_{0.05;26-0} = 110$, but if α = 0.05 and n-k = 15, then $T_{0.05;15-0} = 30$. H0 is not rejected if $T > T_{\alpha, n-k}$.

To evaluate the performance and design parameters of an efficient wetland design, the Comparative Analysis was used. Furthermore, Mežacīruļi and Bergaholm wetlands were compared. The main data sources on retention efficiency of both sites were the doctoral thesis “Small wetlands designed for phosphorus retention in Swedish Agricultural Areas” (Kynkäänniemi 2014) and the technical project “Establishment of the wetland within the framework of project "Wetlands" in Jelgava district real estates "Siltums" and "Vecozoli" (Grinberga 2013).

Results and discussion

Efficiency evaluation

Geranmayeh (Kynkäänniemi 2014) showed that the total P retention efficiency in Bergaholm was around 89 kg/ ha /year and the total suspended solids retention efficiency was around 37 t/ha/ year.

Before calculations it was assumed that in the Mežacīruļi the content of nutrients and suspended solids at the outlet will be less than in the inlet.

The results from the data processing by descriptive method of mathematical statistics indicate that at the outlet of Mežacīruļi, amounts of ammonium, total P and phosphates decreased whilst amounts of total N, total suspended solids and nitric oxide increased (Table 1).

Table 1. **Description of nutrient retention efficiency in the Mežacīruļi. Results of descriptive method of mathematical statistics from 2014 until 2016 (Confidence level 90 %)**

Parameter	pH		$N\text{-}NO_{2+3}$, mg/l		$N\text{-}NH_4$, mg/l		$N_{tot.}$, mg/l		$P\text{-}PO_4$, mg/l		$P_{tot.}$, mg/l		Suspended solids	
	Inlet	Outlet	Inlet	Outlet	Inlet	Outlet	Inlet	Outlet	Inlet	Outlet	Inlet	Outlet	Inlet	Outlet
Number of samples	26	26	26	26	26	26	26	26	26	26	26	26	15	15
Arithmetic mean	7.95	8.08	11.94	12.71	0.68	0.58	13.34	14.54	0.15	0.07	0.182	0.096	10.83	12.08
Median	7.98	8.13	12.20	13.20	1.02	0.29	12.45	15.25	0.05	0.03	0.08	0.06	8.40	10.50
Error	0.07	0.05	1.52	1.38	0.21	0.14	1.80	1.52	0.09	0.01	0.11	0.02	2.36	2.45
Variation	1%	1%	13%	11%	31%	24%	13%	10%	61%	20%	60%	16%	22%	20%
Minimum	6.97	7.53	0.70	0.30	0.01	0.01	1.40	1.80	0.001	0.004	0.007	0.010	1.59	2.90
Maximum	8.48	8.51	32.20	28.90	3.83	2.97	35.60	34.40	2.36	0.28	2.884	0.323	37.00	36.20
Asymmetry	-0.96	-0.51	0.71	0.09	1.94	2.24	0.87	0.31	5.02	1.33	5.03	1.32	1.88	1.49
Excess	1.43	-0.41	0.72	-0.09	3.40	5.51	0.42	0.42	25.41	0.99	25.50	1.32	4.22	2.03

The reason of increasing of total N, total suspended solids and nitric oxide could be the lack of vegetation, because the main nitrogen retention process is denitrification, which need specific conditions as anoxic environment. Also, during the time of measurements, the Mežacīruļi was affected by external conditions such as surface runoff, precipitation and wind, which contributed to the turbulence of water and thus to the increasing of the suspended sediments. For example, during the second decade of March in 2016 the amount of precipitation was 80 mm which is 50 % more than the monthly average value, i.e. 40.6 mm (Latvijas vides, ģeoloģijas… 2016) and during the third decade of March in 2016 wind speed reached 18 m/s (Latvijas vides, ģeoloģijas… 2016).

The reason of decreasing of amount of ammonium was an anaerobic environment in sediments which cause nitrification – bacterial process where ammonium is transformed to nitrate NO_3^-. This process is also positively influenced by current pH level, which contributed activity of denitrification bacteria in sediments.

Three-year average concentration of $P\text{-}PO_4$ and $P_{tot.}$ in the Mežacīruļi has decreased about 50 %. It can be explained by the fact that the wetland was built as sedimentation pond which contribute deposition of P on the bottom. Hence it promotes the treatment of agricultural run-off.

The results of Wilcoxon T-test indicate that the actual value in all cases was higher than the critical value (Table 2).

Table 2. **Results of Wilcoxon T-test method from 2014 until 2016 (Confidence level 95 %)**

	pH	$N\text{-}NO_{2+3}$, mg/l	$N\text{-}NH_4$, mg/l	$N_{kop.}$, mg/l	$P\text{-}PO_4$, mg/l	$P_{kop.}$, mg/l	Suspended solids
R_+	99.0	135.0	145.0	143.0	160.0	148.5	51.0
R_-	-252.0	-216.0	-198.0	-208.0	-191.0	-202.5	-69.0
T	99.0	135.0	145.0	143.0	160.0	148.5	51.0
Comparison	<	>	>	>	>	>	>
$T_{\alpha;n\text{-}k}$	110	110	110	110	110	110	30

Note: H0 is not rejected if $T > T_{\alpha,\ n\text{-}k.}$

In summary, H0 cannot be rejected, which means that there are no statistically significant differences between outlet and inlet parameters in the Mežacīruļi.

Only in one case H0 is rejected: the difference between the pH level in inlet and outlet are significant and this shows that there are favourable habitats for denitrification in the constructed wetland.

Evaluation of efficient design parameters

Hydrology is based on the water retention time (Bastviken 2006). It depends on wetland size, which is very important factor for treatment, and in turn it depends on the catchment area. The high transport of particles usually is caused by erosion of silty loams and the clay particles, which were eroded as aggregates and settled of the same size as silt particles (Bastviken 2006). The small wetlands constructed in agricultural lands as ditches, slow down water velocity and promote deposition of suspended sediments. For these types of wetlands, the recommended size is larger than 0.1% of catchment area (Braskerud 2002). But the size of wetland can affect an area of available land.

Hydraulic efficiency is parameter which indicates how the water is spread in the wetland and how it is affected by the shape, design and placement of inlet and outlet, which in turn are influenced by different factors. Long, narrow wetlands have higher hydraulic efficiency than circular wetlands, resulting in a longer water retention time (Kynkäänniemi 2014). Different extra elements as peninsulas, islands on piles of stones can be used to prolong hydraulic efficiency and to increase biodiversity. Side slopes should be 1:2, not steeper than 1:3 (Jurries 2003) because coasts with small slope gradient promote biodiversity, facilitates the flooding, and the area is easily accessible for the management and maintenance. It also should be adapted for cleaning of the wetland bottom to remove accumulated particles and overgrown vegetation.

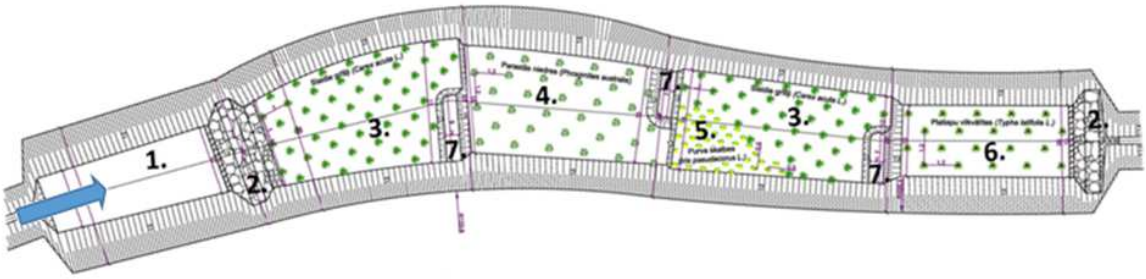
Wetland should has shallow and deep parts. The deep part is recommended to construct up to 2 m depth and the shallow part up to 0.5 m depth (Grinberga & Jansons 2012) depending on which vegetation will be planted there. Considering the climatic conditions of Latvia *Typha latifolia L.*, *Phragmites australis* and *Carex spp.* can be planted in constructed wetland.

Inlet can be filled with gravel to prevent erosion, which works also as a filter for separating coarser impurities. Stone thresholds on triangular spillway can be used to regulate water level in constructed wetland can be used, for example.

Example

Before designing a wetland, such information about factors in the location of wetland is needed as nutrient concentrations, topography, type of soil, land-use etc. After that, exact placement, shape, size and vegetation, should be chosen to get the right type of wetland. Each variant is incomparable because all parameters of design are affected by external factors.

In summary of this study the theoretical example of constructed wetland was made (Figure 3).



Legend
1. sedimentation pond, depth *h* = 1.0m
2. stone threshold
3. *Carex acuta L.*, *h* = 0.3m
4. *Phragmites australis*, *h* = 0.5m
5. *Iris pseudacorus L.*, *h* = 0.3m
6. *Typha latifolia L.*, *h* = 0.8m
7. peninsulas

Figure 3. **Plan of the constructed wetland** (Fig. by L. Strupa)

The constructed wetland consists of five sections. The sedimentation pond and the plantation of *Carex acuta L.* and *Iris pseudacorus L.* are designed for P retention. While for N retention the plantation of *Phragmites australis* and *Typha latifolia L* are used. To increase hydraulic efficiency, water residence time and biodiversity and to improve water aeration stone thresholds and peninsulas are designed.

Conclusions

The Mežacīruļi does not perform the valuable nutrient retention. In order to improve the nutrient retention efficiency, it is necessary to increase the amount of vegetation, such as planting *Typha spp.* or to make a small constructed wetland extension to a depth of 0.3 m for *Carex spp.* to stabilize the sediments.

Further researches about constructed wetlands in Latvia would be advised to build new and differently designed constructed wetland, and then to compare their retention efficiency and design parameters.

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VESELĪBAS ZINĀTNES / HEALTHY SCIENCES

OBSTRUCTIVE SLEEP APNEA RISK ASSESMENT AMONG PATIENTS WITH PULMONARY DISEASE

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Abstract

Obstructive sleep apnea risk assesment among patients with pulmonary disease

***Key words**: Obstructive sleep apnea, pulmonology, shortness of breath, comorbidities*

Introduction: Obstructive sleep apnea (OSA) is a disease that induces a persistent/periodic hypoxia condition. OSA often have an overlap syndrome between other lung disease therefore it is difficult to get a correct diagnosis.

Aim: To identify the risk of OSA among patients, who were hospitalized due to a pulmonary disease.

Materials and methods: A prospective study of 227 patients with a pulmonary disease. Patients were assessed using the STOP-BANG questionnaire. Statistical analysis was conducted using SPSS 23.0 software.

Results: The high-risk group consisted of patients with community acquired pneumonia (n = 42), bronchial asthma (n = 24) and chronic obstructive pulmonary disease (n = 20).

Conclusions: The study confirms that patients with pulmonary disease tend to have a high risk of OSA and they should be examined using polysomnography.

Kopsavilkums

Obstruktīvas miega apnojas risks pacientiem ar plaušu slimībām

***Atslēgvārdi**: obstruktīva miega apnoja, pneimonoloģija, elpas trūkums, blakusslimību risks*

Ievads: obstruktīvu miega apnoja (OMA) ir slimība, kuras klīnisko izpausmju dēļ pacienti atrodas hroniskā hipoksijas stāvoklī. Slimībai nereti novēro pārklāšanās formas ar plaušu slimībām, kas var apgrūtināt diagnostiku.

Mērķis: Identificēt OMA risku pacientiem ar plaušu slimībām, kas ārstēti stacionāri.

Materiāli un metodes: Prospektīvā pētījumā tika iekļauti 227 pacienti ar plaušu slimībām. Pacienti tika novērtēti pēc starptautiski atzītas STOP-BANG anketas, nosakot OSA risku. Datu statistiskā apstrāde veikta ar programmu SPSS 23.0.

Rezultāti: Augsta riska grupā visvairāk bija pacienti ar sadzīvē iegūtu pneimoniju (n=42), bronhiālo astmu (n=24), hroniski obstruktīvu miega apnoju (n=20).

Secinājumi: Pētījums pierāda, ka pacientiem ar plaušu slimībām ir augsts OSA risks un šai riska grupai būtu jāveic polisomnogrāfija.

Introduction

Obstructive sleep apnoea (OSA) is a common medical disorder associated with high morbidity and is being recognized more frequent among certain patient groups. It is the most common type of sleep-disordered breathing and is characterized by recurrent episodes of upper airway collapse during sleep. Patients with OSA are frequently overweight and usually present with a longstanding history of snoring and excessive daytime sleepiness (Gupta 2010).

Several studies suggest that the prevalence of OSA varies in the middle-aged adult group (between 30 and 60 years of age) from 2 - 9% among women and 4 - 24% among men (Young 1993). However, large epidemiologic studies of predominantly white populations estimate the prevalence of OSA syndrome at approximately 3–4% among men and 2% among women. OSA patients may also represent themselves as a loud snorers (up to 85%) and have difficulties

maintaining sleep - due to the recurrent episodes of hypoxia. When awake, patients may experience hypersomnolence, fatigue and impaired ability to concentrate (Kimoff 2016).

Risk factors of OSA are divided into anatomic and related risk factors. Anatomic risk factors are: short or retracted mandible, prominent tongue base or tonsils, rounded head shape and a short neck, neck circumference > 43 cm, thick lateral pharyngeal walls, lateral parapharyngeal fat pads. Other identified risk factors include postmenopausal status, aging, alcohol or sedative use. The most dominant risk factor is also identified – obesity (Kingman 2017).

Inspiratory efforts against a closed upper airway cause paroxysms of inspiration, reductions in gas exchange, disruption of normal sleep architecture, and partial or complete arousals from the sleep. These factors may interact to cause the characteristic symptoms and signs, including hypoxia, hypercapnia and sleep fragmentation (Kingman 2017).

A few studies showcase that OSA may present in the form called “overlap syndrome” with pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and obesity hypoventilation syndrome (Shteinberg 2009). A recent study shows that overlap syndrome patients clearly benefit from continuous positive airway pressure (CPAP) - which is the most common treatment option for OSA patients (Soler 2015). Recent data suggests that OSA is an independent risk factor for asthma exacerbations but there is limited data about other lung disease related overlap, such as community acquired pneumonia (Alkhalil 2009).

Aim

The aim of this research was to evaluate OSA grade of risk for patients with pulmonary disease and identify the differences in OSA risk between patients with various pulmonary diseases.

Materials and methods

In this prospective study 227 patients were surveyed and their medical records were analysed.

The medical records covered time period from January 1st 2016 to December 31st 2016. They were hospitalized due to the pulmonary disease in the Pauls Stradins Clinical University Hospital and Riga East Clinical University Hospital.

Patients were surveyed using international STOP-BANG questionnaire. The following questions were asked and required measurements were made according to the Table 1 (Stop-BANG Questionnaire 2017).

Table 1. **Stop-BANG Questionnaire 2017**

Snoring: Do you snore loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
Tired: Do you often feel tired, fatigued, or sleepy during the daytime (such as falling asleep during driving or talking to someone)?
Observed: Has anyone observed you stop breathing or choking/gasping during your sleep?
Pressure: Do you have or are being treated for high blood pressure?

BMI: Is patients' body mass index(BMI) more than 35 kg/m^2?
Age: Is he/she older than 50?
Neck: Is his/her neck size larger than normal? (Measured around Adams apple) For **male**: is the shirt collar 43 cm or larger? For **female**: is the shirt collar 41 cm or larger?
Gender: Is the patient male?
For every affirmative answer patient get 1 point. The grade of OSA risk is identified by summing up the points.
0 - 2 points: **low risk**
3 - 4 points: **intermediate risk**
5 - 8 points: **high risk** Or "yes" to 2 or more of 4 STOP questions + male gender Or "yes" to 2 or more of 4 STOP questions + BMI > 35kg/m^2 Or "yes" to 2 or more of 4 STOP questions + neck circumference exceeds normal range

We also asked if they were diagnosed for OSA previously.

The following data for each patient were collected: age, gender, BMI, number of hospitalizations, smoking pack years, primary diagnosis, comorbidities, parameters of blood gas - pH, partial pressure of oxygen in the arterial blood (pa O_2), partial pressure of carbon dioxide in the arterial blood (pa CO_2), oxygen saturation (SaO_2).

Patients were divided in groups by BMI:

1) underweight <18.5 kg/m^2
2) normal weight 18.5 – 24.9 kg/m^2
3) overweight 25 – 29.9 kg/m^2
4) obesity >29.9 kg/m^2

Statistical analysis was conducted using SPSS 23.0 software, where the significance level was set at maximum of 5% ($p<0.05$). All statistical tests were two-sided.

Kolmogorov – Smirnov test was used for data distribution; Descriptive Statistics were used to measure central tendency. Frequencies were used to determine most frequently discovered data and percentages.

Independent samples Kruskal Wallis test was used to determine if there are differences between various patient OSA risk groups.

To determine if there were non-random associations between two nominal variables, which represent qualitative properties (e.g. smoker), Pearson Chi-Square coefficient was used.

To determine the impact of the smoking pack years and hospitalization times Spearman's rank Correlation coefficient was used.

The study was conducted with the approval of the Committee on Research Ethics (No. 51/29.10.2015.) and performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki.

Results

The data from 227 patients' who were hospitalized due to pulmonary disease were included in this study. 69.6% (n=158) were hospitalized in Riga East Clinical University Hospital and 30.4% (n=69) were hospitalized in Pauls Stradins Clinical University Hospital. The study included 125 male (55.1%) and 102 female (44.9%) aged from 31 to 92, with median age of 72 years (IQR 61-78).

The most frequent diagnosis was: community-acquired pneumonia (n=115), followed by COPD (n=73) and bronchial asthma (n=51). Less common diagnosis can be seen in Table 2.

Table 2. **Distribution between OSA grade of risk among patients with different diagnosis**

	Low risk	**Intermediate risk**	**High risk**
Community-acquired pneumonia	14	21	42
COPD	2	19	20
Bronchial asthma	3	10	24
ARVI	0	4	10
Acute bronchitis	0	4	10
Hydrothorax	0	9	4
Influenza	0	2	6
Pulmonary fibrosis	0	0	8

80.6% (n=183) of patients had comorbidities such as primary arterial hypertension (n=99), coronary heart disease (n=65), chronic heart failure (n=55), diabetes mellitus (n=40), atrial fibrillation (n=34), myocardial infarction (n=24), atherosclerosis (n=14), gastroesophageal reflux disease (n=13). In 19.4% (n=44) of cases there were 2 comorbidities, 18.9% (n=43) 3 comorbidities, 7.9% (n=18) 4 comorbidities, 5.3% (n=12) 5 comorbidities.

It is statistically significant, that neck size exceeds normal range for males more often than in females ($p=0.046$).

53.7% (n=122) were smokers and median of smoking pack years was 30 (IQR 19-40). Male smokes more often than female ($p<0.001$). Patients with greater smoking pack years are hospitalized more often ($p=0.008$).

The distribution between patients in different OSA grade of risk can be seen in Figure 1.

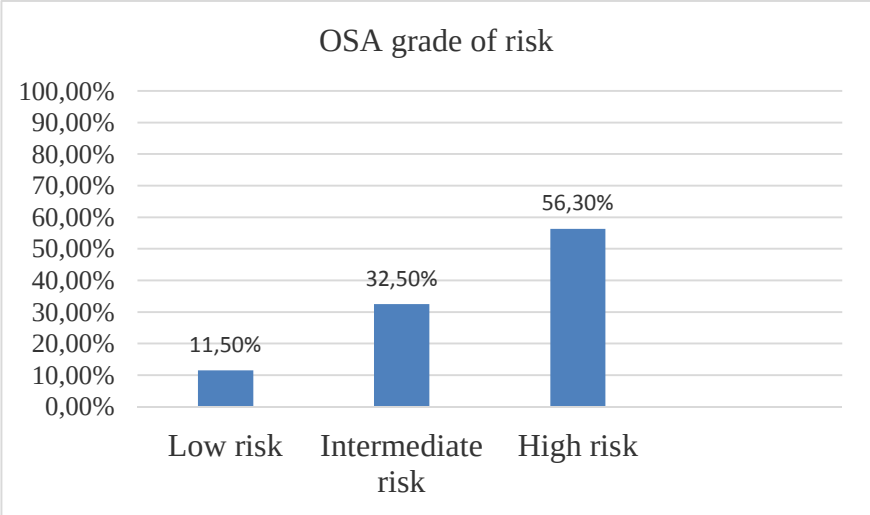

Figure 1. **OSA grade of risk according to the STOP-BANG questionnaire 2017**

32.6% (n=72) of patients had normal weight, 9.7% (n=22) were underweight, 31.7% (n=72) were overweight and 25.6% (n=58) were obese. There are statistically significant results showing that an increase in BMI can affect OSA grade of risk (see Figure 2) ($p<0.001$).

There is difference between median age in each risk group (see Figure 3) ($p=0.026$).

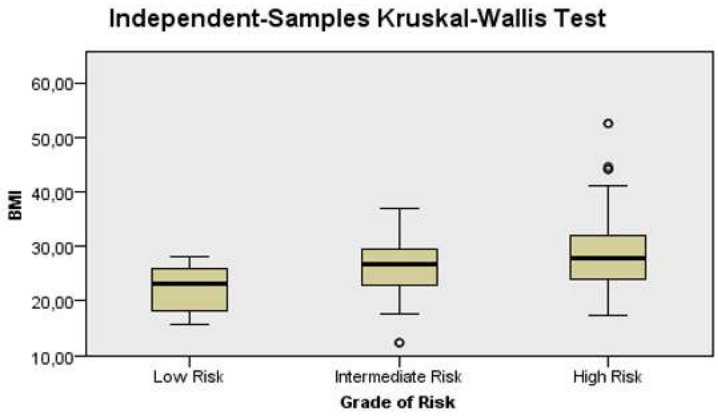

Figure 2. **Distribution of the OSA grade of risk according to the body mass index**

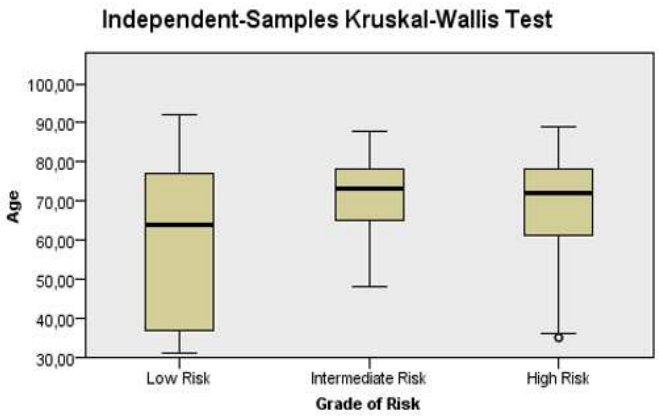

Figure 3. **Distribution of the OSA grade of risk according to the age**

There were no statistically significant data of arterial blood gas parameters and OSA risk due to a little number of registered data.

None of the patients had previously been diagnosed for OSA and only few of them had heard about this disease.

Discussion

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (WHO 2016). The worldwide prevalence of obesity has more than doubled between 1980 and 2014. We can assume it will increase without an active intervention. According to the World Health Organization data, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2014. In research study of Peppard et al. weight gain of 10% was associated with a 6-fold increase in the odds of developing sleep apnea (Peppard 2000).

Differences in the risk factors (e.g. age, gender, serum lipid, diabetes status) suggest that obesity represents a major compensatory mechanism neutralizing intravascular dyslipidemia risk (Wei 2015). Obesity may reduce upper airway calibre due to fact because of adipose tissue deposition as well as through a long volume-dependent effect (Tagaito 2007).

We observed results showing that an increase in BMI can affect OSA grade of risk ($p<0.001$). We would like to suggest that patients with pulmonary disease, who also present risk factors for OSA should be screened at least with some questionnaire (STOP-BANG, Berlin Questionnaire etc.) and overnight oximetry. These patients often are polymorbid - 19.4% of our patients had 2 comorbidities and 18.9% of them had 3 comorbidities what is characteristic for OSA syndrome.

The “golden standard” for the diagnosis of OSA is polysomnography, but it is expensive and time consuming (Pataka 2016). Patient, who would like to undergo an examination of polysomnography in Latvia, must visit a private sleep clinic, it is not available for a general population in a primary care centre - situation is the same as in Greece (Pataka 2016). Some of our patients with the OSA high grade risk were motivated to receive further evaluation but unfortunately due to a technical and financial limitations it was impossible to examine them with polysomnography.

Pataka et al. 2016 suggest that overnight oximetry may be used as a tool for identifying severe OSA. They also did not find an improvement in the predictive values when combined different questionnaires with oximetry, especially in mild and moderate OSA. Stop-Bang questionnaire sensitivities were found to be high even in mild OSA cases, but their specificities were rather low (Pataka 2016).

Retrospective analysis of Davies et al. in 1992 showed that the question “Do you fall asleep during the day, particularly when not busy?” was the best questionnaire predictor of variance in the SaO_2 dip rate; no other question improved this correlation (Davies 1992).

Patients with an "overlap syndrome" of chronic obstructive pulmonary disease and OSA have severe arterial oxygen desaturation due to their low baseline SaO_2 values (Sharafkhaneh 2009). In our research the baseline SaO_2 values were measured in too few cases to obtain statistically significant results.

Increased airway resistance in COPD mainly impairs exhalation contrary with OSA whereas the restriction is during inhalation. Together it can generate a catastrophic outcome (Sharafkhaneh 2009).

In our research, COPD was the second most common diagnosis within all patients and 48.78% (n=20) of them had a high OSA risk grade. This correlates with the number of smokers (53.70 % of patients) and they have been hospitalized more often opposite to the patients with community-acquired pneumonia.

The "overlap-syndrome" typically responds to continuous positive airway pressure (CPAP), oxygen therapy, or both (Sharafkhaneh 2009). Sharafkhaneh et al. suggests that clinicians should strongly suspect OSA in any patient with COPD admitted to the emergency room at night with shortness of breath, choking and/or dyspnea. Especially in the case when the patient is an overweight, middle-aged with a history of snoring (Sharafkhaneh 2009). According to the World Health Organization, COPD will be the third most common cause of death and disability by 2030 in the world, from its current fifth ranking. If we combine this information with the increasing prevalence of an obesity we can predict that overlap syndrome will become more common in clinical practise.

We found out that neck size exceeds normal range for males more often than in females ($p=0.046$) and it is confirmed by Veloro et al. in 2008 that the collar size 40 cm and greater among male adults with symptoms of OSA was 80% sensitive and 67% specific with a positive predictive value of 94% in predicting true OSA. They suggest that collar size may be an independent parameter for determining OSA. This correlation between OSA and neck circumference may reflect "mass loading" (Veloro 2008).

Conclusions

The study confirms that patients with pulmonary disease tend to have a high risk of OSA and should be examined considering it. A standardised evaluation system for OSA high risk patients involving polysomnography is needed. Weight loss oriented dietary recommendations may be useful for all patients, especially in the high OSA risk group, due to significantly increased BMI rates. OSA overlap syndrome must be excluded for patients admitted to the emergency department with dyspnea, especially in overweight patients with COPD.

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SPONTANEOUS BACTERIAL PERITONITIS: ANALYSIS OF THE CONDITION AMONG DECOMPENSATED LIVER CIRRHOSIS PATIENTS IN A SINGLE CENTER IN LATVIA

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Abstract

Spontaneous bacterial peritonitis: analysis of the condition among decompensated liver cirrhosis patients in a single center in Latvia

Key words: *Peritonitis*

Introduction: SBP is frequent and potentially fatal infection in decompensated liver cirrhosis (DLC) patients and is a reason of hospitalization in more than 10% of cases. Early paracentesis (PC) with subsequent peritoneal fluid (PF) analysis (cell count, differential, bacterial culture(BC)) is the main diagnostic procedure. Polymorphonuclear cell (PMN) count in PF of >250cells/mm even with negative PF culture is considered to be diagnostic.
Aim: To study SPB incidence among DLC patients and evaluate diagnostic approach.
Materials and methods: All patients with DLC, who were admitted to hospital over the time of January 2011 to October 2016 in Clinical Center Gailezers (Riga), were retrospectively reviewed. Patients' anthropometric data, initial complains, day of hospital stay (DHS), amount and results of non- and specific laboratory and instrumental investigations and antibacterial therapy (AT) regimes were considered.
Results: From 545 DLC patients, in 28 patients were selected. From them SBP was suspected in 10 and identified in 18 patients. Median DHS was 13 days, SPB median establishment day was 3.5. Therapy was successful in 16 cases; 12 patients died. From all patients, only in 67.9%(N=19) PC was performed, from which PMN count was measured in 8 cases, protein in 7, LDH in 10 and lipase in 13. BC of PF was performed only in 68.4%(N=13), and was positive in 8 cases. Only in 25% of all SBP patients recommended diagnostic volume was performed. Estimated incidence of SPB among DLC patients was 3.6%, 1.1 %, 5.7%, 7.1%, 7.3% and 8.7% in the years 2011-2016 respectively.
Conclusion: SPB incidence in DLC patients was lower than was anticipated, but the numbers of established SBP diagnoses tend to increase. Currently complete diagnostic evaluation for SBP is performed only in 25% of patients. The tactics of establishment of SBP diagnosis are not strictly determined and we conclude that a uniform diagnostic algorithm is required.

Kopsavilkums

Spontāns bakteriāls peritonīts: slimības analīze dekompensētas aknu cirozes pacientu vidū vienas slimnīcas ietvaros Latvijā

Atslēgvārdi: *Peritonīts*

Ievads: Spontānais bakteriālais peritonīts (SBP) ir bieža un potenciāli letāla infekcija dekompensētas aknu cirozes (DAC) pacientiem. SBP ir iemesls aknu cirozes slimnieku hospitalizācijai 10% gadījumos. Agrīnā paracentēze (PC) ar peritoneālā šķidruma analīzi (šūnu skaits, bakteriāls uzsējums) ir galvenā diagnostiskā metode. SBP diagnoze tiek uzstādīta pie polimorfonukleāro (PMN) šūnu skaita peritoneālā šķidrumā >250 šūnas/µl, pat ja peritoneālā šķidruma kultūra ir negatīva.
Mērķis: Izpētīt SBP incidenci DAC pacientu vidū un novertēt diagnostisko algoritmu.
Materiāli un metodes. Tika izanalizētas visu Rīgas Austrumu Klīniskā Universitātes slimnīcas pacientu slimības vēstures, kuri tika hospitlizēti ar iestāšanās diagnozi dekompensēta aknu ciroze laika periodā no 2011. gada janvāra līdz 2016. gada oktobrim.
Rezultāti: No 545 identificētiem pacientiem, 28 tika iekļauti pētījumā. Klīniskās aizdomas par SBP bija 10 no šiem gadījumiem un diagnoze tika apstiprināta 18 gadījumos. Analīzē tika iekļauti antropomētriskie rādītāji, sūdzības iestāšanās brīdī, hospitalizācijas ilgums, nespecifisko un specifisko laboratorisko un instrumentālo izmeklējumu profils un rezultāti, kā arī antibakteriālās terapijas režīmi. Hospitalizācijas ilgums bija 13 dienas (mediāna vērtība), laiks līdz SBP diagnozes uzstādīšanai – 3.5 dienas (mediāna vērtība). Terapija bija veiksmīga 16 gadījumos un 12 gadījumi bija ar letālo iznākumu. No visiem pētījumā iekļautiem pacientiem 67.9% (N=19) tika veikta paracentēze, un 8 no tiem tika analizēts PMN šūnu skaits, 7 - proteīnu daudzums, 10 - laktatdehidrogenāzes līmenis un 13 - lipāze. Peritoneālā šķidruma bakteriologiskais uzsējums tika veikts 13 gadījumos (68,4%), un bija pozitīvs 8 no tiem. Pilnīgs rekomendēts izmeklējumu apjoms tika veikts tikai 25% gadījumu. SBP incidence laika periodā 2010.-2016. bija 3.6%, 1.1 %, 5.7%, 7.1%, 7.3% un 8.7% respektīvi.
Secinājums: SBP incidence dekompensētās aknu cirozes pacientiem bija zemāka par sagaidīto, bet uzstādīto SBP diagnožu daudzums pieaug. Pilnīgs izmeklējumu spektrs, kas tiek rekomendēts SBP diagnozes uzstādīšanai ir veikts tikai 25% gadījumos. SBP diagnozes uzstādīšanas algoritms nepastāv un tā izstrāde ir nepieciešama.

Introduction

Spontaneous bacterial peritonitis (SBP) is a peritoneal fluid infection in absence of any evident source (e.g. hollow organ rupture, intraabdominal abscess, acute pancreatitis, cholecystitis) (Cãruntu 2006.) SBP was mentioned in the literature for the first time in 1907 by Krencker, later by Caroli (1957), Kerr et al. (1963) and Conn et al (1964) (Dever 2015; Koulaouzidis 2009). The condition is met in 10-30% of liver cirrhosis patients with mortality rates 10-46% even with adequate management (Atrauss 2006; Dever 2015).

SBP occurs in patients with cirrhosis of various etiology. The pathophysiologic mechanisms of ascites in liver cirrhosis patients is portal hypertension, splanchnic vasodilatation with relative hypovolemia followed by renal artery vasoconstriction, activation of renin–angiotensin–aldosterone axis with subsequent sodium retention leading to increased hydrostatic pressure, which in combination with decreased oncotic pressure due to hypoalbuminemia and failure of lymphatic drainage produces ascites (Sundaram 2016). Although SBP is a typical complication in liver cirrhosis patients, it can occur in patients with any underlying pathology of ascites (e.g. congestive heart failure, Budd Chiari syndrome) (Green 2015). Pathophysiological hallmark of SBP is thought to be bacterial translocation in immunocompromised host (Bernardi 2010).

Clinical presentation of SBP is variable. In up to 30% of cases it can be asymptomatic and only supported by positive peritoneal fluid culture (bacterascites), but some patients develop sepsis with high fatality rates (Alaniz 2009). Most common symptoms are fever and abdominal pain or discomfort. Other possible signs and symptoms are diarrhea, nausea, vomiting, worsening or unexplained encephalopathy, ileus, renal function impairment, therapy resistant ascites (Green 2015). SBP is associated with high risk of hepatorenal syndrome, development of which results in high mortality rates and worst prognosis (Karel 2006; Alaniz 2009).

SBP is not a clinical diagnosis, therefore the millstone of diagnosis is early paracentesis with ascitic fluid analysis. According to European Association for the Study of the Liver (EASL) guidelines “A diagnostic paracentesis should be carried out in all patients with cirrhosis and ascites at hospital admission to rule out SBP. A diagnostic paracentesis should also be performed in patients with gastrointestinal bleeding, shock, fever, or other signs of systemic inflammation, gastrointestinal symptoms, as well as in patients with worsening liver and/or renal function, and hepatic encephalopathy” (EASL 2010: 404). Based on polymorphonuclear cell count (PMN) and ascitic fluid culture results ascitic fluid infection is classified into five types: spontaneous bacterial peritonitis (PMN ≥250 cells/µl and positive culture); culture negative SBP (PMN ≥250 cells/µl and negative culture); mono-/polymicrobial bacterascites (PMN <250 cells/µl and positive culture); secondary peritonitis (PMNs ≥250 cells/µl and positive polymicrobial culture) (Dever 2015). PMN

count ≥250 cells/µl is diagnostic of SBP but PNM count ≥500 cells/µl is more specific parameter (EASL 2010).

Peritoneal fluid should be collected directly at patients' bedside and inoculated into blood culture bottle (Cãruntu 2006). Culture is positive only in 40% of cases and usually is monomicrobial (Dever 2015). Most common etiologic agents are Gram negative bacteria of intestinal origin, but Gram-positive bacteria also can be causative pathogen. Most common isolates are *Escherichia coli, Streptococcus spp. and Klebsiella* (Sundaram 2014; Dever 2015). The newest diagnostic modality is reagent strips test based on leukocyte esterase identification in urine via coulometric technique (EASL 2010; Dever 2015). This test can be performed at patients' bedside and is especially beneficial in patients with contraindications to paracentesis. Though urine reagent strip test results are available within short time period and its' use can indicate the need for antibacterial therapy initiation, several studies have proved its' low sensitivity and high false negativity rates, therefore the test cannot be used alone for SBP diagnosis establishment (EASL< 2010; Alaniz 2009).

LDH, alkaline phosphatase, total amount of protein, glucose level measurements and gram staining can be utilized for differentiation from secondary peritonitis. Other tests used for differential diagnosis are lipase, amylase, albumin (serum/ascites gradient), triglycerides, bilirubin, cytology, Ziehl-Nielsen staining, and cultures on Lowenstein medium (Cãruntu 2006).

Empirical antibacterial treatment should be initiated as soon as SBP is suspected (EASL 2010). Recommended antibacterial regimen is intravenous third generation cephalosporines (e.g. cefotaxime), alternative is amoxicillin/clavulanic acid. For uncomplicated SBP and in patient who are not receiving long-term prophylaxis with fluoroquinolones antibiotics as levofloxacin, ofloxacin, ciprofloxacin can be used (EASL 2010; Dever 2015). Alternative treatment regimes are ceftriaxone (this strongly protein bound antibiotic is considered to be less effective in liver cirrhosis patients due to low protein synthesis). As acute renal failure is the single most important predictor of death in patients with SBP, plasma volume expansion with albumin infusion is considered beneficial in selected patients (EASL 2010).

Antibacterial prevention of SPB can significantly lower the mortality. Candidates for prophylactic measurements are patient with history of previous SBP, patients with gastrointestinal tract hemorrhage and patients with low total protein level in ascetic fluid. The prophylaxis should be initiated after successful SBP management and be continued till resolution of ascites, liver transplantation or death (Alaniz 2009). In selected patients' ciprofloxacin, norfloxacin, trimethoprim–sulfamethoxazole or rifaximin are used for primary or secondary SBP prevention (EASL 2010).

The aim of our study was no evaluate SBP incidence and management tactics in Clinical Center Gailezers (Rīga) in liver cirrhosis patients.

Material and methods

We retrospectively reviewed clinical records of 545 liver cirrhosis patients, who were admitted to Riga East clinical university hospital Clinical Center Gailezers from January 2011 to October 2016. Only patients with suspected or definitive diagnosis of SBP were included in study. Patient age, gender, complaints at admission, clinical presentation, hospitalization time, number of days till establishment of SBP diagnosis, spectrum of performed investigations and their results as well as antibacterial therapy regimens were considered.

Data was analysed in Microsoft Excel and IBM SPSS 21.0 software. For comparison of categorical variables Fisher exact tests were performed; for scale data – nonparametric Mann-Whitney U test. All numerical results were displayed as median (MED) ± interquartile ratio (IQR) values. P value of 0.05 and less was considered as statistically significant.

Results

28 patients were included in the study. Seven (25%) of patients were female and 21 (75%) were male. Patient age median (ME) value was 59±19 (min=40; max=89) years. The median age value was lower in male patients (55±17; min=40; max=85) than in female patients (63±31; min=5; max 59), p=0,08. Etiology of liver cirrhosis was as follows: alcoholic lived disease (N=9; 32.1%), viral hepatitis C (N=5; 17.9%), viral hepatitis B (N=1; 3.6%), primary biliary cirrhosis (N=1; 3.6%) and unknown (n=4;14.3%). In the rest of the patients there was combination of several causative factors: viral and alcohol induced liver damage (N=6; 21.4%), and combined noninfectious factors (N=2; 7.14%). The most common clinical presentation was fever (N=24; 85.7%) and abdominal pain (N=12; 42.8%). For full spectrum of clinical presentations go to tab. 1 and tab. 2.

Table 1. **Incidence of SBP symptoms in liver cirrhosis patients**

SBP symptomes	N	%
Fever	24	85.7%
Abdominal pain	12	42.8%
Shock	10	35.7%
Confusion	9	32.4%
Nausea	5	17.8%
Vommiting	3	10.7%
Diarhoea	3	10.7%
Ileus	2	7.2%

Majority of patients had coagulopathy of variable degrees (N=25; 89.3%). In 13 (46.3%) hepatorenal syndrome was established, but it’s presence did not significantly influenced the mortality rate (p=0.521) (tab. 2)

Table 2. **Incidence of decompensated liver cirrhosis symptoms in SBP patients**

DLC syndromes	N	%
Coagulopathy	25	89.3%
Hepatorenal syndrome	13	46.4%
Jaundice	12	42.8%
Hypersplenism	11	39.3%
Hepatic encephalopathy	9	32.1%
Variceal bleeding	8	28.6%

From all patient only in 18 (64%) SBP diagnosis was proven, but in 10 (36%) it was clinically suspected. The hospitalization outcome was favorable only in 16 (57%) cases, in the rest of the cases the outcome was lethal. Days of hospital stay were 13 ± 9.75 and days till SBP diagnosis establishment – 3.5 ± 5.75. Paracentesis was performed in 19 (67.8%) patients. Of these 19, in 14 (73.7%) with definitive and in 5 (26.3%) with suspected diagnosis of SBP. The list of investigations performed on peritoneal paracentesis is shown in Fig. 1. Peritoneal fluid culture was performed only in 13 (68.4%) patients and neutrophil count was evaluated only in 8 (42.1). The recommended minimal amount of testing (both culture and neutrophil count) was performed only in 7 (36.8%) of all paracentesis samples which accounts for only 25% of all patients. Culture was positive in 8 cases, where in 6 it was monomicrobial and in 2 – polymicrobial. The most common isolate was *Staphylococcus aureus* (N=2).

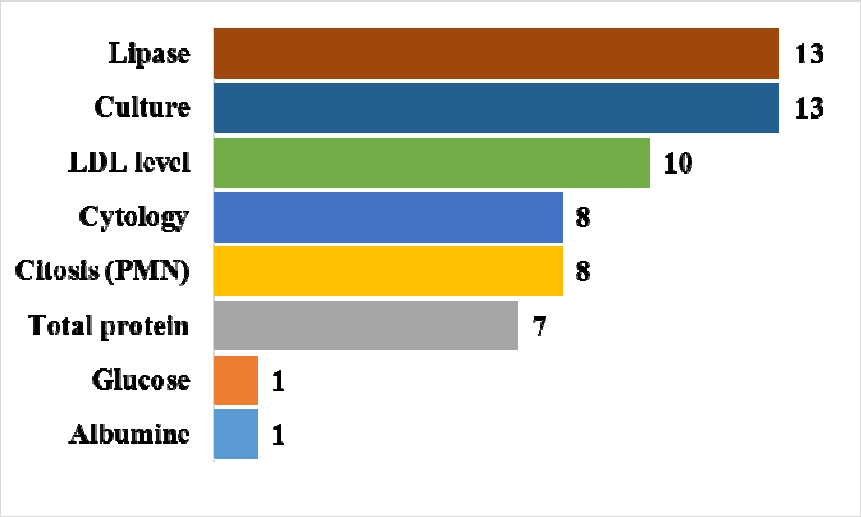

Figure 1. **Tests performed on peritoneal fluid (N=19)**

The most common applied antibacterial therapy regimen was combination of metronidazole and ciprofloxacin (N=13; 46.4%), followed by ceftriaxone (N=7; 25%) and ciprofloxacin as monotherapy (N=5; 17.9%). Duration of antibacterial therapy was 6,5±4 days.

The estimated incidence of SBP in Clinical Center Gailezers over the period of 2011-2016 is shown in tab. 3.

Table 3. **Incidence of SBP among RECUH Gailezers decompensated liver cirrhosis patients in 2011.-2016.**

Year	Incidence per year; %	SPB cases/DLC cases; N
2011	3.6%	5/139
2012	1.1%	1/91
2013	5.7%	5/88
2014	7.1%	7/99
2015	7.3%	6/82
2016	8.7%	4/46

Discussion

The aim of our research was to estimate not only SBP incidence in RECUH Gailezers, but also evaluate its' management tactics. Only patients with documented SBP were included into the study, which explains such a small number of patients (N 28). Even though according to literature data (Atrauss 2006; Dever 2015) the incidence of SBP in liver cirrhosis patients is high (till 40%) and it is considered the most common infectious complication of liver cirrhosis, the maximal incidence in our study was only 8,7%. This is consistent with our findings that early paracentesis was performed in only 67,9% of cases, and minimal recommended tests of ascitic fluid (PMN cell count and culture) were performed in only 25% of those.

In majority of cases SBP diagnosis was established by exclusion of secondary causes of peritonitis or other potential sources of infection. There was no strictly determined diagnostic algorithm, and in each patient various test were performed based on clinicians' personal experience and the level of suspicion It is mentioned in the literature that SBP is not a clinical diagnosis and this diagnosis always should be confirmed by paracentesis (Dever 2015). The low rate of performed paracenteses procedures could be related to high incidence of coagulopathy (N=25; 89,3%) in studied population. But, as many authors note, diagnostic paracentesis should be performed even in presence of coagulopathy, as rates of complication are low even in patients with INR as high as 8.7 and platelet count as low as 19 000 (Dever 2015; Anastasios Koulaouzidis 2009). Several patients from our study refused to undergo the procedure however.

Peritoneal fluid culture was positive only in 46.2% (N=6) of cases from all performed cultures (N=13). This number is similar to numbers, mentioned in literature (Dever 2015; Alaniz 2009). The peritoneal fluid for culture in Cinical Center Gilezers was not routinely sampled at patients' bed with direct specimen inoculation into blood bottle cultures; usually the specimen is transferred to laboratory first, which might influence the culture results (Alaniz 2009). The urine reagent strip test is not performed in Clinical Center Gailezers. All these factors could contribute to low incidence of SBP.

The high index of suspicion as well as routinely performed early paracenhtesis would lead to an increase in numbers of SBP diagnoses as well as to reduced mortality from this condition.

The most common applied therapy regimes (ciprofloxacin and metronidazole or ceftriaxone) were not the first line recommended regimes by existing SBP management guidelines (EASL 2010).

Conclusions

1. Incidence of SBP in liver cirrhosis patients was lower than anticipated, but the numbers of established SBP diagnoses tend to increase.
2. Currently, full recommended diagnostic evaluation for SBP is performed in only 25% of patients.
3. The tactics of establishment of SBP diagnosis are not strictly determined and we conclude that a uniform diagnostic algorithm is required.

Acknowledgement

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SILENT SINUS SYNDROME: A CASE REPORT

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Abstract
***Key words**: Silent sinus syndrome, enophthalmos, hypoglobus, maxillary sinus*
Introduction: Silent sinus syndrome is a rare condition, characterized by spontaneous enophthalmos, hypoglobus in association with obstruction of the ostiomeatal complex (OMC) in absence of any signs of sinonasal disease. Negative pressure due to obstruction of OMC is assumed to cause a gradual collapse of maxillary sinus (MS), resulting in contraction of MS and deformity of orbital wall. Computed tomography (CT) is optimal imaging modality. The definitive treatment is surgical.
Case description: A 25-year-old male presented at the Ophthalmology Emergency room with complaints of light discomfort, small subcutaneous hematoma under the left eye and sudden "fall in" of the left globe. Complaints occurred suddenly at the waking up. Vision with best correction was 1.0, intraocular pressure was within normal limits. Light conjunctival irritation and full-blooded vessels were found in the lower vault of conjunctiva. Lower eyelid fold was vastly deeper than in the other eye. CT was performed and deformity of left MS with pathological content and bone defect in the upper-medial and posterior MS wall was found. Patient rejected further evaluation and treatment.
Conclusions: Due to unconcerned attention to personal health condition patient did not proceed evaluation nor did receive treatment. It is predictable, that patient will seek medical care repeatedly if life quality deteriorating complaints join.

Kopsavilkums
***Atslēgvārdi**: Klusā blakusdobuma sindroms, enoftalms, hipoglobuss, augšžokļa dobums*
Ievads: Klusā blakusdobuma sindroms ir rets stāvoklis, ko raksturo spontāna acābola dislokācija uz mugurpusi un uz leju, kas saistīta ar ostiomeatālā kompleksa obstrukciju bez pazīmēm, kas liecinātu par sinonazālu slimību. Ostiomeatālā kompleksa obstrukcija rada negatīvu spiedienu, kas izraisa pakāpenisku augšžokļa dobuma sabrukumu un orbītas sienas deformāciju. Optimāla diagnostikas metode ir datortomogrāfija. Izvēles metode klusā blakusdobuma sindroma ārstēšanā ir ķirurģiska terapija.
Gadījuma apraksts: 25 gadus vecs vīrietis vērsās Oftalmoloģijas traumpunktā ar sūdzībām par vieglu diskomfortu kreisā acī, nelielu zemādas hematomu zem kreisās acs un acābola dislokāciju. Sūdzības radušās pamostoties no rīta. Izmeklējot pacientu, redzes asums ar korekciju 1.0, intraokulārais spiediens normas robežās. Kreisās acs konjunktīva viegli kairināta, pilnasinīgi asinsvadi konjunktīvas apakšējā velvē. Kreisās puses apakšējā plaksta kroka dziļāka nekā otrā pusē. Datortomogrāfijā vizualizē patoloģisku kreisā augšžokļa dobuma saturu un kaula defektus augšējā mediālā un mugurējā sienā. Pacients atteicās no tālākas izmeklēšanas un terapijas.
Secinājumi: Nekritiskas subjektīvās attieksmes dēļ pacients atteicās no turpmākas izmeklēšanas un terapijas. Paredzams, ka pacients varētu atkārtoti vērsties pēc medicīniskās palīdzības, ja pievienosies dzīves kvalitāti traucējošas sūdzības.

Introduction

Silent sinus syndrome is a rare condition, which is characterized by spontaneous enophthalmos or posterior displacement of the eyeball within the orbit and hypoglobus – downward displacement of the eyeball, that results in facial asymmetry (Lal, Stankiewicz 2015). Silent sinus syndrome is associated with obstruction of the ostiomeatal complex in the absence of any signs or symptoms of inflammatory sinonasal disease (Gomez *et al*. 2014). Ostiomeatal complex is a functional unit which represents pathway for ventilation and drainage of maxillary sinus, frontal

sinus and ethmoidal air cells (Standring 2016). Specific anatomic boundaries of ostiomeatal complex are not defined, but it refers to structures placed between medial orbital wall and middle turbinate – ostia of maxillary sinus, frontal sinus and anterior ethmoidal cells, uncinate process, semilunar hiatus and ethmoid infundibulum (Som *et al*. 2011).

Negative pressure within maxillary sinus due to obstruction of ostiomeatal complex is assumed to cause a gradual collapse of the maxillary sinus, resulting in contraction of maxillary sinus, deformity of orbital wall and increased orbital volume (Gomez *et al*. 2014).

Maxillary sinuses are pyramid-shaped paranasal sinuses, which are located within maxillary bones. The roof of the maxillary sinus is also orbital floor (Drake *et al*. 2015), The air from maxillary sinus is resorbed in the presence of obstruction of ostiomeatal complex. That results in formation of negative pressure within the maxillary sinus, which incites deformation of maxillary sinus by curving inwards of maxillary walls (Cobb *et al*. 2011). Since upper maxillary wall is shared with orbit, deformation of it and contraction of maxillary sinus is followed by increase in orbital volume. Given that, coherent displacement of eyeball ensues. Because of periorbital swelling after collapse of maxillary sinus wall, enopthalmos and hypoglobus may not appear promptly. The degree of enopthalmos correlates with orbital volume ratio (Choi, Kang, Gu 2016).

Possibly, the first case of maxillary sinus opacification and atelectasis was reported by Montgomery in 1964. As a syndrome, Silent sinus syndrome was firstly described in 1994 by Soparkar *et al*., when clinical and pathological features of Silent sinus syndrome were characterized (Ferro *et al.* 2016).

Computed tomography is optimal imaging modality when Silent sinus syndrome is suspected. Computed tomography reveals hypoplastic opacified maxillary sinus with internally retracted antral walls. Also, caudal displacement of orbit contents is found due to depression of orbital floor (Gomez *et al*. 2014).

The treatment of Silent sinus syndrome requires multidisciplinary approach. Definitive treatment for Silent sinus syndrome is always surgical. The first objective of surgical treatment is to provide appropriate aeration of maxillary sinus by establishing a drainage route. Ventilation is restored by removal of obstruction and enlarging the antral ostia. When the drainage route is created, no subsequent volume loss ensues (Cardesin *et al*. 2013). The second objective is to renew the structure of orbit, to restore position of the globe. There are reports of re-expansion of orbital floor with some improvement of malposition of globe in patients who had undergone endoscopic sinus surgery alone, but improvement seldom corresponds to state before the disease (Korn 2017).

Case presentation

A 25-year-old Caucasian male, with no known allergies or significant respiratory medical history, presented at the Ophthalmology Emergency room with complaints of light discomfort,

small subcutaneous hematoma under the left eye, sudden “fall in” of the left eyeball and feeling of slight vision blurring in the left eye. Complaints occurred suddenly at the waking up and lasted for two days until patient sought medical advice. There was neither improvement nor worsening of the complaints in those two days.

Patient had myopia in both eyes and astigmatism in the left eye. Vision in the right eye was 0.3 without correction and 1.0 corrected with 1.25 diopters of myopia. Vision in the left eye was 0.3 without correction and 1.0, corrected with 1.0 diopters of myopia and with 1.0 diopters of astigmatism at an angle of 175 degrees. Vision acuity was tested using the LogMAR chart.

Intraocular pressure was within normal limits. Intraocular pressure in the right eye was 12.3 mmHg and 11.7 mmHg in the left eye. Intraocular pressure was detected using rebound tonometry (Icare device).

On physical examination eye gaps were symmetric. Left lower eyelid fold was vastly deeper than in the right eye (fig. 1). Left eye was 18 prism diopters (Pd) exotropic. Right pupil light reflex was central, but left pupil light reflex was located by the inner pupil margin.

Eye movements were normal and unpainful in all positions of the gaze. The left upper eyelid was slightly restricted in the downgaze (fig. 2).

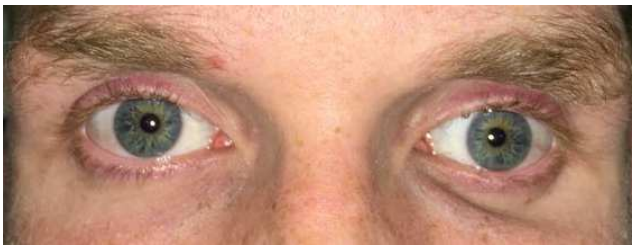

Figure 1. **Deeper left lower eyelid fold (Evita Leikarte’s personal archive)**

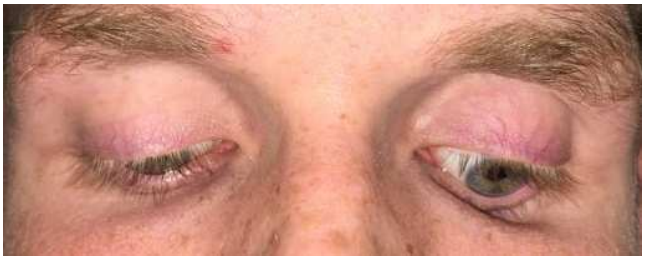

Figure 2. **Restriction of the left upper eyelid in the downgaze (Evita Leikarte’s personal archive)**

The ability of convergence was normal. Pupils were round and symmetric, reaction to light was normal. Color vision was normal in both eyes. Color vision was tested using the Ishihara color plates.

Biomicroscopic examination was performed in both eyes. Light conjunctival irritation and full-blooded vessels were found in the lower vault of conjunctiva in the left eye. There were not any signs of irritation in the right eye. Corneas both, in the right eye and in the left eye, were smooth and glossy. The depth of anterior chambers was symmetrical and normal in both eyes. Contents of anterior chambers were clear in both eyes. There were no pathological changes found in irises. Lenses were transparent, with no opacities.

Pupils were dilated with Tropicamidum 5 mg/ml (Mydriacil 5 mg/ml) eye drops to evaluate the *corpus vitreum* and *fundus oculi*. There were no pathological changes in *corpus vitreum* found after dilatation of pupils. In *fundus oculi* examination, optic nerve heads were yellow-orange, with clear margins. Cup-to-disc ratio was symmetric in both eyes and about 0.3. Neuroretinal rim was marked in all quadrants of the optic nerve head, having its thickest portion inferiorly, then superiorly, then nasally, with the thinnest portion being temporally. There were no pathological changes in macula or periphery of retina. Blood vessels were usually filled and with usual caliber, course and convolution.

Computed tomography was performed to assess orbit and paranasal sinuses. Deformation of the left maxillary sinus with bone defects in the upper-medial and posterior antral walls was found (fig. 3). Computed tomography also demonstrated pathologic content with air inclusions within the left maxillary sinus, either blood or pus (fig. 4). Coronal scan showed increased orbital volume on the left side (fig. 5). Mucosal thickening of the left frontal sinus and left sphenoidal sinus and content in ethmoidal air cells were also found as well as hyperplastic mucosa in the right maxillary sinus.

Both eye globes were symmetric with preserved contours. Trapped air was found in peribulbar space of the left eye.

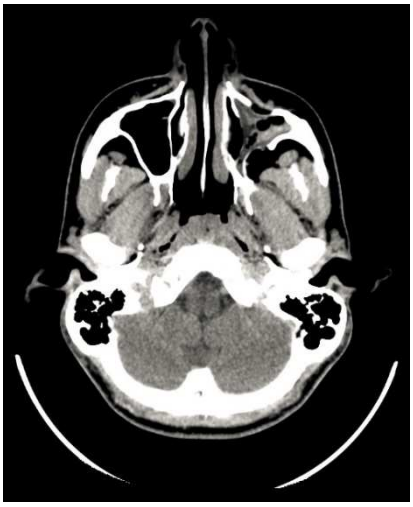

Figure 3. **Deformation of left maxillary sinus walls (Archive of Department of Diagnostic Radiology, Clinical Centre "Bikernieki", Riga East Clinical University Hospital)**

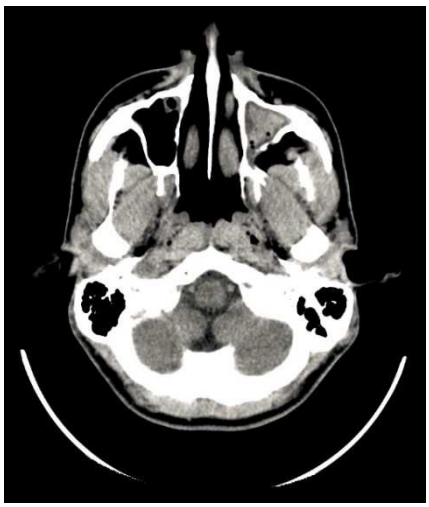

Figure 4. **Pathologic content within left maxillary sinus (Archive of Department of Diagnostic Radiology, Clinical Centre "Bikernieki", Riga East Clinical University Hospital)**

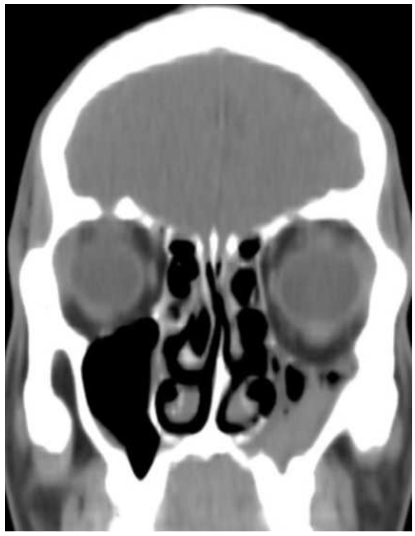

Figure 5. **Increase in left orbital volume (Archive of Department of Diagnostic Radiology, Clinical Centre "Bikernieki", Riga East Clinical University Hospital)**

Discussion

The prevalence of Silent sinus syndrome is unknown, therefor it is difficult to evaluate the role of gender and age. In most reports occurrence of the Silent sinus syndrome is described in adult patients. However, some cases of children patients have also been reported (Chang, Truong 2014). In case series reported by Babar-Craig *et al.* (2011) patients age ranged from 14 to 79 years with the average age of 40.6 years. Case series of patients age ranging from 11 to 70 years with the average age of 43.1 years have been reported by Wise *et al.* (2007). The youngest patient of the Silent sinus syndrome described in literature is 7 years old (Chang, Truong 2014).

Pathophysiology for chronic maxillary atelectasis due to symptomatic sinonasal disease and Silent sinus syndrome is shared. Nevertheless, when patients present with symptomatic rhinosinusitis, contraction of maxillary sinus is usually diagnosed timely due to complaints of

congestion, sinus headache or facial pain. Asymptomatic patients are usually related to the Silent sinus syndrome (Gomez *et al*. 2014).

Enopthalmos and hypoglobus are not pathognomic signs of the Silent sinus syndrome. The diagnosis is based on clinical suspicion and is affirmed by means of radiological imaging – coronal and axial computed tomography scans of paranasal sinuses and orbit. Other possible explanations such as chronic rhinosinusitis, facial trauma, previous sinonasal surgery should be ruled out to confirm the diagnosis of the Silent sinus syndrome (Hira *et al*. 2004).

To treat the obstruction of the ostiomeatal complex and restore ventilation of the sinus, functional endoscopic sinus surgery is performed but opinions for management of the enopthalmos differ (Sesenna *et al*. 2010). There are some reports of spontaneous retraction of orbital floor and natural resolution of enopthalmos after functional endoscopic sinus surgery (Vander Meer *et al*. 2001).

To elucidate endoscopic sinus surgery effect on the postoperative size of affected sinus, Chang and Truong (2014) measured and analyzed height and width of maxillary sinuses. Before surgery height and width of the affected sinus was 61% and 48% of corresponding sizes of the normal sinus. After maxillary antrostomy the height and width of the hypoplastic maxillary sinus increased to 77% and 58% respectively (Chang, Truong 2014). However, most reports suggest that both, sinus surgery and orbital reconstruction, are necessary. The reconstruction of orbital floor may be performed as a single-stage operation, as well as double-stage operation, where reconstruction of orbital floor follows sinus surgery after two months (Sesenna *et al.* 2010).

Uncinectomy may be performed in diverse ways. Maxillary sinus ostium seeker is introduced just behind the uncinate process, to relocate the free edge anteriorly and outwardly bewaring of injury of lamina papyracea. Then the uncinate process is removed in push-pull fashion. After removal of the uncinate process, natural maxillary ostium is identified and subsequently enlarged to complete maxillary antrostomy (Lal *et al.* 2015).

Treatment of eye globe displacement is achieved by replenishing orbit with implants likewise management of fractures of orbital wall. Surgical correction of orbital floor deformity may be performed with multiform biomaterials (Sesenna *et al.* 2010). Implants including autologous bone, porous polyethylene, hydroxyapatite, and titanium mesh are available (Hung *et al.* 2017). A lateral canthotomy and inferior cantholysis promotes broad exposure of the orbital wall when combined with the transconjunctival incision. Lateral canthotomy and inferior cantholysis may not be necessary for patients with laxity of the lower eyelid. The dissection is continued in a preseptal plane to expose the arcus marginalis. Further inferior oblique muscle is disinserted, and after elevation of the periosteum, orbital floor is assessed and implant is placed in the subperiosteal

plane. Reinsertion of inferior oblique muscle follows, conjunctiva and lateral canthal closure is performed (Korn *et al*. 2017).

Conclusion

In this article, clinical and radiological findings of the Silent sinus syndrome have been reviewed. Silent sinus syndrome is a rare condition, which is characterized by spontaneous enophthalmos and hypoglobus, and resultant facial asymmetry. In most cases patients present at Ophthalmology departments, because of facial (ocular) asymmetry and with no symptoms corresponding sinonasal disease, as it was described in this clinical case. In some cases, patients can also seek medical advice at Otorhinolaryngology department. Silent sinus syndrome should be differentiated from chronic rhinosinusitis, also previous surgery or facial trauma should be ruled out. Diagnosis of this condition is based on clinical suspicion, but confirmation with computed tomography imaging is indispensable. The definitive treatment for Silent sinus syndrome is surgical.

Unfortunately, due to unconcerned attention to personal health condition aforementioned patient did not proceed evaluation nor did receive treatment. It is predictable, that patient will seek medical help repeatedly, when the symptoms will worsen or complications, for example diplopia, will join.

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VITALITY OF THE RECENTLY IMPLEMENTED METHOD IN CHILDREN'S CLINICAL UNIVERSITY HOSPITAL: EVALUATION OF MAGNETIC RESONANCE UROGRAPHY DATA

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Abstract
Key words: *Magnetic Resonance Urography, CHOP-fMRU, Congenital Anomalies of the Kidneys and Urinary tract*
Introduction: Congenital anomalies of kidney and urinary tract (CAKUT) accounts for up to 40% of pediatric end stage renal disease. Functional magnetic resonance imaging (MRU) is one of the precise method detecting CAKUT.
Aim: To assess Inter-rater Reliability (IRR) between two evaluators in newly implemented kidney function software CHOP-fMRU in Children's Clinical University Hospital, and detect kidney morphological abnormalities.
Materials and Methods: 29 paediatric patients with hydronephrosis (HN) who underwent MRU were included. Patient age, gender, renal pelvis diameter (RPD), parenchymal thickness (PT), diameter of ureters (DU), grade of HN were recorded. Measurments of renal and calyceal transit time and differential renal function were performed by two evaluators using CHOP-fMRU. IRR was assessed using Interclass Correlation Coefficient (ICC).
Results: Grades of HN were assessed as I, III and IV grades, being 3.4%, 51.7%, 44.8%, respectively. Bilateral, unilateral right and left kidney pathology detected in 17.2%, 24.1%, 58.6%, respectively. Morphological diagnoses detected: UPJ and UVJ obstruction, duplex collecting system, kidney rotation anomalies, horseshoe kidney, cystic anomalies. The mean RPD was 2.19 cm; mean dilatated DU=1.54 cm; mean PH=0.42 cm. ICC results were detect close to value 1 in all measurements (0,67-0,97), $p < 0,05$.
Conclusions: MRU provides high quality morphological and functional assessment in paediatric uroradiology without ionizing radiation. CHOP-fMRU measurements can be safely performed by evaluators with various experiences in radiology.

Kopsavilkums
Atslēgas vārdi: *Magnētiskās rezonanses urogrāfija, CHOP-fMRU, Iedzimtas nieru un urīnceļu patoloģijas*
Ievads: 40% termināla nieru mazspējas izmesls bērniem ir iedzimtas nieru un urīnceļu patoloģijas. Funkcionālā magnētiskās rezonanses urogrāfija (MRU) ir viena no precīzākajām metodēm šo patoloģiju diagnosticēšanā.
Mērķis: Bērnu Klīniskās Universitātes slimnīcā jaunieviestas metodes CHOP-fMRU noteikt starpvērtētāju ticamību (*IRR*) divu vērtētāju mērījumiem, noteikt morfoloģiskās patoloģijas.
Materiāli un metodes: Pētījumā iekļauti 29 pacienti ar hidronefrozi (HN), kuriem veikts MRU izmeklējums. Noteikti pacientu demogrāfiskie dati, nieres bļodiņas AP izmērs, parenhīmas biezums (PB), urīnvadu diametrs (UD), hidronefrozes pakāpe. Divi vērtētāji noteica nieru un kaliču caurplūdes laiku, nieru diferenciālās funkcijas mērījumus, pielietojot CHOP-fMRU programmatūru. IRR tika noteikts, pielietojot starpklašu korelācijas koeficientu (*ICC*).
Rezultāti: Noteiktas I, III, IV pakāpes HN, attiecīgi 17.2%, 24.1%, 58.6%. Morfoloģiskās diagnozes: UPS obstrukcija, UVS obstrukcija, dubultniere, nieru rotācijas anomālijas, pakavveida niere, nieru cistiskas patoloģijas. Vidējais AP izmērs – 2,19 cm, vid. dilatēta UD – 1,54 cm, vid. PB – 0,42 cm. ICC rezultāti pietuvojas vērtībai 1 (0,67-0,97), $p<0,05$.
Secinājumi: MRU nodrošina precīzu nieru morfoloģisko patoloģiju un nieru funkcionālo spēju izvērtēšanu izvairoties no jonizējošā starojuma. CHOP-fMRU metode var tikt droši pielietota vērtētājiem ar dažādu pieredzi radioloģijā.

Introduction

Congenital anomalies of kidney and urinary tract (CAKUT) is a group of structural malformations that result from defects in their morphogenesis. CAKUT include pelviureteric junction obstruction (PUJO), ureterovesical junction obstruction (UVJO), multicystic dysplastic kidneys, single kidneys, vesicoureteric reflux and duplex systems (Mantan 2013). These anomalies cause obstructive uropathy which is blockage of urine drainage from the kidney, ureter, or bladder, localising in any level of urinary tract. The appearance of dilated or enlarged renal pelvis and

calyces is called hydronephrosis (HN), which is a symptom of obstructive uropathy (Mujoomdar 2017). As a result of the blockage, urine backs up into the kidneys, causing dilatation of the ureter, renal pelvis, and renal calyces, that can damage the kidney if not diagnosed and treated properly. CAKUT contributes to chronic kidney disease in approximately 45 – 60 % of pediatric patients, which is irreversible kidney damage that can further progress to end-stage renal disease (Mantan 2013). There is also a higher risk developing chronic and recurrent urinary tract infection (Masnata 2015).

CAKUT is also one of the main reasons of end-stage renal disease (ESRD), accounting for up to 40% of all end-stage renal disease cases in children (Masnata 2015). ESRD is a devastating disorder associated with need for renal dialysis and renal replacement therapy and predispose an individual to hypertension, impaired growth and cardiovascular disease, increasing excessive mortality and cardiovascular morbidity (Harambat 2011).

Detection of HN and kidney abnormalities requires appropriate and reliable imaging method. Nowadays there are many methods for detecting kidney and urinary tract pathologies, for example, ultrasound, renal scintigraphy, voiding cystourethrography and intravenous urography, but everyone of these methods have some limitations. Ultrasound is an operator-dependant method, with sometimes difficult visualization of the end-ureter and method cannot visualize non-dilated ureter. Intravenous urography (IVU) predispose patient to the risk of contrast medium nephropathy and there is ionizing radiation used in IVU. Renal scintigraphy provides kidney functional analysis but presents with poor anatomical resolution, invasiveness and requires radiation exposure. Voiding cystourethrography is invasive and can be only helpful in vesicoeretherl reflux detecting (Hadjidekov 2011; Darge 2010).

Magnetic resonance urography is a highly advanced imaging modality of the urinary tract in children, providing detailed visualization of varous morphologic abnormalities that are difficult to identify or fully evaluate by other imaging modalities, in addition it is non-ionizing and non-invasive method (Jones 2011). MRU is also worthwhile method for early diagnosis of kidney and urinary tract pathologies, evaluation of renal tumors, as well as for operative planning and postoperative assessment (Dickerson 2015). In addition to the morphological imaging, MRU can be used to quantify the renal function, using postcontrast MR urography sequences and appropriate software, for example, CHOP-fMRU *(Children's Hospital of Philadelphia functional MR urography).*

CHOP-fMRU is a software, developed in pediatric radiology department in Children's Hospital of Philadelphia by authors Dmitry Khrichenko and Kassa Darge, first time presented at the Annual Meeting of the Society of Pediatric Radiology (SPR), 2009 (Khrichenko 2009). CHOP-fMRU offers estimation of different kidney quantitative parameters, such as renal and calyceal

transit times (RTT, CTT), differential renal function based on two methods - based on the amount (volume) of enhancing renal parenchyma bilaterally (vDRF) and based on glomerular filtration of contrast material from the blood (Patlak method, pDRF). Quantitative parameters are useful in clinical work, particullary in pediatric urology, e.g. renal transit time shows potential acute kidney injury if the calyceal transit time is delayed asymmetrically. Renal transit time shows if there is urinary tract system obstruction, e.g. system is obstructed and decompensated if the RTT is > 490 seconds, there is compensated system obstruction if the RTT is between 245 – 490 s, if the transit time is less than ***245*** s, the ***system*** is considered nonobstructed. Assessed differential renal function is the most basic and important functional ability of MR urography, showing split renal function based on the generated Patlak numbers (a potential indicator of the glomerular filtration rate (GFR)) (Dickerson 2015).

CHOP-fMRU requires manual segmentation of aorta and parenchyma of both kidneys (detecting pDRF and vDRF), as well as manual locating of slice when contrast is first clearly visible in the collecting system (detecting CTT) and locating of slice when contrast is first clearly visible in the ureter below the kidney (detecting RTT). Despite some manual procedures, method is characterized as user-friendly, fast method, which is easily operated by the average radiologist or MR technician at the same time providing comprehensive automated functional analysis (Khrichenko 2009).

Functional MR urography (fMRU) provides comprehensive functional data that can be subject to variability. To interpret the results of newly implemented method CHOP-fMRU in clinical work, it is crucial to know inter-rater variability of the quantitative kidney functional parameters.

Aim of the study

To assess inter-rater reliability (IRR) between two evaluators in newly implemented kidney function software CHOP-fMRU in Children's Clinical University Hospital, and detect kidney morphological abnormalities.

Materials and methods

In this retrospective study 29 patients with previous diagnosed hydronephrosis who underwent magnetic resonance urography (MRU) June 2016 – January 2017 were included. Inclusion criteria were patient who had MRU examination done and postcontrast T1-W sequence was appropriate for CHOP-fMRU analysis. We excluded patients after nephrectomy, patients with non-assessable function in CHOP-fMRU due to kidney trauma, inappropriate T1-W sequence and those whom contrast medium was not detected even in delayed postcontrast images.

MR urography images were obtained using a combination of two basic approaches - MR hydrography and postcontrast MR urography. MRU exams were performed by 1.5T MRI system.

MR hydrography included imaging using different T2-weighted pulse sequences, e.g. coronal and sagittal fast spin echo (FSE), axial and coronal high-resolution T2-W fat-saturated, two-dimensional (2D) FSE, and three-dimensional (3D) FSE sequences. MR urography images used to create 3D reconstructions, including MIP (Maximum Intensity Projections) and volume rendered images. Postcontrast MR was performed after the administration of intravenous gadolinium-based contrast material and coronal postcontrast dynamic T1-W fat-saturated and delayed T1-W fat-saturated axial sequence with MIP reconstructions were accomplished.

Clinical case with renal dystopia on coronal T2-W image (Figure A) and clinical case with megaureter on coronal T2-W image (Figure B) are shown in **picture 1**. Maximum-intensity projection image is shown on picture 2, C figure, duplex system of the left kidney on T2-W image is shown on **picture 2**, D figure.

Patient preparation before examination included:

– Intravenous hydration using Ringer's solution as stated in the following formula: 4 ml/kg/hr for the first 10 kg of patient's weight; 2 ml/kg/hr for the next 10 kg of patient's weight; 4 ml/kg/hr for each kg above 20 kg patient's weight. If the child is not to be sedated, hydration was peformed at a dose of 10 ml/kg
– Furosemide treatment (0.5–1 mg/kg, up to 20 mg; administered before or during MR urography)
– Insertion of a Foley catheter is in the urinary bladder
– Sedation or general anesthesia (all children under 7 years).

After MR urography has been performed, intravenous gadolinium-based contrast medium (*Omniscan),* was used of a standard dose of 0.1 mmol/kg with a power injector at a speed setting no greater than 0.25 ml/s.

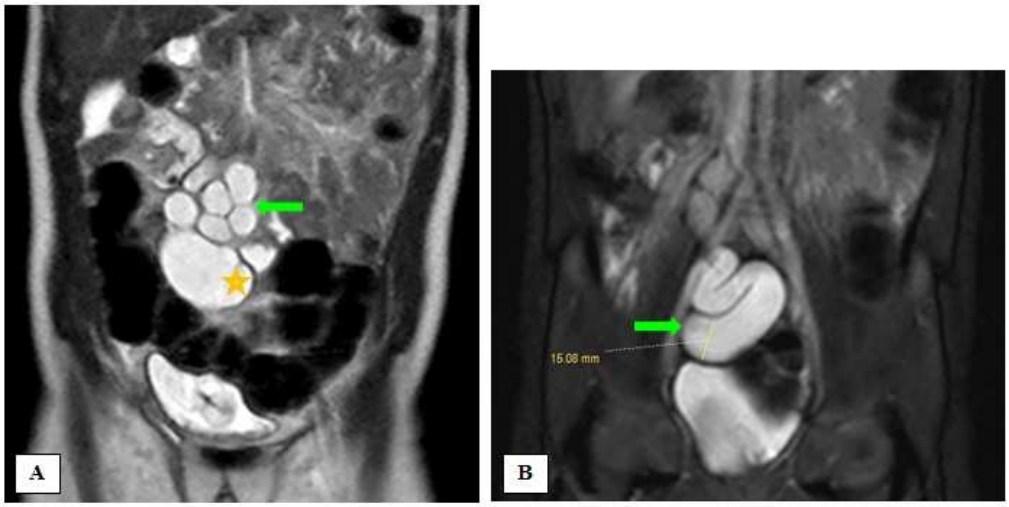


Figure A. Renal dystopia on coronal T2-W image Figure B. Megaureter on coronal T2-W image

Picture 1. **Figures A and B**

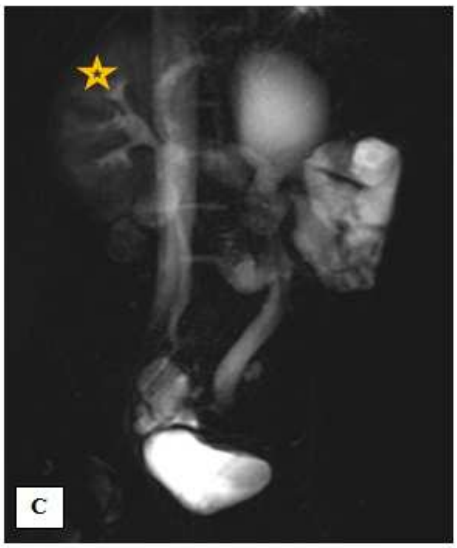


Figure C. Healthy right kidney, coronal volume MIP image

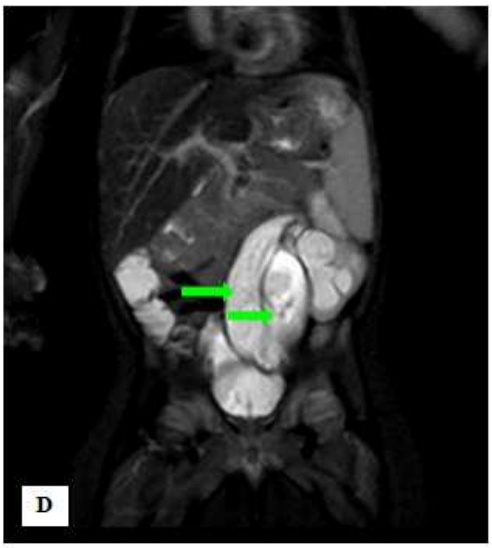


Figure D. Duplex system of the left kidney on coronal T2-W image

Picture 2. **Figures C and D**

Functional analysis with CHOP-fMRU software was performed. Quantitative parameters as Calyceal Transit Time (CTT), Renal Transit Time (RTT), Volumetric Differential Renal Function (vDRF) and Patlak Differential Renal Function (pDRF) were measured by two evaluators - a board certified radiologist and the 6th year medicine student using CHOP-fMRU software.

Inter-Rater Reliabilty (IRR) for CTT, RTT, pDRF and vDRF was assessed using Interclass Correlation Coefficient (ICC) with CI of 95%, p value < 0.05 was considered statistically significant. ICC values were evaluated by commonly-cited cutoffs for qualitative ratings of IRR agreement with IRR being poor for ICC values less than 0.40, fair for values between 0.40 and 0.59, good for values between 0.60 and 0.74, and excellent for values between 0.75 and 1.0 (Hallgren, 2012).

Demographical patient data (age, gender) were assessed, as well as morphological parameters of kideny and urinary tract - anteroposterior renal pelvis diameter (RPD), parenchymal thickness (PT), diameter of ureters (DU), grade of hydronephrosis were recorded.

Grade of hydronephrosis (HN) was assessed using Society for Fetal Urology (SFU) classification, where in grade 0 there is no dilatation of the renal pelvis or calyces. In grade 1 (mild HN), dilatation of the renal pelvis is seen without dilatation of the calyces and there is no parenchymal atrophy seen in the image. In grade 2 (mild HN) dilatation of the renal pelvis (mild) and calyces (pelvicalyceal pattern is retained) is seen with no parenchymal atrophy. In grade 3 (moderate HN), moderate dilatation of the renal pelvis and calyces, also blunting of fornices and flattening of papillae and mild cortical thinning is seen. In grade 4 (severe HN), gross dilatation of the renal pelvis and calyces, which appear ballooned, loss of borders between the renal pelvis and calyces, as well as renal atrophy is seen as cortical thinning (Keays 2008).

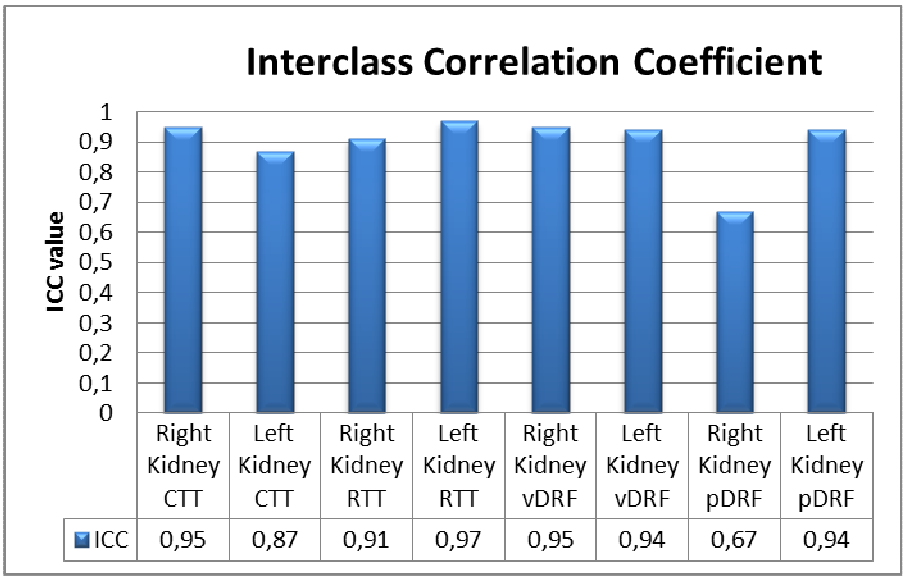
Results

The study included twenty boys and nine girls with median age of 1 year 1 month (range 25 days –17 years). Among all the patients, I, III and IV grade of hydronephrosis were assessed, being 3.4%, 51.7%, 44.8%, respectively. Grade II of hydronephrosis was not detected. Bilateral HN detected in 17.2%, unilateral on the right and unilateral on the left side – 24.1%, 58.6%, respectively. There were different morphological diagnoses detected in this study: ureteropelvic junction obstruction (8 cases), ureterovesical junction obstruction (1), duplex collecting system (4), kidney rotation anomalies (2), horseshoe kidney (4), cystic anomalies (2).

Analyzing structural parameters of kidney and urinary tract, renal pelvis anterior-posterior diameter was measured in 35 segments, being dilated (mean RPD = 2.19 cm) in 33 (94.3 %) segments. In two segments (5.7 %) RPD was defined as “retained RPD”, being in diameter < 1 cm. Thirty-six segments of ureters were analyzed, in 16 segments (44.4 %) there were dilatation of ureters found with mean DU of 1.54 cm; in 20 segments (55.6 %) there was no dilatation of ureters with mean diameter < 0.5 cm. Parenchymal thickness was measured in 36 segments, 31 (86.1 %) segment was thickened (mean size of PT was 0.42 cm), 5 segments (13.9 %) were defined ar „retained PT”, being 0.7 – 1 cm thick.

Summarising two evaluators’ results of functional analysis quantitative parameters, results showed great Inter-rater Reliability (IRR) for all measured parameters - CTT, RTT, pDRF and vDRF with good and excellent values of ICC (0.67 – 0.97) with high 95% CI, shown in Table 1.

Table 1. **IRR showing great agreement being „good” and „excellent” based on ICC values (0.67–0.97)**



Discussion

Functional magnetic resonance urography is a valuable imaging modality for assessing disorders of the pediatric urinary tract, including evaluation of the kidney functional parameters, using CHOP-fMRU. As the method is based on manual segmentation and localizing slices for CTT and RTT detection - obtained data can be subjected to variability. In this study, as the method is newly implemented, a board certified radiologist (the only specialist of this method in clinic) trained the 6th year medicine student in performing measurements in CHOP-fMRU software that could partly make an impact on high ICC values (close to value 1) and could explain great inter-rater reliability agreement.

Due to above-mentioned facts, it would be important to organize practical classes together with board specialized radiologists who have experience using this method.

There are many grading systems for classification of hydronephrosis nowadays, e.g. Society for Fetal Urology (SFU), Urinary Tract Dilatation (UTD) classification and others. Grading hydronephrosis is requisite for further therapy evaluation and management of the disease (surgery planning, need for another examination). SFU classification, which was used in this study, is based on two parameters: urinary tract dilatation and parenchymal thickness. Many authors claim SFU classification due to only 2 parametrs but it is still the most popular postnatal classification used for HN grading; there are some limitations of this classification: it is difficult to distinguish between segmental and diffuse parenchymal thinning (e.g. upper pole parenchyma is retained, lower pole parenchyma is thinner), also the difference between grade III and grade IV HN is not evident. Urinary Tract Dilatation classification is based on six parameters: APD of the renal pelvis, urinary tract dilatation, parenchymal thickness, parenchymal appearance, ureteral status and bladder status; in addition it is said that the UTD classification is valid in predicting surgical intervention, and dilatated ureter as a risk factor provides a preference to SFU classification (Hodhod 2015). As there are some limitations of SFU classification, UTD classification could be potentially preferable.

Conclusions

MRU provides detailed information according to kidney and urinary tract morphologic pathologies, it is non-ionizing method which is one of the most significant advantages in pediatric urology. CHOP-fMRU method provides with accurately kidney functional quantitative parameters which are useful in treatment planning. Functional magnetic resonance can offer comprehensive evaluation information in one examination, that would otherwise require multiple other imaging tests.

As grade III and grade IV hydronephrosis were the most common grades, there is obvious necessity for early evaluation of these pathologies thus preventing complications of CAKUT such

as chronic kidney disease and end-stage renal disease. Society for Fetal Urology could be not the most preferable tool for grading of hydronephrosis.

All assessed Interclass Correlation Coefficient results were close to value of 1, showing great inter-rater realibility (IRR) and conclusion can be made that CHOP-fMRU software can be safely performed by evaluators with various experience in radiology.

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COAGULATION TESTS AND THEIR CORRELATION WITH POST-OPERATIVE BLEEDING THAT REQUIRES A REOPERATION IN CARDIAC SURGERY

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Abstract

Coagulation tests and their correlation with post-operative bleeding that requires a reoperation in cardiac surgery

Key words: *Cardiac surgery, cardiopulmonary bypass, reoperation, INR, activated partial thromboplastin time, prothrombin index*

Introduction: Bleeding is a common cause for early reoperation in cardiac surgery with cardiopulmonary bypass (CPB). Increased postoperative bleeding is associated with more complications and higher morbidity.

Aims: The aim of the study was to retrospectively analyse patient histories and identify if there was a correlation between blood loss intensity in early reoperated patients and platelet count (PLT), activated partial thromboplastin time (APTL), INR, fibrinogen (Fb), prothrombin index (PI), antithrombin III (AT III), activated clotting time (ACT), before or after cardiac surgery with cardiopulmonary bypass.

Materials and methods: The materials used in this work were 46 cardiac surgery patient histories from the medical archives of a Clinical University Hospital. All operations were performed with a sternotomy approach and cardiopulmonary bypass. All patients were reoperated within 24 hours of the primary surgery. The coagulation tests under analysis were platelets, activated partial thromboplastin time, fibrinogen, prothrombin index, INR, antithrombin III, the activated clotting time. The period covered in this study was from January 1st 2015 until December 31st 2016. The study was done retrospectivly. The data was compiled using *Microsoft Excel* and analysed IBM Statistical Package for the Social Sciences® (SPSS) 22nd

Results: From the coagulation tests, correlation was observed in APTT prior to surgery (p=0.05), prothrombin index after surgery (p=0.044) and activated clotting time after surgery (p=0.025).

Conclusions: The coagulation tests that correlated with postoperative blood loss intensity, that is great enough to warrant a reoperation were APTT before and after the first surgery, and postsurgical prothrombin index and activated clotting time after surgery.

Kopsavilkums

Koagulācijas testi un to korelācija ar pēcoperācias asiņošanas intensitāti agrīni reoperētiem sirds ķirurģijas pacientiem

Atslēgas vārdi: *sirds ķirurģija, mākslīgā asinsrite, reoperācija, INR, aktivētais parciālais tromboplastīna laiks, protrombīna indekss.*

Ievads: Asiņošana ir biežs agrīnu reoperāciju cēlonis kardioķirurģijas operācijās, kurās tiek izmantota mākslīgā asinsrite. Pastiprināta pēcoperācijas asiņošana palielina gan komplikāciju skaitu, gan mirstību.

Darba mērķis bija retrospektīvi analizēt agrīni reoperētu pacientu vēstures un izpētīt vai pastāv korelācija starp asins zuduma ātrumu jeb intensitāti (ml/h) un trombocītu skaitu, aktivēto parciālo tromboplastīna laiku, INR, fibrinogēnu, protrombīna indeksu, antitrombīnu III un aktivēto recēšanas laiku pirms un pēc sirds operācijas mākslīgajā asins ritē.

Materiāli un metodes: Materiāli, kas tika izmantoti šajā darbā, bija 46 sirds ķirurģijas pacientu vēstures no klīniskās universitātes slimnīcas arhīva. Visi pētījumā iekļautie pacienti tika operēti ar sternotomijas pieeju un mākslīgo asins riti. Visi pacienti tika reoperēti 24h laikā pēc primārās operācijas. Darbā aplūkotās koagulācijas analīzes bija trombocītu skaits, aktivētais parciālais tromboplastīna laiks, fibrinogēns, protrombīna indekss , INR, antitrombīns III, aktivētais recēšanas laiks. Pētījumā analizētais laika posms bija no 2015. gada 1. janvāra līdz 2016. gada 31. decembrim. Pētijums tika veikts retrospektīvi. Datu apkopošana tika veikta *Microsoft Excel*, bet analīze *IBM Statistical Package for the Social Sciences (SPSS) 22* ®

Rezultāti: No aplūkotajiem koagulācijas testiem korelācija tika novērota aktivētais parciālais tromboplastīna laiks pirms operācijas rezultātā (p=0.05), protrombīna indekss pēc operācijas (p=0.044), kā arī aktivētais recēšanas laiks pēc operācijas (p= 0.025).

Secinājumi: Koagulācijas testi, kas korelē ar pēcoperācijas asiņošanas intensitāti, kas ir pietiekami liela, lai tās ārstēšanai pielietotu reoperāciju bija pirms operācijas aktivētais parciālais tromboplastīna laiks un pēc operācijas protrombīna indekss un aktivētais recēšanas laiks.

Introduction

Most open cardiac surgeries are performed with the help of cardiopulmonary bypass. During the two-year period that is examined in this study there were 2156 such operations in Latvia. That is according to the statistic bureau of the clinical university hospital. The most common reason for early reoperations in cardiac surgery patients is increased postoperative bleeding. According to literature reoperation because of bleeding is necessary for anywhere form 3,1% to 5,9% of patients that undergo open heart surgery with CPB. (Hall 2001, Čanádyová 2012) The most commonly used indications for re-explorative surgery are these three. One bleeding more than 500 ml within the first hour after surgery, more than 400 ml in each of the first two hours, 300 ml per hour the first 3 h or more than 1200 ml within the first 5h. Two if there is suspicion that the cause of the bleeding is surgical. Three a sudden massive bleeding. (Čanádyová 2012)

Increased postoperative bleeding is associated with complications such as increased cost of healthcare, a longer stay in the intensive care unit and a longer over all stay in the hospital. These patients also need more transfusions of blood components like erythrocytes, fresh frozen plasma and thrombocytes and more inotrope medication, for example epinephrine (Hall 2001, Moulton 1996). Mortality is also greater in patients with increased postoperative bleeding, not just because of the re-exploration surgery, but also because of the transfused erythrocytes.

Operations with CPB influence the coagulation system by decreasing thrombocyte functions by up to 50% and decreasing coagulation factors such as factor II, V, IX, X, XII meanwhile increasing fibrinolysis. (Shore-Lesserson 2015) Changes like these can be observer using coagulation tests that are a standard before any type of surgery.

The aim of the study

The aim of the study was to retrospectively analyse patient histories and identify if there was a correlation between blood loss intensity in early re-operated patients and platelet count, activated partial thromboplastin time, INR, fibrinogen, prothrombin index, antithrombin III, activated clotting time, before or after cardiac surgery with cardiopulmonary bypass.

Materials

Materials used in this study were 46 patient histories from the hospital archive. With the help of the statistics bureau all patients that met the study criteria in the time span of two years (2015-2016) were selected.

The inclusion criteria where patients above the age of 18, that were operated using CPB and the operation approach was a sternotomy, all patients were re-operated because of increased bleeding from the draining chest tubes. Exclusion criteria were patients that had a heart tamponade, patients that were re-operated after more than 24h after the primary cardiac surgery and patients whose histories were not available.

The obtained information was patient sex, age, time, length and type of surgery, CPB time, post-surgical blood loss and time until the second surgery. PLT, APTT, Fb, PT, AIII values before and after the first surgery and ACT numbers were assessed before and after CPB. The bleeding intensity or speed was expressed as ml/h and was calculated using the information about operation times and volume of blood lost thru the chest tubes. The time from the end of the primary surgery till the time of the beginning of the redo operation was used in calculations. The anaesthesia time was not included.

Methods

The data was compiled using *Microsoft Excel* and analysed IBM Statistical Package for the Social Sciences® (SPSS) 22nd. All date is represented as the median value ± interquartile range (75%-25%). The nonparametric test *Spearman's rho* was used to asses if there was a correlation between the bleeding intensity and the values of the coagulation tests. Significance level $p>0.05$ (Arhipova 2006)

Results

Patient demographic data. Of 46 patients 32 (70%) were male and 14 (30%) were female. The age of the population 70±13,5 years (Min 43 and Max 83 years). Operation data. 18 patients had heart valve surgery that includes valve replacement or valve plasty. 15 patients had myocardium revascularisation with coronary artery bypass grafting. 13 patients had operations that were either a mix of the first two or an operation that included the ascending aorta. The length of the operations was 3:12 ± 1:22 h and the length of CPB was 97±49 min. Time from the primary surgery until the re-operation was :30±4:42h (MIN 1:10. MAX 18:55 h) The volume of blood lost was 1008±303 ml (Min 250. Max 1930 ml). The calculated bleeding intensity was 152± 106 ml/h (min 51, MAX 1037 ml/h).

Table 1. **Coagulation test results**

Name and unit of measurement	N	Reference interval	Values	MIN/MAX values	Patients, that were within the normal range
PLT before Op 10x9/L*	46	150-410	200±91	13/356	72%
PLT after Op 10x9/L*	32	150-410	132±61	34/214	41%
APTL before Op sec*	44	32-42	34±5	26/71	71%
APTL after Op sec*	25	32-42	35±8	28/89	56%
PI before Op %*	46	80-120	91±24	55/121	67%
PI after Op %*	25	80-120	86±17	86/111	64%
INR before Op*	46	0.8-1,2	1±0.1	0.9/1,3	98%
INR after Op*	25	0.8-1,2	1,1±0.2	1/1,4	96%
Fb before Op g/L*	42	2-4	3,1±0.95	1,2/4,8	79%
Fb after Op g/L*	25	2-4	2,5±0.6	1,6/3,4	100%
AT III before Op%*	30	80-120	104±24	104/133	80%
AT III after Op %*	20	80-120	78±13	59/95	50%
ACT before Op sec*	21	70-180	137±38	94/168	100%
ACT after Op sec *	44	70-180	129±12	100/180	100%

* reference interval (Balode 2008). N- number of values.

The coagulation test that correlated with blood loss ml per hour were before surgery APTT (p=0.037, correlation coefficient 0.416) and postsurgical PI (p=0.044, correlation coefficient -0.406) ACT (p=0.042, correlation coefficient 0.337).

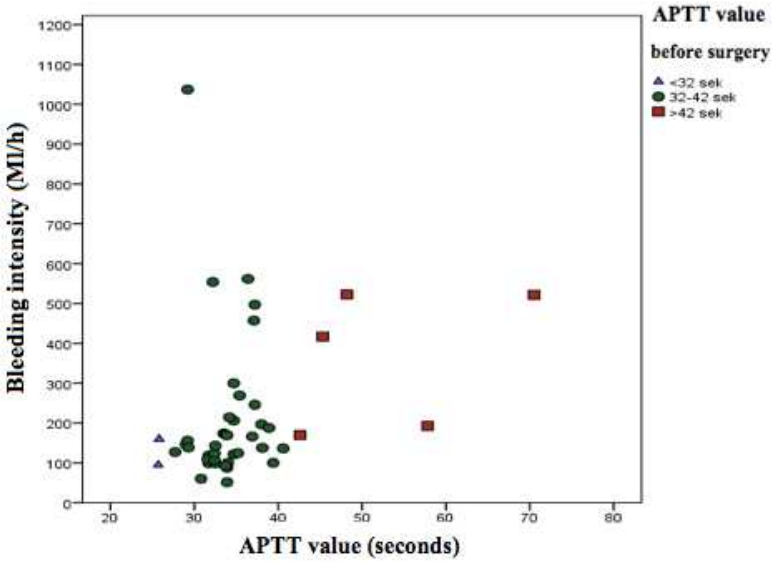

Figure 1. **The correlation between APTT and the postoperative bleeding intensity**

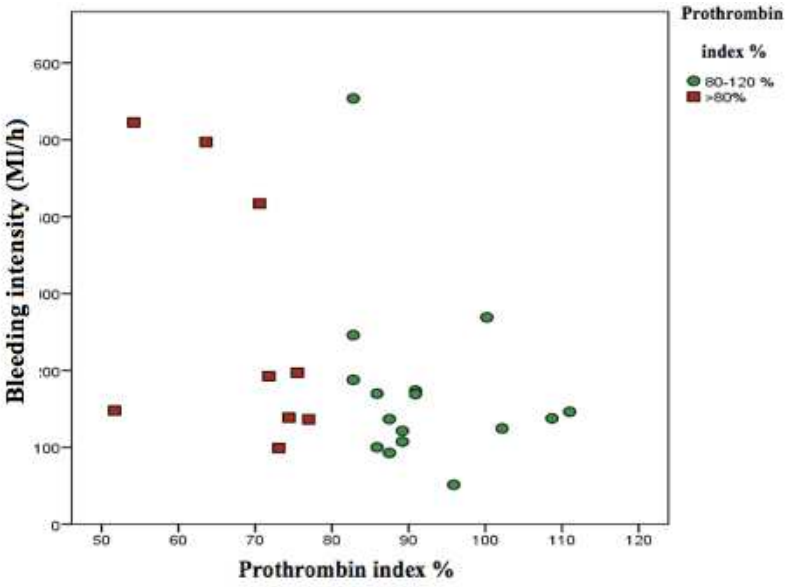

Figure 2. **The negative correlation between PI values and the postoperative bleeding intensity**

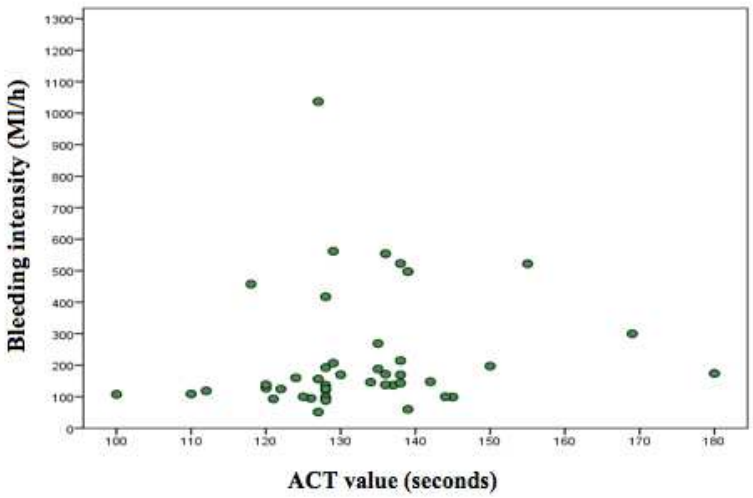

Figure 3. **The correlation between ACT and the postoperative bleeding intensity**

Conclusions

The coagulation tests that correlated with postoperative blood loss intensity, that is great enough to warrant a reoperation were APTT before and after the first surgery, and postsurgical prothrombin index and activated clotting time after surgery.

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IMPORTANCE OF OBSTETRIC ULTRASONOGRAPHY IN PRENATAL SCREENING

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Abstract

Importance of obstetric ultrasonography in prenatal screening

Key words: *prenatal diagnostics, trisomy, amniocentesis (AC), chorionic villus sample (CVS), ultrasonography (USG)*

Introduction: In Latvia, pregnant women undergo first trimester prenatal screening, which includes biochemical analysis and obstetric USG. In first trimester, it can't always detect fetal anatomical pathologies, because of that 2nd trimester USG should be done.

Aim: To evaluate the findings of US during the 1st and 2nd trimester screening, to compare the results of diagnostic procedures performed due to USG findings.

Materials and methods: In the research group (N=174) were included women, who had done AC or CVS and had 1st and 2nd trimester USG. Data were processed with SPSS22 programs and Microsoft Excel 2013.

Results: The average age is 32.96 years (SD= 6.254). In 13 cases, fetal structural anomaly was detected already in 1st trimester USG and 73 cases in 2nd. In 15 cases of 2nd USG there was heart pathology. In 33.1% (n=42) 1st trimester USG found no pathology, but it was found in 2nd trimester ($p<0.0005$). The incidence of fetal chromosomal anomalies was 9.2% (N=16), normal genotype was in 147 cases (84.5%). 28 women had medical abortion. In 46.4% it was because of genetic disorder and in 53.6% due to anatomical anomalies.

Conclusions: USG is extremely important in prenatal screening, especially when it is done in both trimesters, not to miss fetal pathology and timely do medical abortion.

Kopsavilkums

Augļa ultrasonogrāfijas nozīme prenatālajā skrīningā

Atslēgvārdi: *prenatālā diagnostika, trisomija, amniocentēze (AC), horija bārkstiņu biopsija (HBB), ultrasonogrāfija (USG)*

Ievads: Grūtniecēm Latvijā tiek veikts pirmā trimestra prenatālais skrīnings, kas iekļauj bioķīmiskās analīzes un augļa USG. Pirmā trimestra USG ne vienmēr var atklāt augļa anatomiskas patoloģijas, tādēļ jāveic otrā trimestra USG.

Mērķis: Izvērtēt augļa ultrasonogrāfijas atradni pirmājā un otrajā trimestrī,salīdzināt diagnostisko metožu rezultātus,kas tika veiktas balstoties uz USG.

Materiāli un metodes: Pētījuma grupā (N=174) tika iekļautas sievietes, kam tika veikta AC vai HBB un pieejami abu trimestru USG dati. Visi dati tika apstrādāti SPSS 22 programmā un *Microsoft Excel* 2013.

Rezultāti: Vidējais vecums ir 32.96 gadi (SD= 6.254). 13 gadījumos augļa anatomiska patoloģija tika atklāta pirmā trimestra USG, un 73 gadījumos - otrā trimestrī. 15 gadījumos otrā trimestra USG tika atklāta sirds patoloģija. 33.1% (n=42) gadījumu patoloģija netika atrasta pirmā trimestra USG, bet atklājās otrā trimestra USG ($p<0.0005$). Augļa hromosomālo patoloģiju incidence ir 9.2% (n=16), normāls genotips ir 147 gadījumos (84.5%). 28 sievietēm tika veikts medicīnisks aborts: 46.4% dēļ ģenētiskas slimības, un 53.6% dēļ anatomiskām anomālijām.

Secinājumi: USG ir ārkārtīgi svarīga kā daļa no prenatālā skrīninga, it īpaši pirmajā un otrajā trimestrī, lai savlaicīgi atklātu augļa patoloģiju un sniegtu iespēju izlemt par medicīniskā aborta veikšanu.

Introduction

Every year an estimated 303 000 newborns die within 4 weeks of birth due to congenital anomalies (WHO 2016). Statistical data shows that 2–3% of newborns in Europe have at least one congenital anomaly at birth. (Dolk et al. 2010). According to the last Latvia data of new-born morbidity rate, there was 5.7% of congenital malformations in 2015 (SDPC 2016). Congenital anomalies are an important cause of fetal, neonatal and child mortality and morbidity, accounting for 25–30% of infant deaths in Latvia (SDPC 2016, Zīle 2014).

One of the main tasks of perinatal medicine is as early and accurately detects an abnormality of development. (Resta 1997). An early identification of the pregnancy at risk for fetal aneuploidy and anatomic defects gives an opportunity of earlier diagnosis by invasive procedures such as

chorionic villus sampling or amniocentesis. Also, prenatally diagnosed congenital anomaly allows parents to make an informed decision to interrupt or continue pregnancy and prepare for the birth of special child. Moreover, it makes termination of pregnancy less traumatic for couples, who choose this option (Nicolaides et al. 2004).

With incorporation of prenatal screening for fetal aneuploidy into obstetrical practice over the past two decades, the first trimester screening has been shown to be an effective and reliable screening test for congenital anomalies (Driscoll et al. 2008). Pregnant women in Latvia undergo first trimester prenatal screening between 11 and 14 weeks (Legislation of the Republic of Latvia, Sexual and Reproductive Health Law 2002). It is non-invasive evaluation that combines a maternal blood-screening test with an ultrasound evaluation of the fetus to identify risk for specific chromosomal abnormalities, including Down syndrome (trisomy 21) trisomy 18, 13 and other congenital disorders, for example cardiac disorder (Jenkins, Lewis 2007).

Each chromosomal anomaly is characterized by different abnormalities which form syndrome. In the first trimester ultrasound common, chromosomal anomalies are discovered because of increased nuchal translucency (fluid under the skin at the back of the fetal neck). (Snijders et al. 1998). In 21, 13, and 18 chromosome trisomy the nuchal translucency (NT) thickening achieves more than 2.5 mm. This parameter can also identify other chromosomal abnormalities and can be associated with major defects of the cardiovascular and skeletal system, and a wide range of genetic syndromes. Usually, the risk of a fetal chromosomal abnormality increases with higher nuchal translucency measurements (Nicolaides et al. 2002).

To guarantee a good quality of NT measurement all sonographers performing fetal scans should be appropriately trained, the ultrasound equipment must be good quality. It is very important to perform NT measurement in appropriate gestation age. The optimal gestational age for measurement of fetal NT is 11 to 14 weeks (13 weeks and 6 days). The minimum fetal crown-rump length (CRL) should be 45 mm and the maximum 84 mm. It is a good practice to measure NT with the fetus in the neutral position (Bogota-Angel 2007).

Another ultrasound markers that may be a sign of an underlying chromosomal abnormality are:

- Absent nasal bone
- Echogenic bowel
- Pyelectasis
- Ventriculomegaly
- Shortened long bones (humerus,femur)
- Echogenic intracardiac focus
- Choroid plexus cysts (Bogota-Angel 2007).

These markers are non-specific and in some cases maybe transient (Prefumo et al. 2006, The Genetics Team at The Credit Valley Hospital 2008, Renna et al. 2013).

As first trimester US cannot detect all visual fetal anatomical pathologies, it is necessary to perform second trimester screening. As in the 1st trimester, this prenatal screening consists of maternal serum testing and transabdominal ultrasonography (Rezeberga 2016).

A second trimester prenatal US can reveal additional markers, which can increase a risk of fetal chromosomal pathology. It is used to screen for trisomy 21 and 18 as well as open neural tube defects. The second trimester ultrasound is performed between 18 and 21^{+6} weeks' gestation (Bogota-Angel 2007). During US scan, it is possible to assess fetal growth, a detailed investigation of the fetal anatomy, as well as diagnosis markers - nuchal translucency, nasal bone, femur and humerus length (Bega 2007, Rezeberga 2016). In fact, prenatal ultrasound at 18 to 20 weeks can detect major structural anomalies in approximately 60% of such cases (Gagnon 2009). If the abnormalities are present additional genetic counselling and invasive diagnostic procedures are necessary (Nicolaides et al. 2004, Gagnon 2009). In addition, if there are some large fetal anomalies in the brain, heart, lung, gastrointestinal tract, genital organs or the limbs, newborns need further surgery even when their karyotype is normal (Wilson 2002).

There are many research made for evaluating the importance of screening and prenatal diagnosis. Relying on the data of EUROCAT "Prenatal diagnosis of 18 selected congenital anomaly subgroups for registries with complete data from 2011 to 2015" the total cases of anomaly (excluding genetic conditions) was 46532. 18189 (39.1%) of them were diagnosed prenatally. As about chromosomal anomaly, there was 9959 registered cases of which 7259 (72.9%) were diagnosed prenatally (EUROCAT 2016).

Aim

To evaluate the findings of ultrasonography during the first and second trimester screening and to compare the results of diagnostic procedures performed due to US findings.

Materials and methods

A total of 174 women, who underwent invasive diagnostic procedures- amniocentesis (AC) or chorionic villus sampling (CVS) in Riga Maternity hospital during years 2014 and 2015 and had existence of first and second trimester obstetric ultrasonography (USG) were included in the study. Women who had twin pregnancy were excluded from the study group. Data on USG findings, fetal genotype and pregnancy outcome were collected and processed, using SPSS 22 and Microsoft Excel 2013 software.

Results

A total of 174 women were included in the study, aged 17 to 44 years, and the mean age was 32.96 years (SD=6.254).

In 32 cases, fetal structural anomaly was detected already in first trimester USG. The frequency of fetal chromosomal anomalies after ultrasonography findings were as follows: 6.3 %

(N=2) for trisomy 21, 18.8% (N=6) – trisomy 18, 6.3% (N=2) - trisomy 13, 18.8% (N=6) for other chromosomal anomalies (Figure 1) and normal chromosomal profile was found in 16 cases (50%).

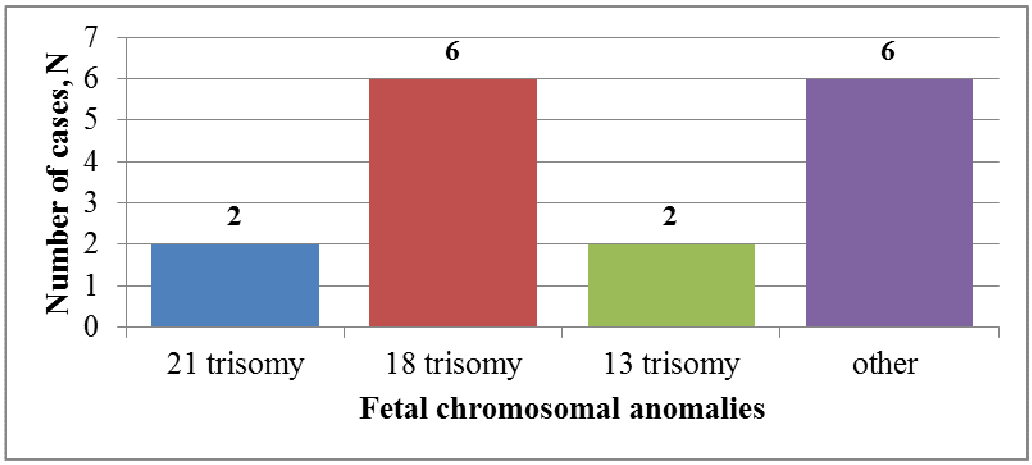

Figure 1. **Frequency of fetal chromosomal anomalies after first trimester ultrasonography**

In 33.1% (N=42) of cases first trimester ultrasonography screening was found negative, but pathology was found in second trimester ($p<0.0005$). There were 10 cases of heart anomaly detected on second trimester screening USG. In most cases, it was combined with other pathologies, excluding one case of left ventricle hypoplasia and ventriculomegaly. Other pathologies found on USG were related to kidneys in 4 cases, bowels and abdomen in 10 cases, CNS (central nerve system) in 10 cases, skeletal in 9 cases, face in 4 cases and one case with multiple anomalies, esophageal atresia and umbilical vessels anomaly (Figure 2).

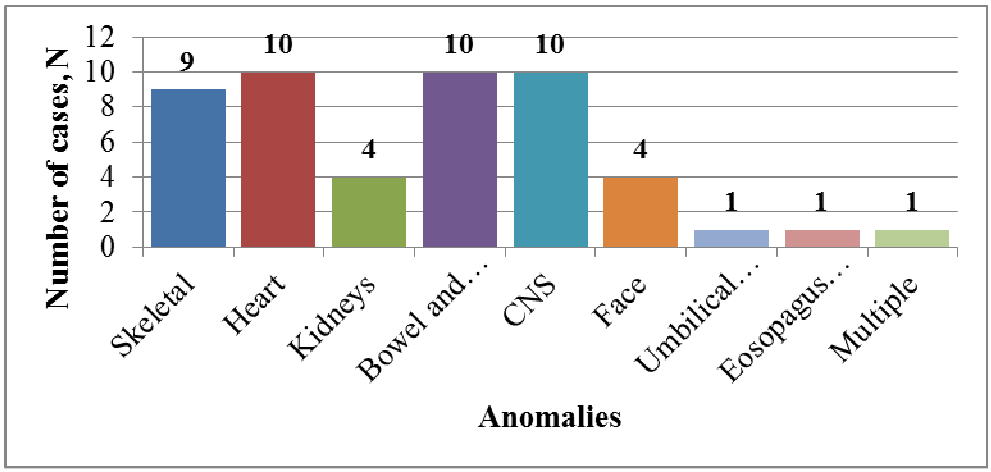

Figure 2. **Frequency of structural anomalies in second trimester screening**

82 women had pathological US findings at second trimester scr=13) of all cases termination of pregnancy was done due to chromosomal disorder and in 53.6%(n=15) of cases due to non-chromosomal (monogenic, multifactorial etc.) pathology.

Discussion

The main laws which determines medical abortion organization in Latvia is Sexual and Reproductive Law and Cabinet Regulation No 590 - Organizational Procedures for the Termination of Pregnancy. Medically indicated abortion can be done due to medical indications, including fetal pathologies, until 22 weeks of pregnancy (21 week and 6 days) after doctor's council. All mother and fetal examination must be done and documented. As it takes time, all examination, including obstetrical USG, invasive diagnostic procedures should be done in time. The main reason in not to miss time when abortion can be done. As study results shows sometimes second trimester USG is done after 22 weeks of gestation. In 7 cases second trimester screening ultrasonography was made after 22 weeks of gestation. Law allows do abortion until 24 weeks of pregnancy, but these cases are included in perinatal mortality rates (Legislation of the Republic of Latvia 2002).

Using obstetrical ultrasonography human factor should be taken in account. Because sometimes doctor's conclusions are subjective. It is also depended on technical equipment. Also, due to embryological development during first trimester screening (11-13 weeks of gestation) not all organs and anatomical structures are already developed.

Many studies have reported about the correlation of nasal bone (NB) presence-absence and trisomy 21 in the 1st trimester (Cicero 2005). Recently, nasal bone assessment in the 2nd trimester for trisomy 21 screening has been started to be widely discussed and studied. Nasal bone length expressed as multiple of the median (MoM) seems to be a useful ultrasound marker for Down syndrome in 2nd trimester fetuses with a high sensitivity and a low false-positive rate (Gianferrari 2007). But isolated NB presence assessment in the 1st trimester was not found to be effective in trisomy 21 detection. Combining this regimen with biochemical screening and NT measurement was suggested to be more effective. (Cicero 2003)

Obido et al has also concluded that nasal bone length expressed as MoM seems to be a useful ultrasound marker for trisomy in 2nd trimester, although the NB length assessment as MoM seems to be a more objective criterion than the assessment of presence or absence in the 1st trimester (Obido 2007).

Combining this marker with other US markers, including: nuchal fold, femur and humeral lengths, choroid plexus cysts, major fetal anomalies, echogenic bowel, pyelectasis, and hypoplastic fifth digits, and biochemical markers could be more effective in screening (Odibo 2007).

Wax et al during their study evaluated trisomy 21 screening performance of the 1st trimester combined screening followed by 2nd trimester genetic US, and results have shown that 2nd trimester US after 1st trimester combined screening may improve trisomy 21 detection at the expense of increasing screen-positive rates (Wax 2009).

Conclusions

Study results shows that obstetric ultrasonography is extremely important in prenatal screening to detect fetal anatomical anomalies. Especially if using it in both first and second trimester. It is a part of prenatal screening as well as biochemical analyzes, maternal and family anamnesis.

It is important to use both USG and biochemical prenatal screening to reach high sensitivity and specificity and detect fetal chromosomal and non-chromosomal disorders already during pregnancy and make medical abortion of woman and her family have such need, as well as to prepare for childbirth or think about intrauterine surgery opportunities, for example fetal *spina bifida* surgery.

Results have shown not all fetal anatomical pathologies are seen in first pregnancy trimester. But majority of fetal chromosomal anomalies are already seen at 1st trimester USG.

However, some markers for chromosomal aneuploidies can be found on 2nd trimester only and most of monogenic eening. 17% (N=14) of them had abnormal karyotype fetus and 83% (N=68) with normal karyotype. The frequency of fetal chromosomal anomalies was as follows: 6.1% (N=5) for trisomy 21, 3.6% (N=3) – trisomy 18, 1.22 % (N=1) - trisomy 13, 6.1% (N=5) for other chromosomal anomalies.

In 15 cases, structural heart pathologies were detected, from which the most severe was one case with left ventricle hypoplasia and ventriculomegaly.

A total of 28 women had medical abortion because of fetal pathology, found by US. In 46.4% (n/multifactorial disorders with prenatal expressivity could not be found on 1st trimester.

There is a need in prenatal care improvement, as not all pregnant women had undergone both trimester screening, including USG, which make difficult to evaluate prenatal screening.

As study is associated with medical documentation analysis, there is were some difficulties, because not in all cases all needed medical data was available. There is a need to continue and expand study to get more accurate results and precise conclusions.

Acknowledgment

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ASSOCIATION BETWEEN ANGIOTENSIN CONVERTING ENZYME GENE AND ARTERIAL HYPERTENSION

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Abstract

Association between angiotensin converting enzyme gene and arterial hypertension

Key words: *Angiotensin-I converting enzyme (ACE), insertion/deletion polymorphism, hypertension, diabetic hypertension*

Introduction: Arterial hypertension (AH) is influenced by genetic, environmental and demographic factors. There are various studies showing controversial relation between *Angiotensin-I converting enzyme (ACE)* gene polymorphisms and AH.
Aim: To find the relationship between *ACE* gene polymorphism and AH in population of Latvia.
Materials and methods: In retrospective study we included 100 patients with AH (AH group) in research group and 34 patients in control group without AH from Pauls Stradins Clinical University Hospital. Blood pressure (BP), biochemical test results, treatment and comorbidities were analyzed for all patients. *ACE* gene genotypes of insertion/deletion (I/D) polymorphism were determined by using polymerase chain reaction (PCR).
Results: The mean age in AH group was 59.5± 8.73 years and in control group 55±5.52 years. The prevalence of homozygous insertion (II), insertion/deletion (ID), and homozygous deletion (DD) genotypes were 23%, 41%, 36% in AH group and 20.6%, 52.9%, 26.5 % in controls (p>0.05). We analyzed comorbidities and identified diabetes mellitus (DM) group (n=16). It was found that there are difference in *ACE* genotype distribution in patient groups with and without DM (in DM group with genotype II was - 0%, ID – 37.5%, DD - 62.5%, in non DM group – genotype II - 27.4%, ID – 41.7%, DD – 31%, p=0.016).
Conclusion: There was not found association between *ACE* gene I/D genotypes or alleles and arterial hypertension. *ACE* gene DD and ID genotype could be a risk factor for diabetes mellitus development in arterial hypertension patients.

Kopsavilkums

Angiotenzīnu konvertējošā enzīma gēna polimorfisma saistība ar arteriālo hipertensiju

Atslēgvārdi*: angiotenzīna-I konvertējošais enzīms (ACE), insercija/delēcija, hipertensija, diabētiskā hipertensija*

Ievads: Arteriālo hipertensiju (AH) ietekmē ģenētiskie, vides un demogrāfiskie faktori. Līdz šim esošajos pētījumos ir publicēti dažādi dati par angiotenzīna konvertējošā enzīma (*ACE)* gēna polimorfismu saistību ar AH.
Mērķis: Noskaidrot *ACE* gēna polimorfismu saistību ar arteriālo hipertensiju Latvijas populācijā.
Materiāli un metodes: Restrospektīvi pētījumā tika iekļauti 100 pacienti ar AH (AH grupa) un 34 pacienti kontroles grupā bez AH no Paula Stradiņa Klīniskās universitātes slimnīcas. Visiem pacientiem tika analizēts asinsspiediens (BP), bioķīmisko testu rezultāti, kā arī bija pieejami dati par pielietoto ārstēšanu un blakusslimībām. *ACE* gēna insercijas/delēcijas (I/D) polimorfisma genotipi tika noteikti izmantojot polimerāzes ķēdes reakciju (PĶR).
Rezultāti: Vidējais vecums AH grupā bija 59,5 ± 8,73 gadi un kontroles grupā 55 ± 5,52 gadi. Prevalence homozigotas insercijas (II), insercijas/delēcijas (ID) un homozigotas delēcijas (DD) genotipiem bija attiecīgi 23%, 41%, 36% AH grupā, un 20,6%, 52,9%, 26,5%, kontroles grupā (p> 0,05). Analizējot blakusslimības, tika izveidota grupa ar cukura diabēta (CD) pacientiem (n = 16). Tika konstatēts, ka pacientu grupā ar un bez CD ir atšķirīga *ACE* genotipu sadale (CD grupā ar II genotipu - 0%, ID - 37,5%, DD - 62,5%, grupā bez CD - II genotips - 27,4%, ID - 41,7%, DD - 31%, p = 0,016).
Secinājumi: Netika atrasta statistiski ticama saistība starp *ACE* gēna I/D genotipu vai alēlēm un arteriālo hipertensiju. *ACE* gēna DD un ID genotips varētu būt riska faktors cukura diabēta attīstībā arteriālās hipertensijas pacientiem.

Introduction

The most frequent chronic disease dealt with by primary care physicians and other medical practitioners is hypertension, which affects approximately one quarter of the population in the world. (Weber 2014, Chockalingam 2006).

National Heart, Lung, and Blood Institute described that hypertension is one of the primary risk factors for heart disease, stroke, kidney disease. Heart Foundation guideline for the diagnosis and management of hypertension in adults recommend to confirm the diagnosis of hypertension when a person's systolic blood pressure is ≥140 mmHg or their diastolic blood pressure is ≥90 mmHg, or both, on repeated examinations (Anderson 2016).

Hypertension is classified as either primary (essential) hypertension or secondary hypertension. Primary hypertension pertains to the bigger number of cases, about 95% of adults with high blood pressure have primary hypertension (Weber 2014). Primary hypertension is the form of hypertension that by definition has no identifiable cause, although various genetic and environmental factors now being studied, with great attention paid to obesity, excessive salt consumption, and low levels of physical activity (Weber 2014). In studies described that approximately 30% of the interindividual blood pressure variability is assumed to be genetically determined (He 2013).

Secondary hypertension accounts for about 5% of all hypertension. In secondary hypertension the cause of high blood pressure is other medical condition that can be identified and in some cases treated (Weber 2014). Chronic kidney disease, renal artery stenosis, pheochromocytoma, excessive aldosterone secretion, and sleep apnea are the main causes of secondary hypertension (Weber 2014). Renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure (Yim 2008).

Angiotensin converting enzyme (*ACE*) is a zinc metallopeptidase which is extensively expressed on the surface of endothelial and epithelial cells. *ACE* is a component of RAS, and it converts angiotensin I to angiotensin II that have cellular grown and proliferating effect and is a potent vasoconstrictor. Angiotensin II is of central importance in hypertension, cardiac remodeling, heart failure and diabetes (Yim 2008, Taubman 2003, Sayed-Tabatabaei 2006).

The *ACE* gene consists of 26 exons and spans 21 kb, on chromosome 17, one of most widely examined variations is a 287 bp DNA fragment insertion (I)/ deletion (D) variant in intron 16 (Naresh 2009).

In various studies was found that *ACE* gene polymorphism play significant role in hypertension (Gesang 2002, Haidari 2014), however there are various studies showing controversial relation between *ACE* gene insertion/deletion (I/D) polymorphisms and AH (Gupta 2009, Ishigami 1995). In one snapshot review there was found that the deletion allele occurs in approximately 55% of the population and is associated with increased activity of the *ACE* enzyme (Gard 2010). They thought that it might be predicted that the D allele, might be associated with pathologies involving increased activity of the renin-angiotensin system. The D allele was associated with an increased risk of hypertension and many other diseases such as pre-eclampsia, heart failure, cerebral infarct,

diabetic nephropathy, encephalopathy, asthma, severe hypoglycemia in diabetes, gastric cancer and poor prognosis following kidney transplant (Gard 2010).

Aim

The aim of this study was to find association between *ACE* gene polymorphism and AH in population of Latvia.

Materials and methods

Study participants. In retrospective study we included 100 patients with AH and 34 patients without AH from Pauls Stradins Clinical University Hospital from 1/09/2016 - 17/02/2017. In AH group, we included patients with clinically confirmed diagnosis of AH according to European Society of Hypertension (ESH) guidelines (Table 1).

Table 1. **Definitions and classification of office blood pressure levels (mmHg)**

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90
The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.			

There were available data from all patients about blood pressure (BP), several biochemical test results such as serum creatinine, glucose level, serum cholesterol (total, low-density lipoprotein, and high-density lipoprotein cholesterol), triglyceride level, used treatment and comorbidities. Analyzing comorbidities there were patients with diabetes mellitus (DM) in group with AH (n=16) and in group without AH only one patient. Further we decided to include individuals into two groups – with DM (n=16) and without (n=84)

Blood samples collection. Approximately 2ml of venous blood was collected in a screw cap tube containing EDTA as anticoagulant and stored at +4°C until DNA isolation. DNA isolation was done using innuPREP Blood DNA Mini Kit (Analytic Jena, Germany) spin columns according to manufacturer protocol.

Genotyping of *ACE* gene I/D polymorphism. PCR was made accordingly to the protocol described before (Castellano 1995), used primer sequences are shown in Table 2.

Table 2. **Primers for *ACE* gene Polymorphism (concentration 10 pmol/µl)**

Nr	Name	5'-3- direction	Tm, °C	Amplicon (bp)
1	***ACE*_F3**	GCC CTG CAG GTG TCT GCA GCA TGT	55	312 bp for D allele 599 bp for I allele
2	***ACE*_R3**	GGA TGG CTC TCC CCG CCT TGT CTC		

PCR product was analyzed in 2% agarose gel electrophoresis, 312 bp long fragment was identified as D allele and 599 bp as I allele (Figure 1).

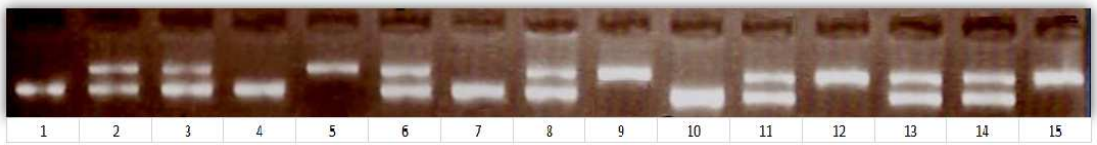

Figure 1. **Agarose gel electrophoresis of PCR products for *ACE* I/D polymorphism. Lanes 1, 4, 7 and 10 show DD genotype; Lanes 2, 3, 6, 8, 11, 13 and 14 show DI genotype; Lane 5, 9, 12 and 15 shows II genotype**

Statistical analysis

Data was analyzed using MS Excel and IBM SPSS version 22.0. Genotype frequencies in the patient and control groups were analyzed using the standard $\chi 2$ statistics test or Fisher exact tests. Correlations were explored using the Spearman rho test. Comparisons were performed with one way ANOVA test. The results were statistically significant when p value was < 0.05.

Results

The mean age in AH group was 59.5± 8.73 years (minimal 38, maximal 83 years) and in control group 55±5.52 years (minimal 44, maximal 65 years), difference was not statistically significant ($p>0.05$).

There were unequal gender distribution between patient and control group – in patient group were 46 males and 54 women, in control group – 7 males and 27 women. There was not found statistically significant association between *ACE* genotype and gander in AH patient group ($p>0.05$).

The prevalence of II, ID, and DD genotypes were 23.0%, 41.0%, 36.0% in AH patient group and 20.6%, 52.9% and 26.5 % in controls ($p>0.05$).

Comparing biochemical data with BP there was found weak negative correlation between LDL and systolic BP (rs = -0.307, p=0.008) and between total cholesterol (TH) and systolic BP (rs=-0.351, p=0.007). Also we found positive correlation between glucose level and stage of AH (rs = 0.386, p=0.001).

Analyzing DM association with *ACE* genotype it was found that there were different genotype distribution in DM group with AH (II genotype 0%, ID – 37.5%, DD - 62.5%) comparing to non-DM group (II genotype for 27.4%, ID – 41.7%, DD –31%; p=0.016).

Analyzing the information regarding arterial hypertension therapy, we found out that 28 patients was using triple therapy, 24 dual therapy and 29 monotherapy, 11 did not use any therapy at all and 8 patients couldn't provide data about their therapy. It was found that therapy with three antihypertensive drugs was used more frequently in patients with DD genotype comparing to DI and II genotype (DD – n=12, 66.7% vs DI – n= 5, 27.8% vs II- n=1, 5.6%, p=0.011). Further we analyzed frequency of antihypertensive agents use in different drug groups such as beta blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme (ACEI) inhibitors and angiotensin II receptor antagonists, other groups within this study was not evaluated. Results showed that patients with DD genotype more frequently was using *ACEI* (p=0.019) (Table 3), while in other groups of medications such association was not found (p>0.05).

Table 3. ***ACE* gene polymorphism association to patients with ACE inhibitor therapy**

Genotype	ACE-inhibitors usage (n)	ACE-inhibitors usage (%)	p value
DD	24	46.2%	P=0.019
ID	15	28.8 %	
II	13	25%	
Total	52	100%	

There were not found statistical correlation between other clinical characteristics and *ACE* gene variants (p>0.05) (Table 4).

Table 4. **The association between *ACE* genotypes and the clinical characteristics in the study population**

Variables	DD Homozygots	Carriers of ID	II Homozygots	P value
BMI (kg/m²)	29.7 ± 3.9	28.6 ± 4.5	31.6 ± 5.3	>0.05
Operating systolic BP (mmHg)	146.8 ± 17.1	142.1 ± 16.8	147.9 ± 13.7	>0.05
Operating diastolic BP (mmHg)	87.6 ± 8.1	86 ± 7.2	88.5 ± 11.2	>0.05
Data are presented as mean ± SE. Comparisons were performed with one way ANOVA test followed by the Tukey's test for multiple comparison.				

Discussion

There are data in the literature that deletion polymorphism in the *ACE* gene is associated with elevated serum and cellular angiotensin converting enzyme levels, and II genotype has lowest enzyme levels comparing to other genotypes (Naresh 2009). In other study was assumed that genetically related factors could include inappropriately high activity of the RAS and the sympathetic nervous system, as well as susceptibility to the effects of dietary salt on blood pressure (Weber 2014). Various studies demonstrate association between *ACE* gene polymorphism and arterial hypertension, diabetes mellitus, kidney diseases (Wang 2015, Eman 2016, Ergen 2004).

Moreover now several classes of pharmacological agents which inhibits synthesis of Angiotensin II (angiotensin II-converting enzyme inhibitors) or blocks its action (angiotensin II receptor antagonists) are produced (Weber 2014) and in Brugt *et al*. study, they have suggested that the response to ACE inhibitors therapy may be influenced by genetic polymorphisms. Another studies approve that D allele of *ACE* gene confers a greater role in genetic variations underlying hypertension (Shanmuganathan 2015, Zhou 2013). Although, Gupta *et al.* reports that *ACE* I/D polymorphism is not a risk factor for the development of essential hypertension. In our study we also have not found association between *ACE* gene I/D genotypes or alleles and arterial hypertension. There is need to continue our study, because of small study population.

Previous studies have indicated that the high angiotensin II level and low bradykinin level in the RAS related to insulin-resistance are risk factors for DM. Type 2 diabetes mellitus (T2DM) is multifactorial disease where environmental factors obesity, sedentary lifestyle and stress have strong influence (Yang 2006, Diapedia Collective 2014). There are studies, which described that DD genotype in the I/D polymorphism of the *ACE* gene is associated with T2DM (Yang 2006). Bhavani *et al.* data showed an association between *ACE* DD genotype and patient with hypertension and diabetes. They found that DD genotype was 1.2 times more common in hypertensive patients with diabetes compared with non-diabetic patients. Bhavani *et al.* suggested that DD genotype in patients with hypertension is associated with an increased susceptibility to diabetic complications, of which diabetic nephropathy is one of the most common. In many studies within different populations (Caucasians, Asians, etc), ethnicity was defined as a factor of tremendous importance in determining the role of ACE gene polymorphism in susceptibility to diabetic nephropathy (Rahimi 2012). That is why, it could be useful to do further research and include new criteria in our patient form like urine sample to detect proteinuria and all related complications of T2DM to find out if there is an association between *ACE* gene polymorphism and diabetic nephropathy in Latvian population.

Conclusions

1. There was not found association between *ACE* gene I/D genotypes or alleles and arterial hypertension.
2. *ACE* gene DD and DI genotype could be a risk factor for diabetes mellitus in arterial hypertension patients.

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METASTATIC CLEAR CELL RENAL CELL CARCINOMA: A CASE REPORT

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Abstract

Metastatic clear cell renal cell carcinoma: a case report

Key words: *clear cell renal cell carcinoma, metastatic renal carcinoma, RCC*

The case report demonstrates a 50-year-old male with metastatic clear cell renal cell carcinoma, who regularly attends oncologist since 2009. Due to CT data patient had metastasis (MTS) in vertebrae L2, and he has received palliative actinotherapy (AT). Further investigations have revealed primary right side RCC. In 2010 patient had palliative right-sided nephrectomy and histology revealed clear cell RCC with signs of severe intratumoral inflammation, grade 3 according to Fuhrman. Patient received therapy with INF α-2a till April 2011. In March 2011 patient appeared with pain in left shoulder, MTS in the head of left humerus on skeletal scintigraphy and X-ray. Due to pain syndrome patient received AT and bisphosphonates was initiated. Because of negative dynamic of disease in May 2012 AT course was repeated. In September on X-ray pathologic fracture of left humerus without dislocation and on CT solitary MTS in left lung appeared. In January 2013 resection of proximal part of left humerus and endoprosthetics was performed, later therapy with Pazopanib was initiated. In November – no data of disease progression, no pathologic findings in chest and abdomen, patient continues treatment with Pazopanib. In November 2016 patient had complete disease remission.

Kopsavilkums

Klīniskais gadījums: metastātiska nieru gaišo šūnu karcinoma

Atslēgvārdi*: nieru gaišo šūnu karcinoma, metastātiska nieru karcinoma, NK*

Klīniskais gadījums demonstrē 50 gadus vecu vīrieti ar metastātisku nieru gaišo šūnu karcinomu, kas kopš 2009. gada regulāri apmeklē onkologu. CT tika atklātas metastāzes (MTS) skriemeļos L2 līmenī, un paliatīva aktinoterapija (AT) tika uzsākta. Turpmāki izmeklējumi atklāja primāru labās puses nieres karcinomu (NK). 2010. gadā pacientam tika veikta paliatīva labās puses nefrektomija, un histoloģiskā izmeklēšanā tika atklāta gaišo šūnu NK ar intratumorālu iekaisumu, *grade* 3 pēc *Fuhrman*. Pacients līdz 2011. gada aprīlim saņēma terapiju ar INF α-2a. 2011. gada martā pacientam parādījās sūdzības par sāpēm kreisajā plecā. Izmeklējot pacientu, skeleta scintigrāfija un Rtg uzrādīja MTS kreisās puses *humerus* galviņā. Sakarā ar sāpju sindromu pacients saņēma AT un bifosfonātus. 2012. gada maijā slimības negatīvas dinamikas dēļ AT kurss tika atkārtots. Septembrī Rtg uzrādīja patoloģisku kreisā *humerus* galviņas lūzumu bez dislokācijas, CT atklāja atsevišķu MTS kreisā plaušā. 2013. gada janvārī pacientam tika veikta kreisā *humerus* proksimālās daļas rezekcija ar endoprotezēšanu, vēlāk terapija ar Pazopanib tika uzsākta. Novembrī datu par slimības progresiju nebija, patoloģiskas atradnes krūškurvī un vēdera dobumā netika konstatētas, pacients turpina saņemt terapiju ar Pazopanib. 2016. gada novembrī pacientam tika konstatēta slimības pilna remisija.

Introduction

The most common type of kidney cancer is renal cell carcinoma (RCC). RCC is a heterogeneous group of tumors arising from the epithelium cells within the renal tubules (Moch 2013). RCC accounts for about 3-4% of all adult malignancies (Pili *et al*. 2014). RCC is more common among men with the male-to-female ratio range between 1.5:1 and 2:1 (DeCastro *et al*. 2008; DeVita *et al.* 2011). In 80% of the cases RCC occurs within the age 40 to 69 years with peak incidence in the sixth decade (Pascual *et al.* 2008). Utmost (about 70%) of the new cases of RCC occurred in countries with high levels of human development (Stewart *et al*. 2014). RCC mostly occurs in sporadic form, but in 2-4% cases it is heritable. Several autosomal dominantly inherited syndromes are associated with RCC, major are von Hippel-Lindau disease, hereditary leiomyomatosis and RCC, hereditary papillary renal cancer and Birt-Hogg-Dubé syndrome (Eble *et al*. 2004).

The most common histologic subtype of RCC is clear cell carcinoma, which accounts for 70% to 80% of all RCC. Less common tumors are papillary (10–15%), chromophobe (about 5%), and collecting duct (<1%) RCC (Deng and Melamed 2012; Stewart *et al.* 2014). Because of clear cell RCC very vascular stroma, haemorrhagic areas can frequently appear (Moch 2013). There is suggestion based on past immunohistochemical analyses that clear cell RCC are derived from the proximal tubules (Thoenes *et al.* 1986). Due to the presence of necrosis some clear cell RCC may have a cystic appearance, and is associated with increased aggressivity of the tumors, but there also may be found genuine neoplastic cysts formed by RCC (Eble *et al.* 1998). In 3-5% RCC demonstrates sarcomatoid changes, which is associated with wider venous tumor extension and poor prognosis (Moch *et al.* 2000; de Peralta-Venturina *et al.* 2001; Rabbani *et al.* 2004). Some RCC have intense inflammatory response with lymphocytic or neutrophilic infiltrate formation (Sconocchia *et al.* 2009) that predicts worse outcome (Morra *et al.* 2011).

The most common path of clear cell RCC metastasizing is via the vena cava and its major sites of spread are lungs, bones, regional lymph nodes and liver (Pili *et al*. 2014). Less common is retrograde spread along the paravertebral veins, testicular or ovarian vein, intrarenal veins or along the ureter. Clear cell RCC is well known for its ability to metastasize even after 10 years or more. Regardless of the size, all clear cell tumors are considered to be malignant (Eble *et al*. 2004).

Case report

50-year-old male is regularly attending oncologist since 2009. Due to CT data patient had metastasis (MTS) in vertebrae L2, and he has received palliative actinotherapy (AT) 13 GY in 2009. Further investigations have revealed primary right side RCC. In 2010 patient had consultation of oncourologist in Oncology Centre of Latvia and palliative right-sided nephrectomy was performed. Histology result: clear cell RCC with signs of severe intratumoral inflammation, grade 3 according to Fuhrman. Patient received therapy with INF alpha-2a till April 2011, in dosage 3 – 9 MIU 3x/weekly. In March 2011 patient appeared with pain in left shoulder, MTS in the head of left humerus on skeletal scintigraphy and X-ray. Due to pain syndrome patient received AT (8 GY) and started therapy with bisphosphonates. Because of negative dynamic of disease, increasing of pain and MTS (40x66 mm) finding in the head of left humerus on X-ray, in May 2012 AT course was repeated (3 GY x 10). In September on X-ray pathologic fracture of left humerus without dislocation and on CT solitary MTS in left lung (19x23 mm) appeared. In January 2013 patient had consultation in the Hospital of Traumatology and Orthopaedics in Riga and resection of proximal part of left humerus and endoprosthesis with Delta Extend followed, later therapy with Pazopanib was started. In November – no data of disease progression, no pathologic findings in chest and abdomen, patient continues treatment with Pazopanib. In November 2016 patient had complete disease remission.

Discussion

In the study case of 50-year-old male with diagnosis of clear cell RCC is described, that corresponds with observations mentioned above that sporadic RCC is more common among men with peak incidence in the sixth decade. RCC remains primarily a surgical disease and without complete tumor excision cure is rarely achieved (Rini *et al*. 2009; Kroeger *et al*. 2014).

Due to rich vascularization RCC has a high tendency to metastasize, lungs and bones are one of the most common sites of spread. In our case, the metastatic disease presented in the vertebrae L2, head of left humerus and lungs, which is quite usual metastatic site for clear cell RCC. Metastasectomy of a solitary lesion can provide quite high overall 5-year survival rate (35–60%), but its benefit is tightly associated with the metastasis site. The good prognosis criteria for patients who are supposed to undergo surgery are solitary metastasis, metachronous metastasis with a free of recurrence period longer than 12 months, good health condition, and age under 60 years (Bigot *et al*. 2013). The time between metastasectomy and the last control was 3 years and patient was in complete remission, so relatively good prognosis may be expected. According to European Association of Urology guidelines it is recommended to perform nephrectomy combined with IFN in patients with metastatic renal cell carcinoma, who are in good performance status and suitable for operative treatment. Pazopanib in several clinical trials have been reported as safe and efficient in patients with advanced or metastatic RCC (Sternberg *et al*. 2010), which was preferred treatment agent in our case.

RCC grading is based on the microscopic morphology of tumor with hematoxylin and eosin staining, and the most widely used grading system is Fuhrman's grading system, which can be applicable to all types of renal cancer. In Fuhrman's original study nuclear grade occurred to be the most significant prognostic factor. It was observed that 5-year survival rate for grade 1 to 4 were 64%, 34%, 31% and 10% (Fuhrman *et al*. 1982). Later it was reported that there are correlation between Fuhrman's grade and tumor stage, size, venous tumor thrombi, as well as lymph node and systemic metastases (Ficarra *et al*. 2009). Clear cell RCC are relatively large and are more likely to have high nuclear grade, what correlates with a compromised prognosis (Frank *et al*. 2003; Lane *et al*. 2007; Thompson *et al*. 2009). If distant MTS occurs in RCC 5-year survival is 0-10% (Campbell *et al*. 2016). In our case, 6-year survival has been observed after histological finding of grade 3 clear cell RCC in patient with metastatic disease.

Conclusion

It is proven that pathologic stage of RCC is most important prognostic factor for cancer outcome. 5-year survival rate for grade 3 according to Fuhrman is 10%, but there also were reported cases with prolonged survival. Complete tumor excision is efficient in achieving of disease improvement. Pazopanib is effective in treatment of patients with metastatic RCC.

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ANTIRETROVIRAL THERAPY EFFECT ON PREGNANCY OUTCOMES AND COMPLICATIONS IN HIV INFECTED PATIENTS

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Abstract

Antiretroviral therapy effect on pregnancy outcomes and complications in HIV infected patients

Key words: *HIV, pregnancy, antiretroviral therapy (ART)*

Introduction: In 2016 HIV incidence in Latvia was 15.2:100 000 inhabitants. Till this year 54 vertical transmission (VT) cases have been reported. ART is used to reduce VT risk and considered to be safe during pregnancy.

Aim: Analyze the effect of ART during pregnancy on pregnancy complications, outcomes and neonatal period complications.

Materials and methods: Retrospective analysis of 281 delivery histories (2010-2016) with diagnosis B20 ICD-10 in Riga Maternity hospital. Obtained data was statistically analyzed in MS Excel 2013 and IBM SPSS 22 programs.

Results: There was no significant difference in pregnancy related complications between the groups ($p>0.05$). Receiving of ART were associated with choice of delivery type ($p<0.0005$). 60% of patients with vs 22% without ART had elective Caesarian section (CS); 25.9% vs 30% had emergency CS; 9.7% vs 44% had physiologic and 4.3% vs 4% had pathological vaginal delivery. Mean length, head and chest circumference were higher in newborns of mothers who received ART during pregnancy ($p<0.05$). Neonatal period complication rate were lower in patient group with ART (46.5% vs 64%; $p=0.028$).

Conclusions: Use of ART during pregnancy is important aspect of antenatal care of HIV infected women. There is association between ART and the choice of delivery type. ART is important for neonatal complication reduction.

Kopsavilkums

Anitretrovirālas terapijas ietkeme uz grūtniecības iznākumu un sarežģījumiem HIV inficētām pacientēm

Atslēgvārdi*: HIV, grūtniecība, antiretrovirāla terapija (ART)*

Ievads: Latvijā HIV incidence 2016. gadā bija 15.2 uz 100 000 iedzīvotājiem. Līdz šim gadam bija 54 vertikālās transmisijas (VT) gadījumi. ART pielieto, lai samazinātu VT risku un tā ir uzskatāma par drošu grūtniecēm.

Mērķis: Analizēt kā ART lietošana grūtniecības laikā ietekmē grūtniecības sarežģījumus, iznākumu un neonatālā perioda komplikācijas.

Materiāli un metodes: Veikta 281 dzemdību vēstures retrospektīva analīze (2010-2016) Rīgas Dzemdību namā ar diagnozi B20 SSK-10. Dati tika statistiski apstrādāti Microsoft Excel 2013 un IBM SPSS 22 programmās.

Rezultāti: Netika atrasta statistiski ticama atšķirības starp grūtniecības sarežģījumiem starp grupām (ar pret bez ART: 92.4% pret 94%; $p>0.05$). Tika noteikta saistība starp ART lietošanu un dzemdību veidu ($p<0.0005$). 60% pacientēm ar ART pret 22% bez ART dzemdības atrisināja ķeizargrieziena ceļā (ĶG); 25.9% pret 30% - akūts ĶG; 9.7% pret 44% - fizioloģiskas dzemdības un 4.3% pret 4% patoloģiskas vaģinālas dzemdības. Vidējais garums, galvas un krūšu apkārtmērs bija lielāki jaundzimušajiem, kuru mātes saņēma ART ($p<0.05$). Neonatālā perioda komplikācijas bija retākas grupā, kas saņēma ART (46.5% pret 64%; $p=0.028$).

Secinājumi: ART grūtniecības laikā ir būtisks aprūpes aspekts HIV inficētām sievietēm. Ir saistība starp ART un dzemdību veidu. ART ir svarīgs neonatālo komplikāciju mazināšanai.

Introduction

Human immunodeficiency virus (HIV) infection is serious problem all over the world, and also in Latvia. In past years incidence of HIV ranges from 12.8 to 17.1 per 100 000 habitants. In year 2016 it was 15.2 per 100 000. 30.7% of new HIV cases are in group of age to 30 years old. (SPKC 2017)

World Health Organization (WHO) recommends a four-component approach to the HIV prevention: primary prevention of HIV among women, prevention of unintended pregnancy, prevention of vertical transmission and care of HIV infected women and her family. (Cant 2012-39)

As one of HIV transmission types is vertical transmission, there is HIV screening during pregnancy. Till year 2016 there are documented 54 vertical transmission (VT) cases to newborn in Latvia. To prevent VT, HIV screening tests is done and antiretroviral therapy (ART) is prescribed. In Latvia in 98% of pregnant women HIV test is done during pregnancy or delivery. At that moment HIV positive woman is also tested on hepatitis C, tuberculosis, sexually transmitted diseases. (Rezeberga 2015, 13) Before the use of ART incidence of vertical transmission was quite low in Europe (13%), high in Africa (60%) and ranged from 14% to 33% in United States. Use of perinatal prophylaxis can decrease VT risk to less than 1-2% (without breastfeeding). But ART is not available to every pregnant woman: in low-income countries only 57-62% of women use ART during pregnancy. But in North America this percent is almost 97%. Perinatal transmission is complex process, which is influenced by multiple risk factors: maternal (clinical staging, viral load, low CD4 leucocytes count, viral phenotype and genotype, older age, cigarette smoking), fetal (chorioamnionitis, low birth weight, prematurity), obstetrical (vaginal delivery, invasive procedures during pregnancy and delivery, prolonged premature rupture of membranes), immune factors. (Cant 2012 – 38, Cohn 2015 – 1595, 1598, Gagnon 2016 – 51, Maartens 2014)

Antiretroviral therapy is used to control viral load and prevent perinatal transmission. All women should start ART until 24 weeks of gestation. Longer ART is associated with decreased mother to child transmission: women who started ART before pregnancy are less likely to transmit HIV infection, compared to those who started treatment only during pregnancy. In case if woman has high baseline viral load, count of leucocytes is low, and if co-morbidities are present (hepatitis B or C infection, recurrent genital herpes simplex virus), it is important to start ART before 20-24 weeks of gestation, already in first trimester. (Bull 2015 – 275, Maartens 2014, Rezeberga 2016 - 605)

Even in high income countries (for example United Kingdom) over a half of pregnant women present late for antenatal care, but small proportion of infected women are undiagnosed during delivery. (Bull 2015 – 273)

Most studies in developed countries suggest that untreated HIV infections is associated with increased risk of preterm birth, stillbirth. And most studies in developing countries report an increased risk of preterm birth, low birth weight, intrauterine growth restriction, stillbirth, and infant death. Factors that are associated with an increased risk of preterm birth and low birth weight in HIV infected women group includes: previous adverse pregnancy outcome, hypertension, multiple gestation, smoking, bleeding, alcohol use, low maternal weight, *Trichomonas vaginalis* infection, other sexually transmitted infections. (Watts 2011 – 480-481)

In studies in industrialized countries was concluded that maternal HIV infection is not associated with fetal abnormalities, preterm delivery, low birth weight, or specific pregnancy

related abnormalities. (Massad 2004, Tuomala 2002) But in developing countries reports have noted increased incidence of low birth weight and preterm delivery. In one recent study was reported, that HIV infection is significantly associated with stillbirth, premature delivery, small for gestational age, neonatal mortality. Using in ART zidovudine alone is associated with higher odds to these outcomes, comparing with complex therapy using. (Cohn 2015 - 1600)

There is controversial opinion if ART is associated with preterm delivery. (Bull 2015 - 277) As well as ART toxicity to mother and fetus among patients receiving complex therapy, including protease inhibitors (PI). The results about effect of ART on preterm delivery in conflicting. Most European studies have shown increased rate of preterm delivery among women received ART, in contrast most American studies have not shown such correlation. (Gagnon 2016: 51) Data form African countries is also mixed. (Bull 2015 – 277)

In Pediatric HIV/AIDS Cohort study result have shown that 18.6% of the 1869 singleton births among HIV infected women were preterm, 89% of whom used three-drug combination ART during pregnancy. In adjusted models, the odds of preterm birth and spontaneous preterm birth were higher among mothers using PI during the first trimester (adjusted OR, 1.55 and 1.59, respectively) but not among mothers using non-nucleoside reverse transcriptase inhibitors or triple nucleoside regimens during the first trimester. Combined ART exposure starting later in pregnancy was not associated with increased risk. (Cohn 2015: 1600)

There is also no united opinion about antiretroviral drug toxicity to fetus. Previous guidelines underline that efavirenz is toxic, so advised not to use it during pregnancy. But recent studies have shown that there is no additional teratogenicity comparing with other ART. (Bull 2015: 275)

Caesarian section is first choice of delivery to decrease VT risk, but mode of delivery does not affect transmission if viral load is suppressed by ART. (Maarens 2014)

Aim

The aim of the study is to analyse the effect of ART during pregnancy on pregnancy complications, outcomes and neonatal period complications.

Materials and methods

Retrospective analysis of 281 HIV positive pregnant women delivery histories with diagnosis B20 ICD-10 during time period of 2010 till 2016 in Riga Maternity hospital archive and statistics were performed. Data about patients age, prior pregnancies, deliveries and abortions, antenatal care, ART, pregnancy complications, delivery term, delivery type and comorbidities, as well as information about newborns sex, birth weight, height, head and chest circumference, Apgar score (at 1, 5 and 10 minutes after birth), congenital abnormalities and neonatal complications were collected using patients medical records. Obtained data was processed and statistically analyzed in Microsoft Excel 2013 and IBM SPSS version 22 programs. The normality of data distribution was

assessed using Shapiro–Wilk test. Data was analyzed using Pearson's Chi square test and Student's t-test. The significance threshold was set at 0.05.

Results

ART during pregnancy received 185 women, 51 haven't received ART and in 45 cases there was no information about ART during pregnancy. The mean age of women who received ART was similar to women who didn't receive ART (28.29 years vs. 28.57 years). It is statistically significant that women who received ART during pregnancy had antenatal care (ANC) more frequently (n=181, 97.8% vs n=20, 39.2%; p<0.0005) and earlier (M=11.9 week vs M=17.4 week; p=0.001). It was observed that women, who received ART during pregnancy also more often received ART before pregnancy (n=26, 23.4% vs n=2, 5.4%; p=0.015). There was no significant difference in pregnancy related complications between the groups (with ART vs without ART: n=171, 92.4% vs n=47, 94%; p>0.05). Intrauterine growth restriction more frequent occurred in women without ART (with ART vs without ART: n=33, 17.8% vs n=14, 27.5%), but this observation also was not significant (p>0.05). There were observed difference in delivery type associated with receiving of ART (p<0.0005). 111 (60%) patients with ART vs 11 (22%) patients without ART had elective Caesarian section (CS); 48 (25.9%) vs 15 (30%) had emergency CS. 18 (9.7%) vs 22 (44%) had physiologic delivery and 8 (4.3%) vs 2 (4%) had pathological vaginal delivery.

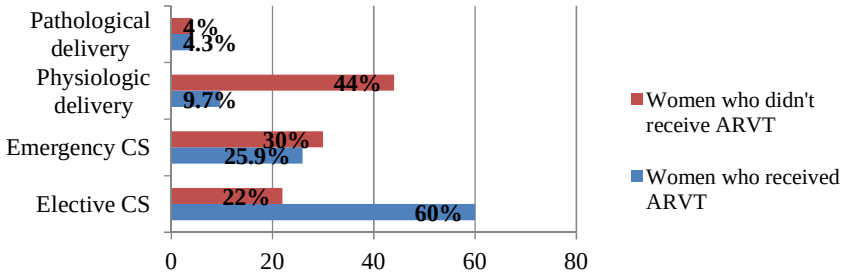

Figure 1. **Frequencies of delivery types associated with receiving of ART, %**

There were no statistical significance in preterm birth within the groups (with ART vs without ART: n=24, 13% vs n=10, 19.6%; p>0.05), furthermore there were no association between prematurity and trimester when ART was initiated. There were observed that the rate of congenital abnormalities are not associated with exposure of ART (p>0.005) Mean value of length (with ART vs without ART: M=50.27 vs M=49.08 cm; p=0.039), head circumference (M=34.03 vs M=33.58 cm; p=0.046) and chest circumference (M=32.63 vs M=31.86 cm; p=0.04) were higher in newborns of mothers, who received ART during pregnancy.

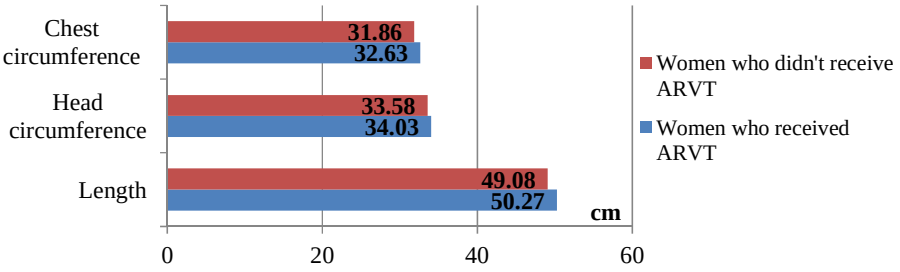

Figure 2. **Mean length, chest and head circumference of newborns, cm**

Neonatal period complication rate were lower in patient group with ART during pregnancy (n=86, 46.5% vs n=32, 64%; p=0.028). There are also found that there is difference in rate of neonatal period complications associated with receiving ART before pregnancy (with vs without ART before pregnancy: n=8, 29.6% vs n=61, 50.8%; p=0.046). In patient group without ART more often were observed such co-morbidities as alcohol abuse (11.8% vs 1.6%; p=0.004) and drug abuse (45.1% vs 22.2%; p=0.001). Among all HIV positive pregnant women the most common comorbidities were hepatitis C (n=111, 47%), sexually transmitted diseases (n=66, 28%) and drug abuse (n=64, 27.1%).

Discussion

In past years there were concerns about ART, because of findings of Swiss (Lorenzi *et al*. 1998) and several others studies (Boer *et al*. 2007; Townsend *et al.* 2007; Grosch-Woerner *et al*. 2008), which reported high prematurity rates in women on ART. Our study didn't detect an association between ART and prematurity, furthermore few other studies (Tuomala *et al*. 2002; Tuomala *et al*. 2005) have reported similar results. These findings show that there may be other undetected risk factors for prematurity that could be related to limited observational data. In other studies where found that such factors as maternal age, CD4+ T-lymphocyte cell count less than 200 cells/mm3 and use of injecting drugs have association with preterm delivery (Martin *et al.* 2009). In a meta-analysis of 13 cohorts highly active antiretroviral therapy (HAART) compared with no therapy was not associated with preterm delivery, but there were association if HAART was started before or during the first trimester (Kourtis *et al.* 2007). Our study didn't reveal an association between prematurity and trimester of ART initiation. Past reports that are similar to our findings shows that substance use is inversely associated with receiving ART (Sohler *et al.* 2007; Rough *et al.* 2015). Because substance use can affect treatment outcomes, it may be an important factor influencing ART safety. Numbers of studies have been made due the concern of teratogenic

potential of certain antiretroviral medications, but in our study were observed that there is no association between ART during pregnancy and congenital abnormalities.

Conclusions

Use of ART during pregnancy is important aspect of antenatal care of HIV infected women. There is association between ART and the choice of delivery type. ART during pregnancy is important for neonatal complication reduction.

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MORPHOLOGICAL AND CLINICAL CHARACTERISTICS IN PATIENTS WITH PRIMARY MYELOFIBROSIS

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Abstract

Morphological and clinical characteristics of patients with primary myelofibrosis

Key words: *bone marrow, myelofibrosis, megakaryocytes, cellularity, trephine biopsies*

Background: Primary myelofibrosis is rare hematological disease in which atypical megakaryocytes and granulocytes proliferate in bone marrow causing formation of fibrous tissue. PM clinical signs include hepatomegaly, splenomegaly, anemia, leukopenia or leukocytosis and thrombocytopenia or thrombocytosis. The aim of the study was to determine morphological and clinical findings in patients with primary myelofibrosis.

Methods: In retrospective study morphological data of bone marrow trephine biopsies, clinical blood count and visual diagnostic tests were evaluated in 130 patients with PM. Selected patients had bone marrow trephine biopsy performed in Riga Eastern Clinical University Hospital between 2010 and 2015.

Results: Of 130 patients 60 (46,2%) were males and 70 (53,8%) females. Average age was 67,1 years. In 73 (56,2%) cases PM was diagnosed in fibrotic stage, while in 57 (43,8 %) cases in pre-fibrotic stage.

Atypical, hyperlobulated megakaryocytes were observed in 69 (55,1%) cases, atypical, hyperlobulated and hypolobulated megakaryocytes in 42 (32,3%) cases and atypical hypolobulated megakaryocytes in 15 (11,5%) cases. Cluster forming megakaryocytes were found in 108 (83,1%) cases, while diffuse placement was found in 22 (16,9%) cases.

Hypocellularity was observed in 13 (10%), normocellularity in 39 (29,9%) and hypercellularity in 78 (60,1%) cases. Following stages of myelofibrosis was recognized: MF0 44 (33,8%), MF1 23 (17,7%), MF2 38 (29,2%), MF3 25 (19,2%).

In radiological studies splenomegaly was detected in 111 cases with average spleen size of 18,3 cm. Hepatomegaly was found in 26 cases with average liver size of 16,1 cm.

Conclusions: Statistical analysis demonstrated significant variations in clinical findings depending on stage of the disease.

- Negative correlation was found between extent of fibrosis in bone marrow and red blood cell, white blood cell and platelet count. Weak negative correlation was observed between extent of fibrosis and hemoglobin level.
- Most frequently disease is diagnosed in fibrotic stage

Kopsavilkums

Morfoloģiskās un klīniskās pazīmes pacientiem ar primāro mielofibrozi

Atslēgas vārdi: *kaulu smadzenes, mielofibroze, megakariocīti, celularitāte, trepānbiopsija*

Ievads: Primārā mielofibroze ir reta hematoloģiska saslimšana kuras gaitā atipiski megakariocīti un granulocīti proliferē kaulu smadzenēs izraisot fibrozi. Primārās mielofibrozes klīniskā aina raksturojas ar hepatomegāliju, splenomegāliju, anēmiju, leikopēniju vai leikocitozi un trombocitopēniju vai trombocitozi. Pētījuma mērķis ir raksturot morfoloģisko ainu un klīnisko atradi pacientiem ar primāro mielofibrozi.

Materiāli un metodes: Retrospektīvā pētījumā tika apkopoti 130 pacientu morfoloģiskie, klīniskie un laboratoriskie dati, kam tika veikts kaulu smadzeņu trepānbiopsijas izmeklējums Rīgas Austrumu klīniskās universitātes slimnīcas Hematoloģijas centrā laika posmā no 2010. līdz 2015. gadam.

Rezultāti: 60 (46,2%) no 130 pacientiem bija vīrieši un 70 (53,8) sievietes. Vidējais vecums bija 67,1 gads. 73 (56,2%) gadījumos primārā mielofibroze tika diagnosticēta fibrotiskajā stadijā, kamēr 57 (43,8%) gadījumu pre-fibrotiskajā stacijā.

Hipercelularitāti konstatēja 13 (10%) gadījumu, normocelularitāti 39 (29,9%) gadījumu un hipocelularitāti 78 (60,1%) gadījumu. Pētījumā atzīmēja sekojošas PM stadijas: MF0 44 (33,8%), MF1 23 (17,7%), MF2 38 (29,2%), MF3 25 (19,2%) gadījumu.

Atipiski, hiperlobulēti megakariocīti tika konstatēti 13 (10%) gadījumos; atipiski, hiperlobulēti un hipolobulēti megakariocīti 42 (32,3%); atipiski, hipolobulēti megakariocīti 15 (11,5%) gadījumu. Klasterus (*cluster*) veidojošie megakariocīti tika novēroti 108 (83,1%) gadījumu, kamēr difūzi izvietoti megakariocīti tika konstatēti 22 (16,9%) gadījumu.

Radioloģiskajos izmeklējumos splenomegālija tika atrasta 111 gadījumos, vidējais liesas izmērs kraniokaudāli – 18,3cm. Hepatomegālija tika konstatēta 26 gadījumos, vidējais aknu izmērs - 16,1cm.

Secinājumi:

- Veicot datu statistisko analīzi, apstiprinājās, ka laboratoro rādītāju lielumu atšķirība dažādās PMF stadijās ir būtiska.
- Tika atrasta negatīva korelācija starp fibrozes pakāpi kaulu smadzeņu bioptātā un eritrocītu, leikocītu un trombocītu skaitu, kā arī konstatēta vāji negatīva korelācija starp fibrozes pakāpi un hemoglobīna līmeni asinīs.
- Visbiežāk slimība tiek diagnosticēta fibrotiskajā stadijā.

Introduction

Primary myelofibrosis (PMF) is myeloproliferative disease which is characterized by initial fibrous tissue formation in bone marrow. PMF incidence in the world is relatively low this disease is included in Orphan data base. Few epidemiological studied has been made on the subject. (Moulard et al. 2014) (Orphanet 2007)

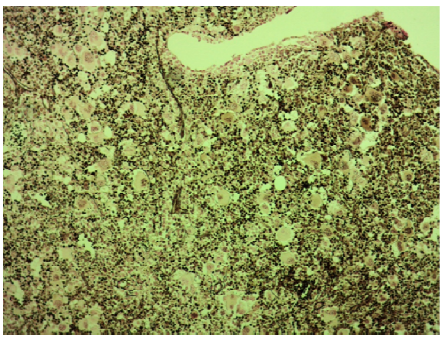
Initial stage of the disease is associated with hypercellularity in bone marrow. In later stages bone marrow becomes hypocellular. With bone marrow insufficiency extramedullar hematopoiesis is taking place in liver and spleen causing hepatomegaly and splenomegaly. In complete blood count anemia is commonly observed with WBC and PLT count ranging from leukocytopenia to leukocytosis and from thrombocytopenia to thrombocytosis. (Swerdlow et al. 2008) (Tefferi 2013) (Tefferi & Pardanani 2015)

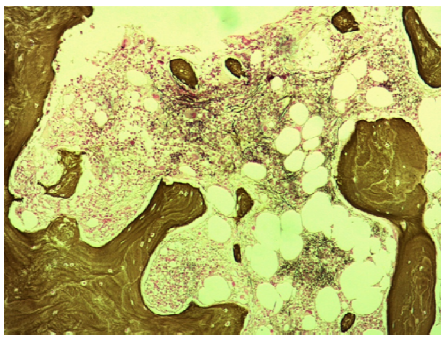
Specific factors causing PMF are unknown, however studies mention several factors that may be provoking the disease. Genetic mutations also play role in pathogenesis. (Hoermann et al. 2015) (Swerdlow et al. 2008) (Verstovsek 2010)

Life expectancy in PE patients depends on several factors. Risk assessment scores has been developed which help to predict course of disease. Leading causes of death in PMF patients are thromboembolic episodes, acute myeloid leukemia and arterial hypertension. (Bose & Verstovsek 2016) (Cervantes et al. 2006)

The aim of the study was to determine morphological and clinical findings in patients with primary myelofibrosis in Latvia. Acquired data will be compared to data found in literature.

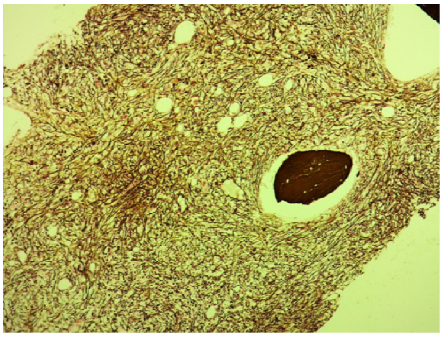
Picture 1. Bone marrow fibrosis. **MF0**. Gordon-Sweet reticulin method, 100x

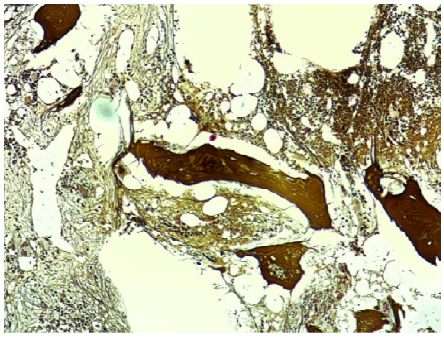




Picture 2. Bone marrow fibrosis. **MF1**. Gordon-Sweet reticulin method, 100x

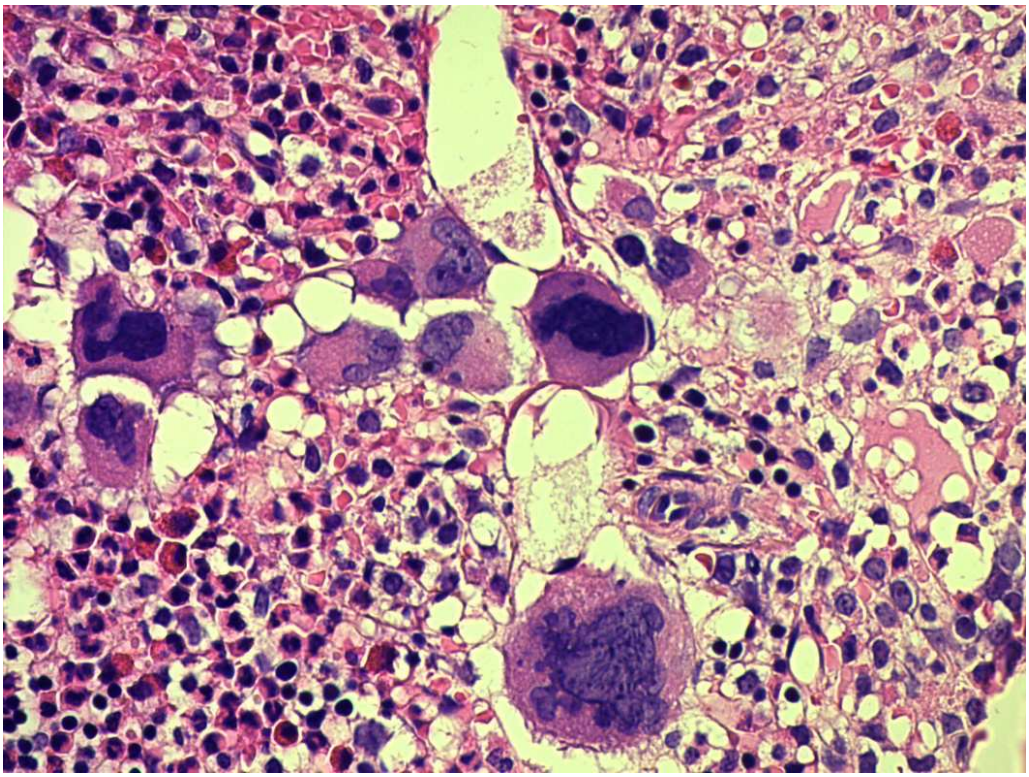
Picture 3. Bone marrow fibrosis. **MF2**. Gordon-Sweet reticulin method, 100x





Picture 4. Bone marrow fibrosis. **MF3**. Gordon-Sweet reticulin method, 100x

Picture 1 – 4. **PMF grading. Gordon – Sweet reticulin method, 100x**



Picture 5. **Atypical megakaryocytes, H&E, 400x**

Material and Methods

In retrospective study morphological data of bone marrow trephine biopsies, clinical blood count and visual diagnostic tests were evaluated in 130 patients with diagnosis primary myelofibrosis. Selected patients had bone marrow trephine biopsy performed in Riga Eastern Clinical University Hospital between 2010 and 2015. Bone marrow trephine biopsy materials

stained with hematoxylin and eosin, Giemsa and Gordon-Sweet reticulin method were selected and analyzed.

World health organization (WHO) diagnostic criteria 2008 was used (Arber et al. 2016): **World Health Organization (WHO) Diagnostic Criteria for Primary Myelofibrosis (PMF)**

Table 1. **World Health Organization (WHO) Diagnostic Criteria for Primary Myelofibrosis (PMF)**

Primary Myelofibrosis (PMF)	Major criteria	Minor criteria
Proliferation and atypia of megakaryocytes accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 on a scale of 0 to 3	•	
Not meeting WHO criteria for ET, PV, BCR-ABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasm	•	
Presence of JAK2, CALR or MPL mutation or in the absence of these mutations, presence of another clonal marker or absence of reactive myelofibrosis	•	
Anemia not attributed to a comorbid condition		•
Leukocytosis $\geq 11 \times 10^9$ /L		•
Palpable splenomegaly		•
LDH increased to above upper normal limit of institutional reference range		•
Leukoerythroblastosis		•
Diagnosis requires meeting all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations		

During morphological evaluation of megakaryocytes following classification was used to describe megakaryocyte size:

- small
- small-medium
- medium-large
- large

Bone marrow cellularity was evaluated by certified pathologist.

Grading of fibrosis in bone marrow trephine biopsies was assessed using following classification: **Consensus on the grading of myelofibrosis (MF)** (Thiele et al. 2005)

Table 2. **Consensus on the grading of myelofibrosis (MF)**

Grading	Description
MF0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow
MF1	Loose network of reticulin with many intersections, especially in perivascular areas
MF2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

Clinical parameters were evaluated using complete blood count, where white blood cell, red blood cell, platelet count and hemoglobin levels were taken in consideration:

Table 3. **Complete blood count with reference intervals**

Complete blood count	Reference interval	Units
WBC	4 – 9	(10^3/μL)
RBC	4 – 5,5	(10^6/ μL)
Hemoglobin level	130 - 165	g/L
Platelet count	150 - 400	(10^3/ μL)

Ultrasound and computer tomography data was used to determine liver and spleen size. Liver was measured and hepatomegaly diagnosed if right lobe size exceeded 13cm. Spleen was measured in craniocaudally and splenomegaly was diagnosed if spleen size exceeded 11cm.

Data acquired during process was analyzed using biological statistics methods. Normal distribution was calculated and taken into consideration selecting statistic methods. In descriptive statistics arithmetic mean and standard deviation was used for data with normal distribution. For other data median and quartile dispersion was used. Pearson χ^2, Fisher's exact test and Spearman correlation was applied. Data was analyzed using *IBM SPSS* and *Microsoft Excel* software.

Results

Of 130 patients 60 (46,2%) were males and 70 (53,8%) females. Average age was 67,1 years. Number of cases studied from each year: 2010 – 17; 2011 – 19; 2012 – 22; 2013 – 31; 2014 – 26; 2015 (until October) – 15.

In 73 (56,2%) cases PMF was diagnosed in fibrotic stage and in 57 (43,8%) cases in pre-fibrotic stage.

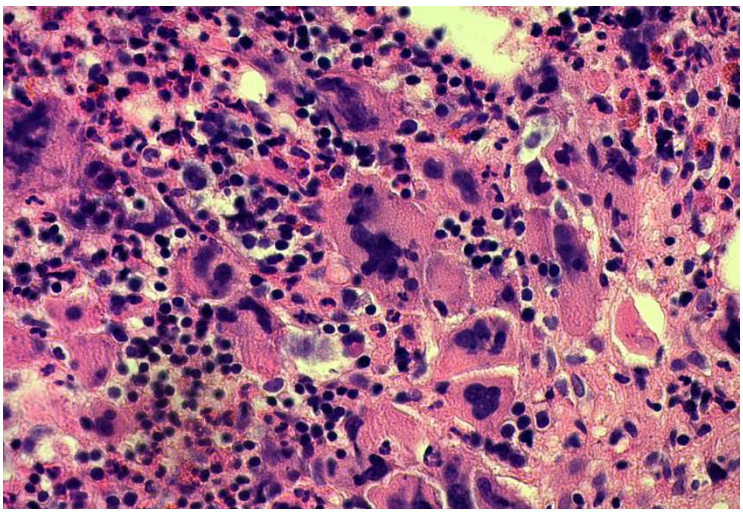
Total

Atypical hyperlobulated megakaryocytes were observed most frequently – in 69 (53,1%) cases. Atypical hyperlobulated and atypical hypolobulated megakaryocytes in same biopsy were found in 42 (32,3%) cases. In 15 (11,5%) of cases atypical hypolobulated megakaryocytes were recognized. In 2 (1,5%) cases atypical hyperlobulated and normal megakaryocytes were observed. Atypical hypolobulated and normal megakaryocytes were found in 2 (1,5%) cases (see graph 1).

Megakaryocyte distribution by size (see graph 2):

- Small - 12 (9,3%)
- Small-medium - 33 (25,6%)
- Medium-large - 9 (6,2%)
- Large - 5 (3,9%)
- Different size - 71 (55%)

In 108 (83,1%) cases megakaryocytes were grouped in clusters and in 22 (16,9%) cases diffuse placement was found.



Picture 6. **Cluster forming, atypical MKC. H&E, 400x**

Hypercellularity was found in 13 (10%) of cases, normocellularity in 39 (29,9%) and hypocellularity – in 78 (60,1%) of cases.

Following myelofibrosis grades were observed (see graph 3):

- MF0 – 44 (33,8%)
- MF1 – 23 (17,7%)
- MF2 – 38 (29,2%)
- MF3 – 25 (19,2%)

Splenomegaly was found in 111 patients with median spleen size craniocaudally 18,3 cm. Hepatomegaly was diagnosed in 26 cases with median liver size of 16,1 cm.

Blood tests were acquired for 129 patients:

Table 4. **Complete blood count in 129 patients**

Complete blood count	Minimum	1. quartile	Median	3. quartile	Maximum	Units
RBC	1,35	2,78	3,8	4,33	7,38	$x10^6$/ µL
WBC	0,66	5,55	8,8	14,95	67,0	$x10^3$/µL
PLT	17,0	133,5	293	625	2740	$x10^3$/µL
Hb	39	85	105	123	178	g/L

Pre-fibrotic stage

56 patients were diagnosed in pre-fibrotic stage. Average age in this group was 67,9 years. 27 (48,2%) were males and 29 (51,8%) females.

Atypical hyperlobulated megakaryocytes were observed in 36 (64,3%) cases. Atypical hyperlobulated and atypical hypolobulated megakaryocytes were found in 13 (23,2%) cases. In 1 (1,8%) case atypical hyperlobulated and normal megakaryocytes were observed. Atypical hypolobulated and normal megakaryocytes were found in 1 (1,8%) case (see graph 1).

Megakaryocyte distribution by size (see graph 2):

- Small - 3 (5,4%)
- Small-medium – 13 (23,2%)
- Medium-large - 4 (7,1%)
- Different size - 36 (64,3%)

In 52 (92,9%) cases megakaryocytes were grouped in clusters and in 4 (7,1%) cases diffuse placement was found.

Hypercellularity was found in 13 (10%) of cases, normocellularity in 39 (29,9%) and hypocellularity – in 78 (60,1%) of cases.

Following myelofibrosis grades were observed (see graph 3):

- MF0 – 36 (64,3%)
- MF1 – 19 (33,9%)
- MF2 – 1 (1,8%)

Splenomegaly was found in 40 (71,4%) patients with median spleen size 17 cm. Hepatomegaly was diagnosed in 8 (14,3%) cases with median liver size of 16,3 cm.

Complete blood count in patients with pre-fibrotic PMF

Table 5. **Complete blood count in patients with pre-fibrotic PMF**

Complete blood count	Minimum	1. quartile	Median	3. quartile	Maximum	Units
RBC	1,35	2,91	3,99	4,46	7,38	$x10^6$/ μL
WBC	1,40	6,0	11,5	20,87	46,93	$x10^3$/μL
PLT	18,0	176,8	406,5	823	2740	$x10^3$/μL
Hb	39	87,25	110	126,5	156	g/L

Fibrotic stage

73 patients were diagnosed in fibrotic stage. Average age in this group was 66,9 years. 32 (43,8%) were males and 41 (56,2%) females.

Atypical hyperlobulated megakaryocytes were observed in 33 (45,2%) cases. Atypical hyperlobulated and atypical hypolobulated megakaryocytes were found in 28 (38,4%) cases. In 10 (13,7%) of cases atypical hypolobulated megakaryocytes were recognized. In 1 (1,4%) cases atypical hyperlobulated and normal megakaryocytes were observed. Atypical hypolobulated and normal megakaryocytes were found in 1 (1,4%) cases (see Fig. 1).

Megakaryocyte distribution by size (see Fig. 2):

- Small - 9 (12,3%)
- Small-medium - 20 (27,4%)
- Medium-large - 4 (5,5%)
- Large - 5 (6,8%)
- Different size - 35 (47,9%)

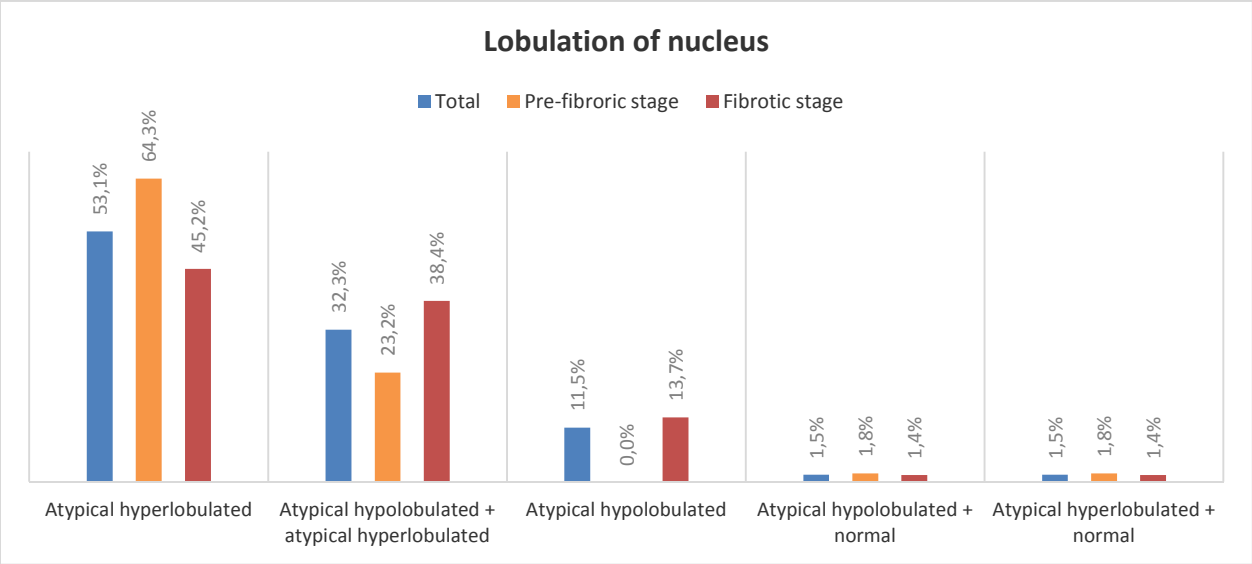


Figure 1. **Lobulation of nucleus**

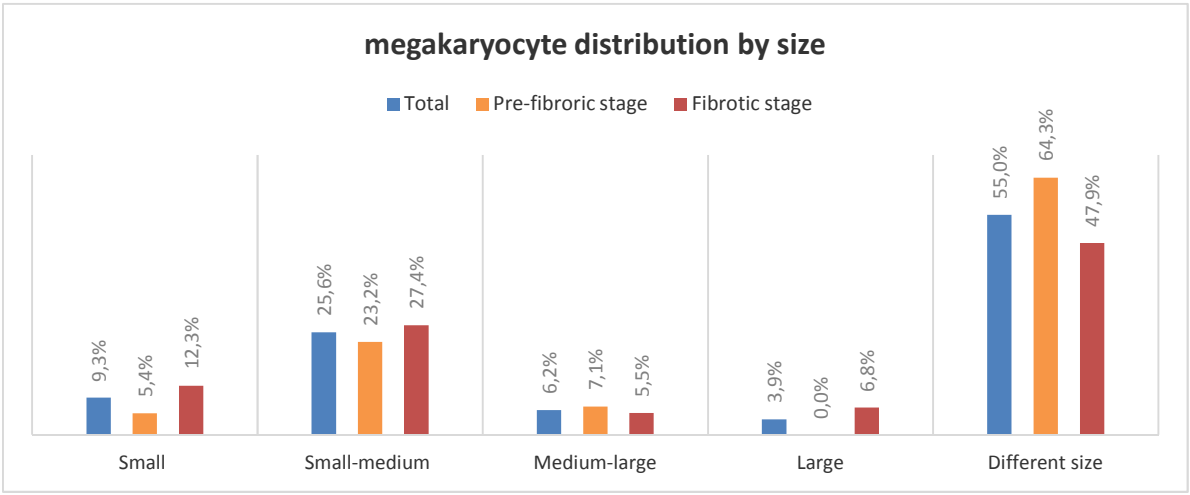


Figure 2. **Megakaryocyte distribution by size**

In 56 (76,7%) cases megakaryocytes were grouped in clusters and in 17 (23,3%) cases diffuse placement was found.

Following myelofibrosis grades were observed (see Fig. 3):

- MF0 – 7 (9,0%)
- MF1 – 4 (5,5%)
- MF2 – 37 (50,7%)
- MF3 – 25 (34,2%)

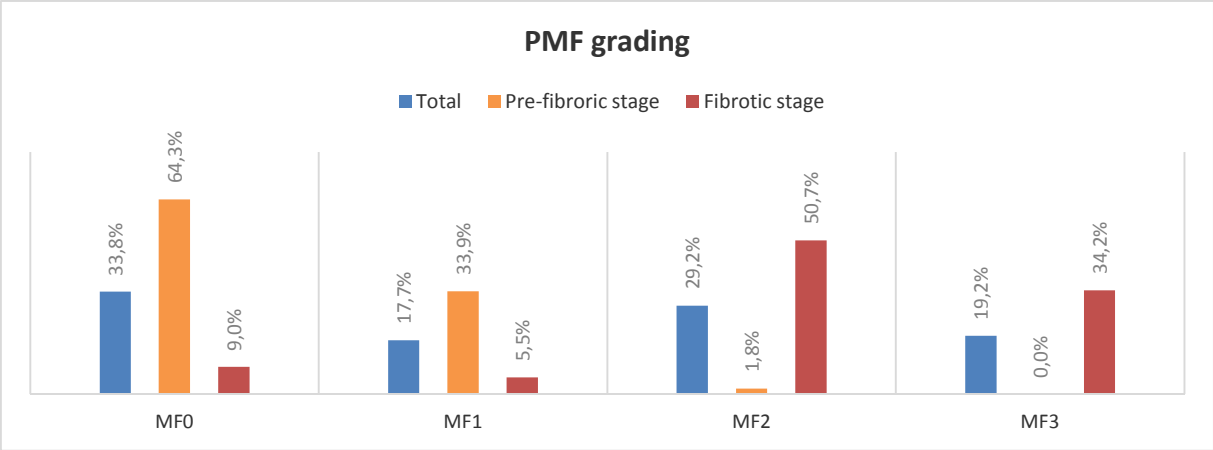


Figure 3. **PMF grading**

Splenomegaly was found in 43 (58,9%) patients. Hepatomegaly was diagnosed in 19 (26%) cases.

Complete blood count in patients with fibrotic PMF

Table 6. **Complete blood count in patients with fibrotic PMF**

Complete blood count	Minimum	1. quartile	Median	3. quartile	Maximum	Units
RBC	1,58	2,66	3,53	3,96	7,3	$x10^6$/ µL
WBC	0,66	5,01	7,1	13,05	67,0	$x10^3$/µL
PLT	17,0	129	250	453	1791	$x10^3$/µL
Hb	43	82,5	99	117	178	g/L

Statistical analysis

Statistical analysis showed negative correlations between PMF grade and RBC count (p=0,11; r= -0,224), WBC count (p= 0,018; r= -0,208) and platelet count (p= 0,005; r= -0,248). Weak negative correlation was observed between PMF grade and Hb level (p= 0,038; r= -0,183).

Discussion

PMF is included in *Orphanet* database for rare diseases. *Orphanet* reports incidence of 9 cases per 100 000 per year, however *Moulard et. al***.** reports that PMF incidence in European Union is 0,3 cases per 100 000 persons per year. This difference may be explained by fact, that not in all cases primary myelofibrosis is differentiated from secondary myelofibrosis. According to collected data there were 130 PMF cases over 5 years – approximately 1,3 cases per 100 000 per year. (Orphanet 2007) (Moulard et al. 2014)

Moulard et al. also points out small number of studies done on primary myelofibrosis epidemiology – only 6 journal articles and 4 internet databases. Latest publications mention 4-year ongoing research in Lithuania, although this study is still in progress and no data has been published about PMF epidemiology in Lithuania yet.

Primary myelofibrosis is usually diagnosed in sixth or seventh decade of life. In Europe average age when PMF is diagnosed is 69-76 years. **Invalid source specified. Invalid source specified.** According to this study in Latvia average age of PMF patients is 67 years. *Rava et al.* concludes that approximately 22% of PMF patients are younger than 56 years. In this study 20,2% of patients were younger than 60 years, youngest patient was 28 years old.

One of WHO criteria for primary myelofibrosis is JAK2 mutation. None of patients included in this study had been tested for JAK2 mutation. According to WHO criteria, in case of negative cytogenetic testing or when testing is not possible all secondary myelofibrosis causes should be excluded. (Swerdlow et al. 2008)

In primary myelofibrosis workup bone marrow morphology, clinical signs and laboratory tests are essential. In pathology publications one of the problems mentioned is unavailability of information about patient's clinical symptoms. (Raya et al. 2014) Closer cooperation of hematologist, pathologist and radiologist should be encouraged to improve diagnostic process.

In most cases primary myelofibrosis is diagnosed in fibrotic stage. WHO reports that 60-70% of patients are diagnosed in fibrotic stage (Moulard et al. 2014). According data collected in this study situation is similar in Latvia – 56 % of patients is diagnosed in fibrotic stage of the disease.

According to literature anemia is one of the symptoms associated with PMF, while WBC and platelet count can be both increased and decreased (Reilly et al. 2012). In this study patients had anemia, WBC count was both increased and decreased and platelet count variated from thrombocytopenia to thrombocytosis.

One of the leading causes of death in primary myelofibrosis patients is thromboembolism. In literature thromboembolism in PMF patients is mentioned in 7,2-11,6% (Barbui et al. 2010) (Cervantes et al. 2006). In our data in 3,8 % patients had at least one thromboembolism episode.

Pozdnyakova et al. concludes that stage of fibrosis correlates with patient clinical signs, laboratory tests and predicts outcome of the disease (Pozdnyakova et al. 2014). In this study statistical analysis showed negative correlations between PMF grade and RBC, WBC and platelet count. Weak negative correlation was observed between PMF grade and Hb level. Study hypothesis was that stage of fibrosis correlates with patient complete blood count. During study this hypothesis was confirmed.

Conclusions

- Statistical analysis demonstrated significant variations in clinical findings depending on stage of the disease;
- Negative correlation was found between extent of fibrosis in bone marrow and red blood cell, white blood cell and platelet count. Weak negative correlation was observed between extent of fibrosis and hemoglobin level;

- Primary myelofibrosis is most often diagnosed in sixth decade;
- Most frequently disease is diagnosed in fibrotic stage;
- Anemia was commonly observed in complete blood count. WBC, PLT count varied from leukopenia to leukocytosis and from thrombocytopenia to thrombocytosis

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SPINAL CORD IMAGING IN PATIENTS WITH MS AND CORRELATION WITH LESIONS IN BRAIN AND OPTIC NERVE INVOLVEMENT

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Abstract

Spinal cord imaging in patients with MS and correlation with lesions in brain and optic nerve involvement

Key words: *multiple sclerosis, spinal cord, brain, optic neuritis, lesions, MRI*

Background: Multiple sclerosis is one of the most common immune-mediated diseases affecting CNS. Despite the fact that MS MRI findings are broadly described in literature, the relation between lesion distribution in spinal cord and brain is still unclear. The goal of the study was to analyze lesion distribution in spinal cord and correlation with brain and optic nerve involvement.

Methods: In this retrospective study MRI data of 32 patients between 01.01.2014 and 31.12.2014 with diagnosis multiple sclerosis (ICD-10 G35) was interpreted. Acquired data was statistically analyzed and categorized by lesion type, location, size and activity. Correlation was analyzed between lesions in spine, brain and optic nerve involvement.

Results: 126 spinal cord lesions were found in total, on average 3.9 (SD 2,4) per patient, with mean median lesion length of 14,4 (SD 7,3) mm. 74 (59%) lesions were detected in cervical and 52 (41%) in thoracic spinal cord. 20 (16%) lesions were active (contrast enhancing). Regarding length of lesions, most lesions (76%) compared to vertebral body were equal in size or smaller. Lateral and posterior axial distribution of lesions were predominant compared to anterior and central. 102 (81%) lesions were focal, well defined but 24 (19%) were diffuse lesions involving entire spinal cord.
A significant correlation between number of lesions and presence of optic neuritis (p=0,938, R=-0,14) or between number of lesions and presence of active lesions in the brain (p=0,895, R=0,25) was not found.

Conclusions:

- Lesions in spinal cord most frequently were found in cervical part of spinal cord at C2-C5 level.
- Involvement of lateral and posterior spinal columns was predominant compared to anterior column and central part of spinal cord in axial MRI scans.
- No significant correlation was detected between number of lesions in spinal cord and number of active, enhancing lesions in brain or between number of lesions in spinal cord and optic neuritis.

Kopsavilkums

Muguras smadzeņu bojājumu magnētiskās rezonanses raksturojums multiplās sklerozes pacientiem un to korelācija ar galvas smadzeņu un redzes nervu bojājumiem

Atslēgas vārdi: *multiplā skleroze, muguras smadzenes, optiskais neirīts, galvas smadzenes, perēkļi, MR*

Ievads: Multiplā skleroze ir viena no biežākajām autoimūnajām saslimšanām, kas skar CNS. Neskatoties uz to, ka MR atrade MS gadījumā literatūrā ir plaši aprakstīta, trūkst datu par perēkļu savstarpējo saistību galvas un muguras smadzenēs. Pētījuma mērķis ir raksturot patoloģiskos bojājumus muguras smadzenēs un noteikt to iespējamo saistību ar perēkļiem galvas smadzenēs, to aktivitāti un redzes nervu bojājumiem.

Materiāli un metodes: Retrospektīvā pētījumā tika apkopoti MR izmeklējumu dati 32 pacientiem ar multiplo sklerozi (SSK-10 G35) laika posmā no 01.01.2014 līdz 31.12.2014. Ievāktie dati tika statistiski analizēti un sadalīti kategorijās pēc perēkļu veida, izmēra un aktivitātes. Tika veikta korelācijas analīze starp bojājumiem muguras smadzenēs, galvas smadzenēs un optiskā nerva iesaisti.

Rezultāti: Kopumā atrasti 126 bojājumi, kas ir vidēji 3,9 bojājumi (SD 2,4) uz 1 pacientu. Bojājumu vidējais garums bija 14,3 (SD 7,3) mm. 74 (59%) bojājumi atradās cervikālajā daļā, bet 52 (41%) torakālajā daļā. 20 (16%) bojājumu bija aktīvi (kontrastvielu krājoši). Lielākā daļa (76%) bojājumu bija 1 muguras skriemeļa garumā vai īsāki. Aksiālā plaknē bojājumi biežāk atradās laterālajos 63 (74%) un mugurējos 44 (52%) stabos salīdzinājumā ar priekšējiem 22 (15%) stabiem un centrālo daļu 33 (22%). 102 (81%) bojājumu bija fokāli, labi norobežoti, bet 24 (19%) saplūstoši.
Netika atrasta nozīmīga korelācija starp bojājumu skaitu muguras smadzenēs un optisko neirītu (p=0,938, R=-0,14), kā arī starp bojājumu skaitu muguras smadzenēs un bojājumu skaitu galvas smadzenēs (p=0,895, R=0,25).

Secinājumi:

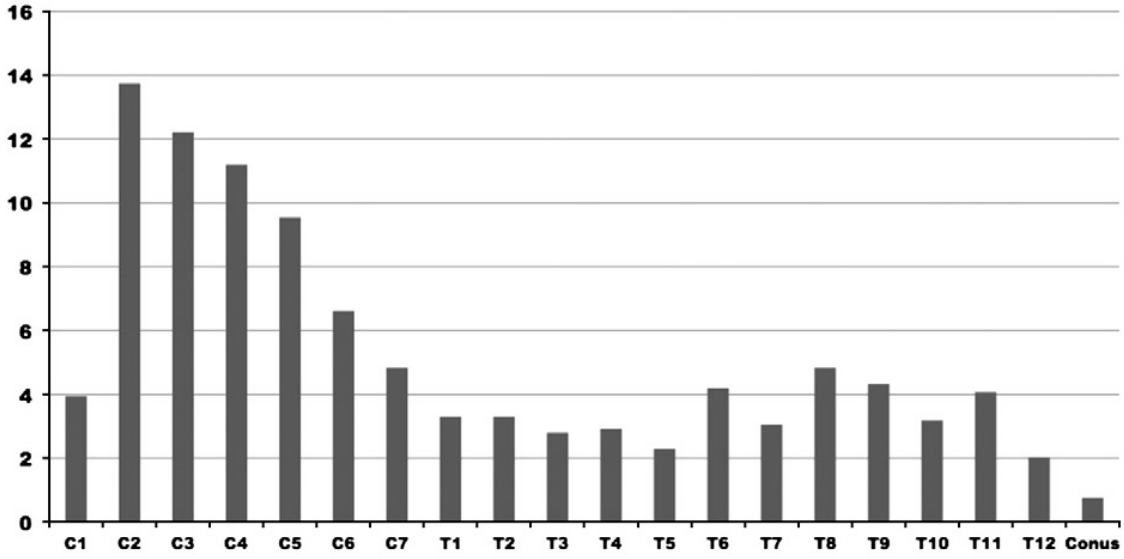
- Lielākā daļa bojājumu atradās muguras smadzeņu kakla daļā C2-C5 līmenī.
- Biežāk tika skarti muguras smadzeņu laterālie un mugurējie stabi, salīdzinājumā ar priekšējiem stabiem un centrālo daļu.
- Netika atrasta stingra korelācija starp bojājumu skaitu muguras smadzenēs un aktīvu, kontrastvielu krājošu perēkļu skaitu galvas smadzenēs, kā arī starp bojājumu skaitu muguras smadzenēs un optisko neirītu.

Introduction

Multiple sclerosis (MS) is common, chronic immune-mediated disease that affects central nervous system. The estimated number of people with MS in the world is 2,5 million. (World Health Organization 2008) (Hersh & Fox 2014) In MS immune system damages myelin sheath of axons causing array of neurological symptoms. Common symptoms in MS include sensory loss and paresthesia, muscle cramps, bladder, bowel and sexual dysfunction, cerebellar symptoms, optic neuritis, etc. (DH Miller et al. 2008) (Scolding 2001) (Bastianello et al. 2000). Etiology in MS is unknown, however genetic predisposition together with trigger factors (virus infection, vitamin D deficiency, etc.) may provoke onset of the disease. After appearance of first symptoms self-sustained immune process is established (National Multiple Sclerosis Society 2015).

MRI is golden standard in MS diagnosis. MRI findings are positive in 95% of MS patients. MRI is used in workup, to monitor clinical development over time and to verify therapy results (Ge 2006) (Gass et al. 2015).

Lesions in cervical part of spinal cord, especially at C2 level are observed more frequently than lesions in thoracic part **Invalid source specified.Invalid source specified.**. In *Wei Qiu, et al.* study 61,7% of lesions were located in several segments of spinal cord, 30,6% in cervical part, 7,2% in thoracic part and 0,4% in cerebellum **Invalid source specified.** In *Weier et al.* study 59% of focal lesions were located in cervical part of spinal cord and in 16% of cases lesions were found only in cervical part of spinal cord (Weier et al. 2012).



Picture 1. **Lesion distribution in spinal cord. Measured in sagittal plane**. (Qui et al. 2011)

Weier et al. research on lesion distribution in spinal cord columns measured in axial plane report following results: 33-35% of lesions were located in lateral columns, 26% of lesions were found in posterior column, 4% in central part of spinal cord and 2% in anterior column (Weier et al. 2012). Lesion size measured in sagittal plane is less than 1 vertebral body (Qui et al. 2011).

Despite the fact that MS MRI findings are broadly described in literature, the relation between lesion distribution in spinal cord and brain is still unclear. The goal of the study was to analyze lesion distribution in spinal cord and correlation with active lesions in brain and optic nerve involvement.

Material and Methods

In retrospective study MRI data and radiology reports of patients with multiple sclerosis (ICD-10 G35) between 01.01.2014 and 31.12.2014 were analyzed. Data was acquired from Riga Eastern Clinical University Hospital (RECUH) data base. MRI archive data was accessed and analyzed for spinal cord lesion size, location and activity. Data describing brain lesions, lesion activity and cranial nerve neuritis was obtained from radiology reports using "Ārsta birojs" database. 32 patients met criteria and were included in the study. Patient inclusion criteria:

- Proven multiple sclerosis (ICD-10 G35)
- MRI performed with standard MS protocol
- Lesions found in spinal cord

Parameters analyzed in spinal cord MRI:

- Lesion location
- Lesion size craniocaudally in mm (in sagittal plane)
- Lesion size compared to vertebral bodies (in sagittal plane)
- Lesion anterior-posterior (AP) size (in axial plane)
- Lesion lateral size (axial plane)
- Affected spinal cord columns (anterior, posterior, central and lateral)
- Lesion characteristics (focal or diffuse)
- Enhancement
- Total number of focal lesions

MRI standard protocol used in image acquisition:

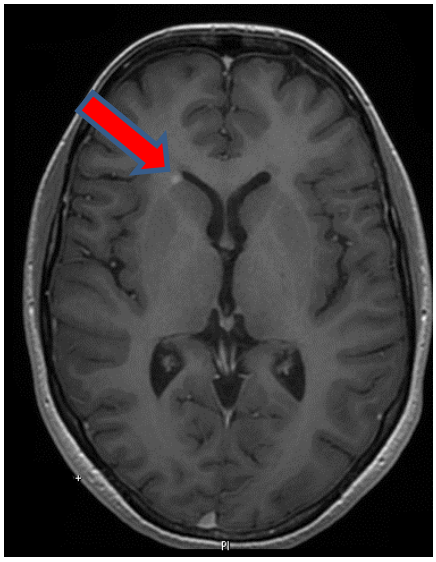
- T1 SE/FLAIR sagittal post contrast
- T2 FSE sagittal
- T2 STIR sagittal
- T2 Gradient-echo (MERGE) axial.

Data acquired from "Ārsta birojs" database:

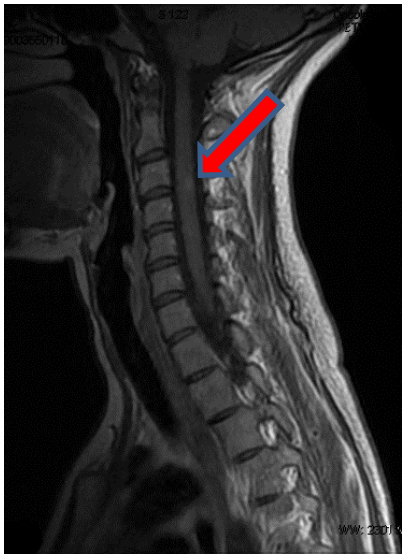
- Gender
- Age
- MS form (cerebrospinal; cerebral; spinal)

- MS type (Relapsing-Remitting; Secondary-Progressive; Primary-Progressive; Progressive-Relapsing)
- Brain involvement (no lesions in brain; non-enhancing lesions in brain; enhancing lesions in brain)
- Optic neuritis (negative; unilateral; bilateral)

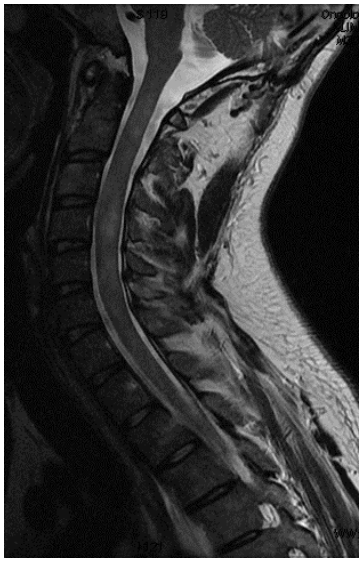
Data was statistically analyzed using *Microsoft "Excel 2016"* un *IBM "SPSS Statistics" V.22*



Picture 2. **Active, enhancing lesion in white matter, in periventricular region (axial, post contrast T1 IR FSPGR)**



Picture 3. **Single enhancing lesion in cervical part of spinal cord at C3/C4 level (+c T1 FLAIR sagittal)**



Picture 4. **Diffuse lesions in cervical part of spinal cord (FRFSE)**

Results

Of 32 patients 20 (63%) were females and 12 (37%) males. Patient age ranged from 18 to 60 with average age of 40 (SD 2) years.

All patients had lesions in brain. Information about MS clinical type was available for 20 (63%) patients. 15 patients had relapsing-remitting MS, 3 had secondary-progressive MS and 1 patient had primary-progressive MS.

Active, enhancing lesions was observed in 9 (28%) cases. Unilateral neuritis was diagnosed in 10 (31%) cases and bilateral neuritis also in 10 (31%) cases; in 12 (38%) cases optic neuritis was not diagnosed.

Lesions in spine were evaluated from upper part of C1 to Th12/L1 margin. In 4 (13%) cases lesions were diagnosed only in cervical part of spinal cord, 3 (9%) only in thoracic part. In 25 (78%) cases lesions were located both in cervical and in thoracic part. In 11 (34%) enhancing lesions were observed.

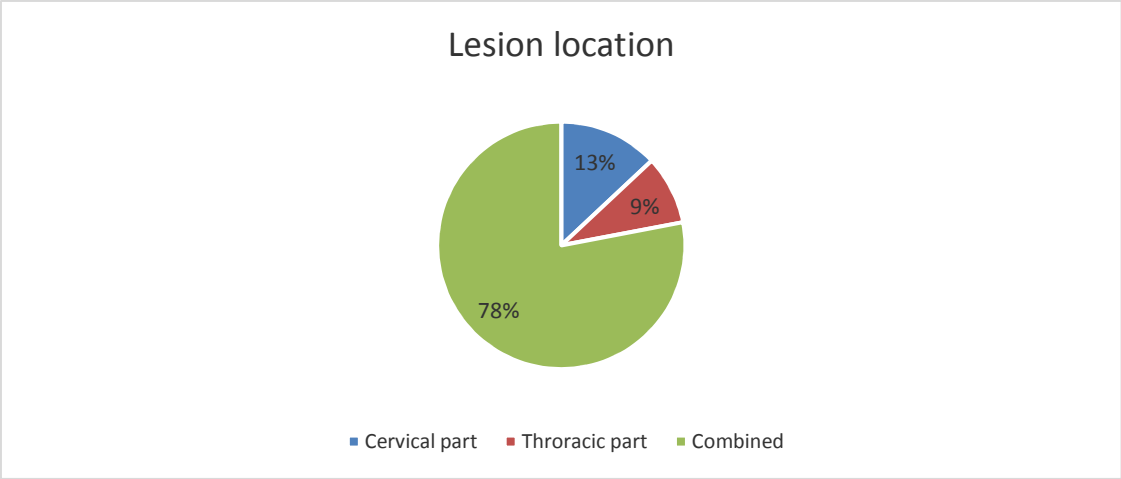


Figure 1. **Lesion location**

126 lesions were found in total with average of 3,9 (SD 2,4) lesions per patient. 74 (59%) lesions were located in cervical part and 52 (41%) in thoracic part of spinal cord. In T1 post contrast 20 (16%) of lesions were enhancing. 102 (81%) were focal lesions and 24 (19%) diffuse lesions.

Average size for focal lesions was 12,4 (SD 7,3) mm. Most frequently – in 77 (76%) cases lesions were equal in size of 1 vertebral body or smaller. 85 (67%) lesions were measured in axial plane. No axial scan was performed or image quality prevented doing correct measurement in 41 (33%) lesions.

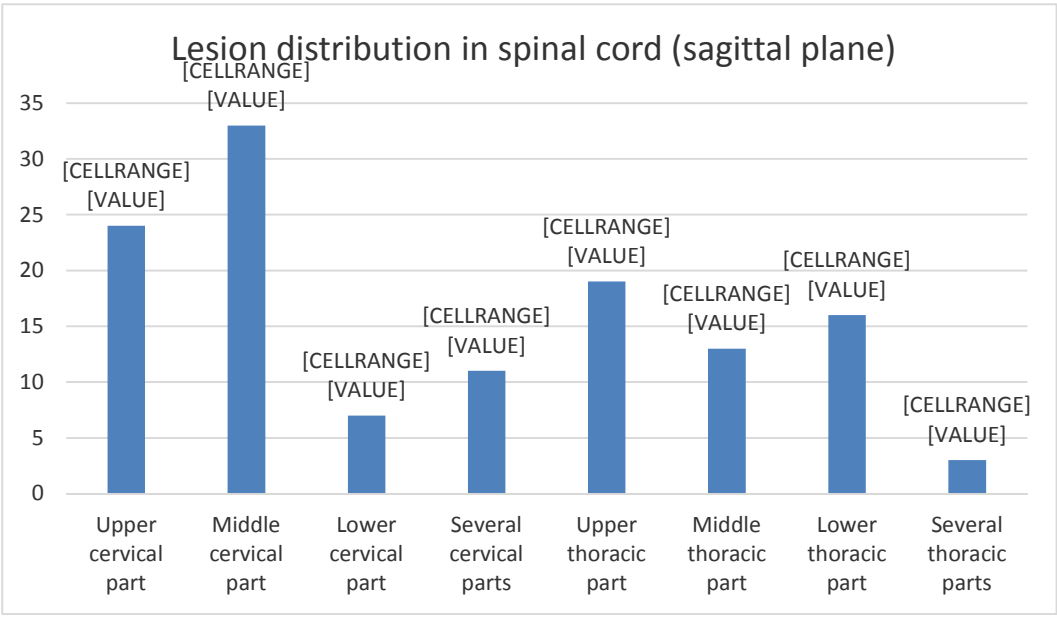


Figure 2. **Lesion distribution in spinal cord. Measured in sagittal plane**

85 lesions were measured in axial plane. 63 (74%) lesions were located in lateral columns of spinal cord, 44 (52%) in posterior column, 32 (22%) were located in central part and 22 (15%) were located in anterior column of spinal cord.

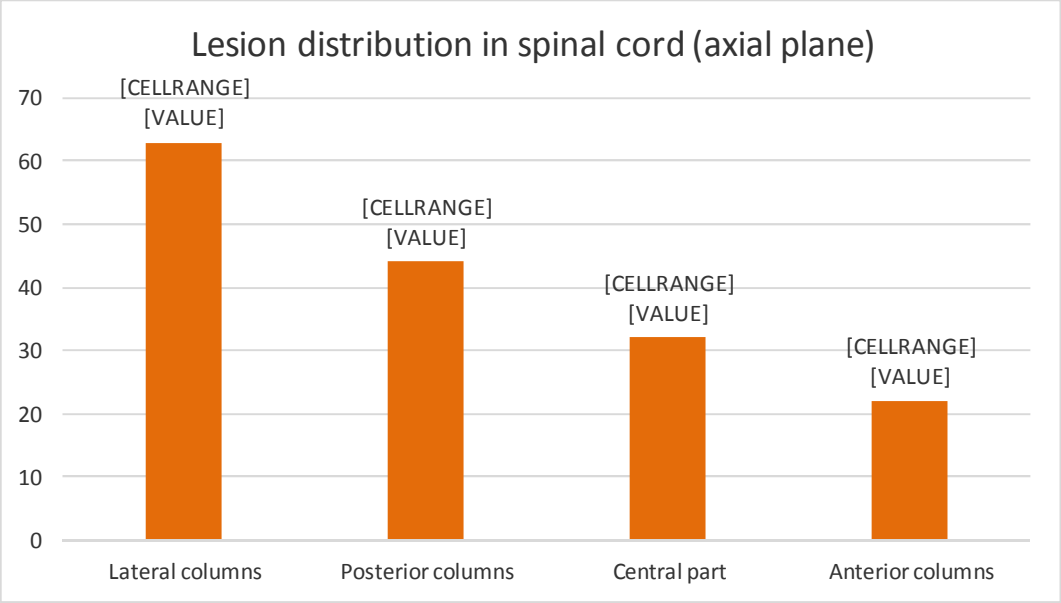


Figure 3. **Lesion distribution in spinal cord. Measured in axial plane**

Cervical part

74 lesions were observed in cervical part of spinal cord, 61 (82%) of which were focal and 13 (18%) diffuse. 9 (12%) lesions were enhancing. 24 (19%) of lesions were found in upper cervical part (C1-C2), 33 (26%) were found in middle cervical part (C3-C5) and 7 (6%) were observed in lower cervical part (C6-C7). 11 (9%) lesions affected several parts of cervical spinal cord.

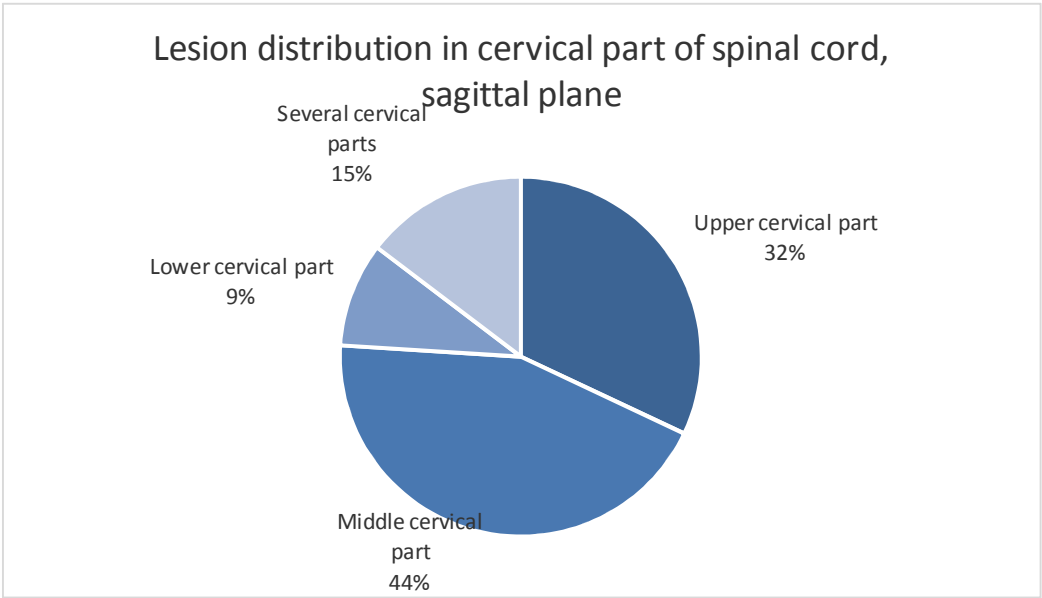


Figure 4. **Lesion distribution in cervical part of spinal cord, sagittal plane**

Average lesion size in cervical part of spinal cord measured in sagittal plane was 11,4 (SD 7,0) mm. Lesions ranged from 2 to 39 mm. Average lesion size in anterior-posterior direction measured in axial plane was 4,0 (SD 1,6) mm and ranged from 0,5 to 7,4 mm. Lesion size in lateral

direction was measured in 46 lesions with average lesion size of 5,2 (SD 2,4) mm. Size ranged from 1 to 11,4 mm.

Thoracic part

52 lesions were found in thoracic part, 41 (79%) of which were focal and 11 (21%) diffuse lesions. 11 (21%) lesions were contrast enhancing. 19 (15,1%) lesions were located in upper thoracic part of spinal cord (Th1 – Th4), 13 (10,3%) lesions were found in middle thoracic part (Th5-Th8) and 16 (12,7%) lesions were detected in lower thoracic part of spinal cord (Th9-Th12). 3 (2,3%) lesions affected several parts of thoracic spinal cord.

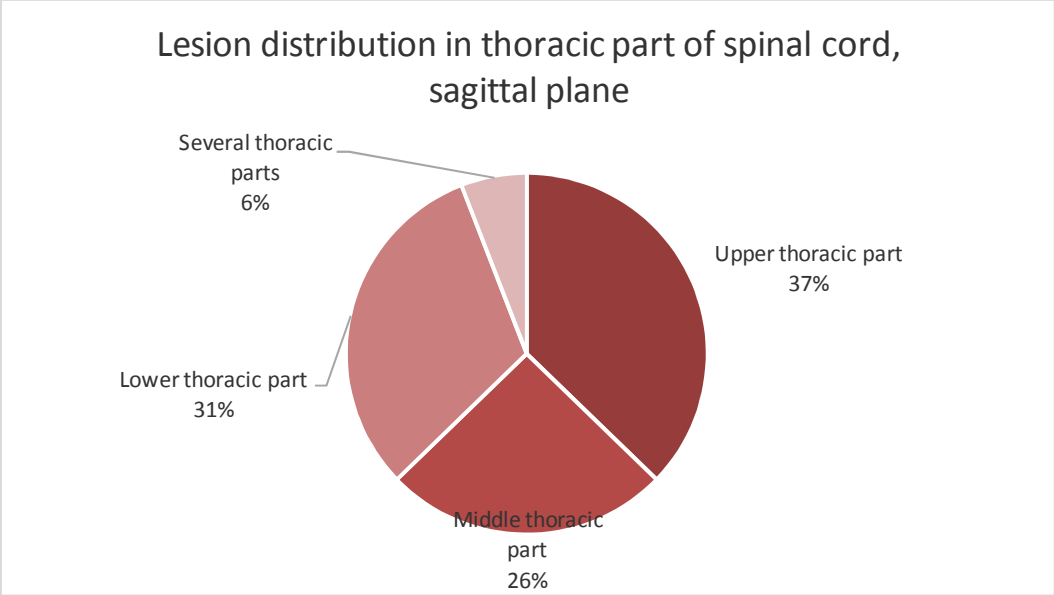


Figure 5. **Lesion distribution in cervical part of spinal cord, sagittal plane**

Average lesion size in thoracic part of spinal cord measured in sagittal plane was 13,8 (SD 7,5) mm. Lesions ranged from 2 to 34 mm. Average lesion size in anterior-posterior direction measured in axial plane was 3,4 (SD 1,1) mm and ranged from 1,3 to 6,3 mm. Lesion size in lateral direction was measured in 25 lesions with average lesion size of 4,5 (SD 1,5) mm. Size ranged from 1,8 to 7,6 mm.

Correlation between lesions in spinal cord, lesions in brain and optic nerve involvement

Statistical analysis didn't show significant correlation between number of lesion in spinal cord and optic neuritis ($p=0,938$, $R=-0,14$) or between number of lesions in spinal cord and number of enhancing lesions in brain ($p=0,895$, $R=0,25$).

Discussion

RECUH data indicates that the disease mostly affects people in middle age. Approximately 2/3 of patients were females. Average age of patients and female predisposition conforms with World Health Organization data. (World Health Organization 2008)

In study group all patients had lesions in brain – there were no cases with isolated lesions in spinal cord. That corresponds with the fact that isolated spinal cord forms are rarely observed. (Weier et al. 2012) (Bastianello et al. 2000) (Tropp et al. 1998)

Nine (28%) patients with spinal cord and brain involvement had active, enhancing lesions in brain. Optic neuritis was found in 20 (62%) cases. These numbers positively correlate with data found in literature. (Weier et al. 2012) (DH Miller et al. 2008)

In 25 (78%) cases lesions were located in both in cervical part and in thoracic part of spinal cord. Isolated lesions in cervical part were found in 4 (13%) cases and isolated thoracic lesions – on 3 (9%) cases. 126 lesions were found in 32 patients, with average of 3,9 (SD 2,4) lesions per patient. This corresponds with data from other studies (average of 1,4 - 4,2 lesions per patient) (Weier et al. 2012) (Qui et al. 2011) (Tropp et al. 1998) (Thielen & Miller 1996). Of 126 lesions 74 (59%) were observed in cervical part of spinal cord and 52 (41%) in thoracic part. This agrees with *Weier et al. study* (Weier et al. 2012). Correspondence of data indicates that mentioned distribution, multiplicity and different activity of lesions in spinal cord is typical finding in MS patients.

81 % of all lesions were focal, well defined, scar-like lesions and 19 % were diffuse, often semi-enhancing lesions.

Longitudinal length of lesions measured in height of vertebral bodies is international and standardized method for describing defects in spinal cord caused by injury, inflammation, ischemia, tumor and other cases. This method is applied in numerous international studies and allows comparison of data, course of disease and therapy results. Results acquired during this study positively correlates with data of several international studies, which demonstrates similar course of multiple sclerosis across different regions (Qui et al. 2011).

Diffuse lesions affecting entire spinal column were observed in 2 cases.

In post contrast series in 11 (34,4%) cases contrast enhancing lesions were found, which constituted 15,9% of all lesions. These figures are relatively close to figures reported by *Isabelle Trop, et al.*, where 52% patients had enhancing lesions, which constituted 14% of all lesions.

Lesions in axial plane were both local and diffuse. Often several spinal columns were affected. Data indicates that lateral columns (74,1%) and posterior column were affected mostly, while central part (21,8%) and anterior column (15%) were affected less frequently. Several other studies reported similar results.

Middle part of cervical spinal cord (C3-C5) were affected most frequently with 26% of all lesions observed in this region. 19% of lesions were located in upper cervical part (C1-C2) and 6% were located in lower cervical part (C6-C7). *Wei Qiu, et al.* reports similar comparable results - 18% of lesions located at C1-C2 level, 35% at C3-C5 level and 9% at C6-C7 level. (Qui et al. 2011)

15% of lesions were found in upper thoracic part of spinal cord (Th1-Th4), 10% in middle thoracic part (Th5-Th8) and 13% of all lesions were located in lower thoracic part of spinal cord (Th9-Th12). *Wei Qiu, et al.* reports 13% of lesions found at Th1-Th4, 14% at Th5-Th8 and 15% at Th9-Th12 level. (Qui et al. 2011)

Thus results describing lesion distribution in cervical and thoracic part of spinal cord correlates with *Wei Qiu, et al.* study results. (Qui et al. 2011)

Statistical analysis didn't show significant correlation between number of lesion in spinal cord and optic neuritis (p=0,938, R=-0,14) or between number of lesions in spinal cord and number of enhancing lesions in brain (p=0,895, R=0,25). Other studies report similar results. (Jiwon et al. 2015)

Conclusions

- Lesions in spinal cord most frequently were found in cervical part of spinal cord at C2-C5 level
- Involvement of lateral and posterior spinal columns was predominant compared to anterior column and central part of spinal cord in axial MRI scans.
- No significant correlation was detected between number of lesions in spinal cord and number of active, enhancing lesions in brain.
- No significant correlation was detected between number of lesions in spinal cord and optic neuritis.

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MASTERS BASKETBALL PLAYERS HEART RATE AS INDICATOR OF TRAINING AND COMPETITION INTENSITY

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Abstract

Masters basketball players heart rate as indicator of training and competition intensity

Key words: *heart rate, masters athletes, exercise intensity*

Introduction: Increasing count of older athletes and their desire to compete is new phenomenon around the world. One way to estimate exercise intensity is to see how often heart is beating during physical activity.

Aim: To evaluate masters basketball training and competition intensity by using players heart rate.

Materials and methods: 16 men (n = 16) participated in the study. A pulse oximeter was used to heart rate monitoring. Each measurement was taken under natural training and competition conditions before, during and after physical activity. Maximal heart rate (HR_{MAX}) for each participant was calculated by formula "220 - age". Collected statistical data were analyzed by *IBM SPSS V22.0* software. A significance level of $p < 0.05$ was applied.

Results: The average heart rate during training was 133 ± 10 [95% CI: 128-138] beats per minute but during games - 148 ± 13 [95% CI: 142-154] beats per minute, $p < 0.001$. Mean value of the players average heart rate percentage of their HRmax during training was 78 ± 6 [95% CI: 75-81] percent, but during competitions - 87 ± 6 [95% CI: 84-90] percent, $p < 0.001$.

Conclusion: Masters basketball players heart rate during competitions was higher than during training. Most players ran competitions with heart rate corresponding high intensity.

Kopsavilkums

Veterānu basketbolistu sirdsdarbības frekvence kā treniņu un sacensību intensitātes indikators

Atslēgvārdi: *sirdsdarbības frekvence, veterānu sportisti, slodzes intensitāte*

Ievads: Pieaugošais vecāka gadagājuma atlētu skaits un viņu vēlme sacensties ir jauns fenomens visā pasaulē. Viens veids, kā novērtēt slodzes intensitāti, ir noteikt, cik bieži fiziskās aktivitātes laikā sitas sirds.

Darba mērķis: Novērtēt veterānu basktebolistu treniņu un sacensību intensitāti, izmantojot spēlētāju sirdsdarbības frekvenci.

Materiāli un metodes: Pētījumā piedalījās 16 vīrieši (n = 16). Sirdsdarbības frekvences noteikšanai tika izmantots pulsoksimetrs. Katrs mērījums tika veikts dabiskos treniņu un sacensību apstākļos pirms un pēc fiziskās aktivitātes, kā arī tās laikā. Katra spēlētāja maksimālā sirdsdarbības frekvence tika aprēķināta izmantojot vienādojumu "220 - vecums". Datu statistiskā apstrāde tika veikta programmā *IBM SPSS V.22.0* ($p < 0.05$).

Rezultāti: Vidējā sirdsdarbības frekvence treniņu laikā bija 133 ± 10 [95% TI: 128-138] sitieni minūtē, bet spēļu laikā - 148 ± 13 [95% TI: 142-154] sitieni minūtē. Vidējā vērtība no spēlētāju vidējās sirdsdarbības frekvences procentuālā lieluma no viņu maksimālās sirdsdarbības frekvences treniņu laikā bija 78 ± 6 [95% TI: 75-81] procenti, bet sacensību laikā - 87 ± 6 [95% TI: 84-90] procenti, $p < 0.001$.

Secinājumi: Veterānu basketbolistu sirdsdarbības frekvence sacensību laikā bija augstāka nekā treniņos. Lielākā daļa spēlētāju sacensības aizvadīja ar sirdsdarbības frekvenci, kas atbilst augstai intensitātei.

Introduction

Heart rate monitoring is non-invasive, not expensive and time-efficient method which are receiving increasing interest for monitoring fitness and endurance performance responses. (Buchheit 2016). Demographic development towards "aging population" and a tendency of "sportification" of society are two social trends which promote an academic interest in the sport of the elderly over the past decades (Tischer et al. 2011). Populations aging around the world during previous and this century has achieved unprecedented levels and is expected to continue to do so over the next 50 years (Sander et al. 2015). At the same time, there is a growing number of people that have become involved in sports activities including older participants (Tischer et al. 2011).

The definition of masters athlete is person older than 35 years who either trains for or only takes part in specifically for older participants designed athletic competitions. Why 35 years, because this is the age at which cardiovascular issues tend to become the biggest cause of morbidity (Trappe 2001). Many of these athletes already have a great experience as competitors and they just continue their athletic pursuits after the end of their sports careers, meanwhile, other individuals return to the sport after extended periods of inactivity or participate and train occasionally (Tayrose et al. 2015).

Until now it was believed that more exercise is more beneficial as many of the exercise-related health benefits exhibit a dose-response relationship. However, latest studies have suggested that different exercise intensities may provide diverse health benefits, independent of exercise dose (McGarrah et al. 2016). Intensity is the level of effort during physical activity. The relative intensity is the percentage of oxygen uptake (aerobic capacity) reserve required to perform an activity. Because of the generally linear relationship between the heart rate and percentage of oxygen uptake, heart rate is used to monitor relative intensity in practice (Buchner 2016).

To use heart rate as an indicator of physical activity intensity need to know its percentage part of the person's maximal heart rate (Mann et al. 2013). Maximal heart rate (HRmax) is the highest heart rate a subject can achieve in an all-effort to the point of exhaustion. As there is not always an opportunity to measure HRmax values directly need to rely upon regression equations based on age. The most commonly used equation is the "220 – age" formula, proposed by *Fox et al.* at 1971 (Camarda et al. 2008). Target heart rate is between 50 to 85 percent of maximal heart rate, where 70 percent is a border between moderate and vigorous intensity, but 85 percent – between vigorous and high intensity (Fletcher 2016).

Too much and too little training load may lead to overtraining and detraining, respectively, an appropriate training dose at the individual level may allow optimal improvements in performance (Buchheit 2016). For most adults and masters athletes moderate to vigorous intensity aerobic exercise is required (Garber et al. 2011). Basketball is considered to be an explosive, high-intensity sport (Fort-Vanmeerhaeghe et al. 2016).

Material and methods

16 male masters basketball players (mean age 49 ± 6 years) from four different teams participating in the *MaxiBasket* league were included in the study. Inclusion criteria were regular training and competition attendance. The subjects were familiarized with the experimental procedure and provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Riga Stradiņš University Ethic Committee.

Prospective data were collected in real training and competition conditions. Heart rate was taken by the *CONTEC*^{TM} Pulse Oximeter CMS50D1 which was put on the left hand index finger.

The first measurement was taken before warm up, second to fourth – immediately after leaving basketball court during players change, but the last measurement was taken shortly (2-5 min) after stretching. Each measurement was repeated in two different training and games.

Maximal heart rate for each participant was calculated by formula "220 - age" which are widely used in the world. 70% of the individual's HRmax was taken as the boundary between moderate and vigorous intensity, but 85% - between vigorous and high intensity.

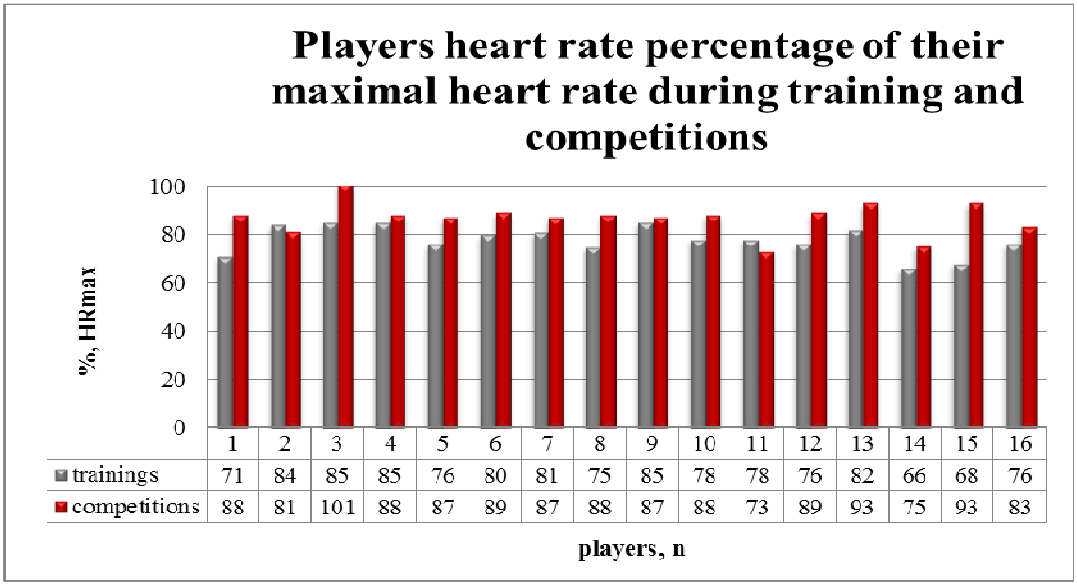
The statistical processing of data was carried out in *IBM SPSS V22.0* software. The descriptive statistics and T-test were used. The parametric data are represented as a mean ± standard deviation. A significance level of $p < 0.05$ was applied.

Results

The average age of participants was 49 ± 6 years. The average heart rate before training was 72 ± 13 [95% confidence interval (CI): 66-78] beats per minute, but before competitions – 79 ± 12 [95% CI: 73-85] beats per minute. There is no statistically significant difference between both parameters ($p = 0{,}109$). The average heart rate during training (133 ± 10 [95% CI: 128-138] beats per minute) was statistically significantly lower than during games (148 ± 13 [95% CI: 142-154] beats per minute), $p < 0.001$. Difference between heart rate after training and competition is not quite statistically significant, respectively 94 ± 16 [95% CI: 86-102] and 104 ± 10 [95% CI: 99-109] beats per minute, $p = 0.05$.

Average heart rate increasing during training was 61 ± 13 [95% CI: 55-67] beats per minute and was no statistically significantly different from heart rate increasing during competitions – 69 ± 19 [95% CI: 60-78] beats per minute, $p = 0.135$.

The first figure shows each player average heart rate percentage of his maximal heart rate.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
trainings	71	84	85	85	76	80	81	75	85	78	78	76	82	66	68	76
competitions	88	81	101	88	87	89	87	88	87	88	73	89	93	75	93	83

Figure 1. **Players average heart rate percentage of their maximal heart rate during training and competitions**

Mean value of the players average heart rate percentage of their HRmax during training was 78 ± 6 [95% CI: 75-81] percent, but during competitions, it was statistically significant higher, respectively, 87 ± 6 [95% CI: 84-90] percent, $p < 0.001$. Only two players average heart rate during training was below 70%, all the rest men trained with the heart rate between 70 to 85% which represent vigorous intensity. During competitions, only four players average heart rate was homologous to vigorous intensity, but the remaining 12 men played basketball with the heart rate over 85% of their maximal heart rate.

Discussion

In many western countries, people are living longer and longer. Over the past decade, higher growth in relation to participation in sports activities observed directly among older people rather than children, young people or younger adults. Overall, masters athletes represent a unique population (Tischer 2011).

However, there is still contradictory findings in the literature about measures of resting, exercise, and recovery heart rate, most of them are related to methodological inconsistencies and/or misinterpretation of the data. Author provide evidence that measures derived from recordings of resting and exercise heart rate are likely the most useful monitoring tools (Buchheit 2016).

This research main purpose was to compare the masters basketball training and competition load intensity using players heart rate. Both benefits and risks depend on the applied effort during physical activity, especially in older age. Calculation of players average heart rate percentage of their HRmax shows that basketball game is vigorous and high intensity physical activity. Also *Tessitore et al.* study results show that 97% of masters basketball match time is spent at heart rate more than 70% of HRmax (Tessitore et al. 2006) But *Montgomery et al.* conclude that during real basketball match physiological requirements are significantly higher than during simulated game (Montgomery et al. 2010).

Personal observations in training and games suggest that the increase of the load during basketball is temporary and repeated. This is also evidenced by two consecutive studies: *Narazaki et al.* at their work affirm that 34.1% of basketball game time is spent running and jumping, 56.8% walking but 9.0% standing (Narazaki et al. 2009). But the Lithuanian researchers in their work notes that each player during the match executes up to 50 jumps and 10% of the movements contains 10-20 meters long sprint race (Pliauga et al. 2015).

The most often cited and used formula for maximal heart rate in textbooks and papers in exercise physiology and in fitness programs and the fitness industry is 220 – age. This equation relationship tends to increase with increasing age. Another equation used to predict HRmax is the regression model proposed by Tanaka et al, the 208 – (0.7 x age) formula. But authors concluded

that their prediction equations proposed by Karvonen (220 – age) and Tanaka (208 - 0.7 x age) are similar in estimating HRmax in male and female subjects 12 to 69 years old (Camarda et al. 2008).

"There is strong evidence that regular moderate or vigorous physical activity reduces the risk of premature mortality and coronary artery disease, stroke, high blood pressure, adverse lipid profile, type 2 diabetes mellitus, metabolic syndrome, osteoporosis, colon cancer, breast cancer, and obesity". But the effect on the body from higher intensity physical activities still is being studied. Although regular physical activity decreases the risk of sudden cardiac death and myocardial infarction, there is evidence that high intensity exercises acutely increases the risk of these events. However, the results are ambiguous (Buchner 2016).

Conclusions

Masters basketball players heart rate during competitions was statistically significantly higher than during training, but there was no difference between heart rate increasing during both events. Most players ran training with heart rate corresponding vigorous intensity, but competitions – corresponding high intensity.

Acknowledgement

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COMPARISON OF SPO2/FIO2 TO PAO2/FIO2 AS DIAGNOSTIC TOOLS FOR ACUTE RESPIRATORY DISTRESS SYNDROME

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Abstract

Comparison of SpO2/FiO2 to PaO2/FiO2 as diagnostic tools for ARDS

Key words: *ARDS criteria, fraction of inspired oxygen*

Acute respiratory distress syndrome (ARDS) definition includes specific partial pressure of oxygen in arterial blood (PaO2). Arterial gas analysis is rarely performed outside intensive care units, so ARDS has tendency to be diagnosed late. The aim of the study was to find out whether ratio of arterial oxygen saturation (SpO2) which means the fraction of oxygen-saturated hemoglobin relative to total hemoglobin in the blood to fraction of inspired oxygen (FiO2) can be used in place of traditional PaO2/FiO2 ratio. To achieve the aim 32 clinical cases were analyzed. Correlation between traditional PaO2/FiO2 parameter and SpO2/FiO2 was investigated. Authors concluded that SpO2/FiO2 ratio can be used as diagnostic test in patients with ARDS.

Kopsavilkums

SpO2/FiO2 un PaO2/FiO2 kā ARDS diagnostisko testu salīdzinājums

Atslēgas vārdi: *ARDS kritēriji, ieelpotā skābekļa frakcija*

Akūtu respiratoru distresa sindromu (ARDS) definē Berlīnes kritēriji, kas iekļauj tostarp skābekļa parciālo spiedienu arteriālajās asinīs (PaO2). Tā kā asins gāzu analīze tiek realizēta ārpus intensīvās terapijas nodaļām, ARDS ir tendence būt diagnosticētam novēloti. Darba mērķis bija noskaidrot, vai arteriālo asiņu skābekļa saturācijas, kura nozīmē attiecību starp ar skābekli piesātināto hemoglobīnu un kopējo hemoglobīnu, un ieelpota skābekļa frakcijas attiecība (SpO2/FiO2) var tikt izmantota ARDS diagnostikai PaO2/FiO2 vietā. lai sasniegtu mērķi tika analizētas 32 slimības vēstures. Tika analizēta korelācija starp PaO2/FiO2 un SpO2/FiO2. Autori secināja, ka SpO2/FiO2 attiecība var tikt izmantota kā diagnostiskais tests pacientiem ar ARDS.

Introduction

Acute respiratory distress syndrome (ARDS) is defined by Berlin Criteria:

- acute onset over 1 week or less of a known clinical insult or new or worsening respiratory symptoms;
- bilateral opacities consistent with pulmonary edema detected on CT or chest radiograph;
- PaO2/FiO2 (P/F) ratio <300mmHg with a minimum of 5 cmH20 PEEP[1] or CPAP[2];
- must not be fully explained by cardiac failure or fluid overload; need objective assessment to exclude hydrostatic edema if no risk factor present. (Ranieri et al. 2012)

As arterial blood analysis and mechanical lung ventilation are rarely performed in non-intensive care units, so it could be difficult to identify ARDS according to Berlin criteria. It delays diagnostics and increases length of hospitalization and mortality rate. ARDS still has a mortality rate of 40%. (Walkey Allan et al. 2012)

[1] PEEP – positive end expiratory pressure
[2] CPAP – continuous positiveairwaypressure

An alternative criterion is ratio of saturation of peripheral oxygen to fraction of inspired oxygen ratio (SpO2/FiO2), which doesn't require any special ventilation parameters and is more easily to obtain. (Rice et al. 2007; Riviello et al. 2016) The aim of study is to accept or deny SpO2/FiO2 as trustful and easy-to-perform tool for diagnosing ARDS. Authors analyzed correlation between these ratios in patients with ARDS (Pearson rank correlation) and compared SpO2/FiO2 in survivor and non-survivor group (T-test) to find out prognostic value of this ratio.

Materials and methods

Study is retrospective multicenter in Latvia. Clinical cases of period from January 1, 2012 to December 31, 2015 were taken for analyze.

Inclusion criteria were age more than eighteen years and ARDS diagnosis, confirmed by traditional criteria. An exclusion criterion was NYHA class III–IV heart failure, because it was difficult to differentiate cardial lung oedema from ARDS in patients if echocardiography was not performed. 25 cases out of 32 were included in further analysis.

Patients were divided into survivor and non-survivor group with aim to compare SpO2/FiO2 and PaO2/FiO2 in both and see if these parameters have prognostic value. PaO2, SpO2, FiO2, neutrophil, thrombocyte and C-reactive protein levels closest to time of diagnosis confirmation and on third day after diagnosis confirmation were interpreted. Neutrophil and thrombocyte levels were registered because they are believed to affect course of respiratory distress. Inflammation marker was registered as a marker of process severity. Vasopressor therapy was registered if provided during hospitalization.

Correlation between traditional PaO2/FiO2 parameter and SpO2/FiO2 was investigated. Correlation between inflammation marker levels and outcome was analyzed. Data analysis using IBM SPSS 24, MS Excel.

Results

25 clinical cases (13 males, 12 females) were included in further analysis. Median age was 49 (21-80) years. Pneumonia was most common (60%) main diagnosis among them; other etiologies were trauma, pancreatitis, sepsis, intoxication.

For 14 patients (56%) outcome was poor, 11 (44%) patients recovered. Median hospital length of stay was 23 days for survivors and 15 for non-survivors.

29% percent of patients received vasopressor therapy.

Pearson rank correlation coefficient (r) between SpO2/FiO2 and PaO2/FiO2 was 0,79 ($p<0,001$) on the day of diagnosis and 0,631 ($p<0,05$) on the third day. (Tab. 1)

Table 1. **Correlation between SpO2/FiO2 and PaO2/FiO2**

		PaO2/FiO2 on 1st day of diagnosis	SpO2/FiO2 on 1st day of diagnosis
PaO2/FiO2 on 1st day of diagnosis	Pearson Correlation	1	0,790
	Sig. (2-tailed)		0,000
		PaO2/FiO2 on 3rd day of diagnosis	SpO2/FiO2 on 3rd day of diagnosis
PaO2/FiO2 on 3rd day of diagnosis	Pearson Correlation	1	0,631
	Sig. (2-tailed)		0,003

T-test showed statistically significant difference in SpO2/FiO2 on third day after diagnosis confirmation between non-survivor (mean 132,74±SD 31,18) and survivor group (mean 168,85±SD 43,38; p<0,05). (Fig. 1) No such correlation was found for PaO2/FiO2 meanings.

SpO2 also has significant difference in survivor (91±5,85) and non-survivor (84±8,06) group (p<0,05). (Fig. 2)

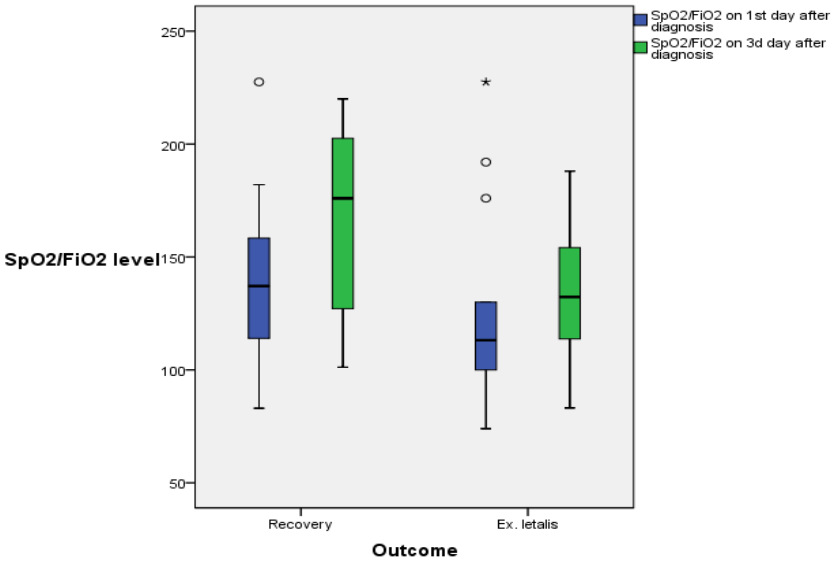

Figure 1. **Difference in SpO2/FiO2level in survivor and non-survivor group**

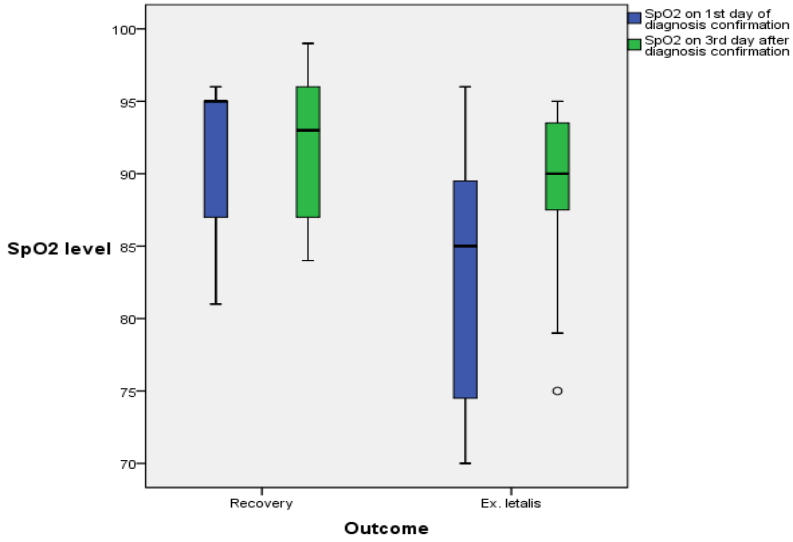

Figure 2. **Difference of SpO2 level in survivor and non-survivor group**

Other parameters (thrombocyte, neutrophil level, C-reactive protein) did not show significant differences in these two groups. Presence of vasopressor therapy did not shown statistically significant correlation with outcome.

Discussion

Thrombocyte level was registered because it seems to have a significant role in ARDS pathogenesis. Platelets increase thromboxane-A2 and P-selectin, induced expression of ICAM-1 on endothelial cells, and these in turn led to increased neutrophil activation. Inhibition of platelet-neutrophil aggregation resulted in reduced neutrophil recruitment, increased animal survival time, and less hypoxia. (Hemang, Daryl 2015)

Limitation of this study is amount of analyzed clinical cases. Although there were included cases with ARDS as main diagnosis and as complication as well, there was difficult to get all possible patient histories, because clinicians usually write ARDS in the end of diagnosis, but searching system recognize diagnosis only until third complication.

Length of hospitalization is not strongly associated with ARDS severity because in some patients ARDS was diagnosed at arrival, but in other it developed after nosocomial pneumonia and length of stay was specified by other condition.

Conclusions

- SpO2/FiO2 ratio strongly correlates with PaO2/FiO2 ratio, therefore it can be used as a test for diagnosing ARDS;
- SpO2/FiO2ratio is significantly lower in non-survivor group so it could be used as prognostic marker in patients with ARDS;
- SpO2 alone could be used as prognostic marker in patients with ARDS;
- In this study inflammation markers and thrombocyte level do not have prognostic value.

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PREVALENCE OF DEPRESSION SYMPTOMS AMONG PROGRAMMERS, COMPARING WORK EXPERIENCE AND GENDER

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Abstract
Key words: *Programmers, Depression, Stress, Information technologies, PHQ-9*
Introduction: In recent years the number or programmers employed in information technology field has increased significantly. Countless risk factors can influence depression rates, some being associated with workplace environment, isolation and stress. Work in smaller and financially less stable enterprises can also contribute to mental health decrease.
Aim: The aim of this study was to determine if there is a correlation between work experience in programming and depression symptom prevalence and the potential risk factors.
Materials and methods: Programmers were interviewed online using Patient Health Questionnaire 9 and questions about their work environment. Statistical data interpretation and procession was performed with MS Excel 2013 and IBM SPSS 20.0.
Results: In total 90 programmers were surveyed, aged 22 to 54 (mean 29.17±5.53), 25,6% women and 74,4% men. Respondent evaluation using PHQ-9 revealed; 61.11% (n=55) of all respondents did not score enough points (≥10) for diagnosis of depression. 38.89% (n=35) had a total score ≥10 points. PHQ-9 score ≥10 has sensitivity of 88% and a specificity of 88% for Major Depressive Disorder. In male group 25,37% (n=17) presented with mild depression symptoms, 33,3% (n=30) of the respondents presented with moderate and above moderate depression symptoms. In female group 43,48% (n=10) had mild symptoms and 21,74% (n=5) presented with moderate and severe depression symptoms. There was no significant correlation found between work experience and depression (p >0,05).
Conclusions: Work experience in programming does not increase the prevalence of depression symptoms. Prevalence of depression symptoms among programmers is higher in males compared to females. Prevalence of depression symptoms is higher among programmers employed in smaller enterprises.

Kopsavilkums
Atslēgvārdi: *Programmētāji, Depresija, Stress, Informācijas tehnoloģijas, PHQ-9*
Ievads: Pēdējo gadu laikā ir strauji palielinājies nodarbināto skaits ar programmēšanu saistītos uzņēmumos. Dažādi faktori var ietekmēt depresijas biežuma palielināšanos nodarbinātajiem, kuri ikdienā strādā par programmētājiem, tas var būt, stress darbā, manipulācijas ar lielu datu apjomu, dažādu programmēšanas valodu apguve un pielietošana. Darbs mazākos un zemāk atalgotos uzņēmumos, salīdzinot ar lielākām kompānijām, var radīt lielāku risku depresijas attīstībai.
Mērķis: Pētījuma mērķis ir noteikt vai programmētājiem ar lielāku darba stāžu ir lielāks risks depresijas simptomu attīstībai un, vai to ietekmē citi potenciālie riska faktori.
Materiāli un metodes: Programmētāji tika anonīmi intervēti tiešsaistē, izmantojot Pacientu Veselības aptauju – 9 (*PHQ-9*) un aptauju par apstākļiem darba vietā. Datu statistiskajai analīzei tika izmantota MS Excel 2013 un IBM SPSS 20.0.
Rezultāti: Pētījumā piedalījās 90 programmētāji, vecumā no 22 līdz 54 (29.17±5.53), 25,6% sieviešu un 74,4% vīriešu. Aptaujāto izvērtēšana, izmantojot PHQ-9 atklāja, ka 61,11% (n=55) no visiem respondentiem nesasniedza pietiekoši daudz punktu depresijas diagnozei (≥10 punkti). PHQ-9 vērtējums ≥10 ir 88% jutīgs un 88% specifisks depresijas diagnozes uzstādīšanai. Vīriešu grupā 25,37% (n=17) novērota vieglas depresijas simptomātika, savukārt 33,3% (n=30) saņēma vērtējumu, kas atbilst vidējas un smagākas depresijas pakāpes simptomātikai. Sieviešu grupā 43,48% (n=10) novēroti vieglas depresijas simptomi, vidējas un smagākas depresijas pazīmes atzīmēja 21,74% (n=5). Nav korelācijas starp darba stāžu programmēšanā un depresijas simptomu prevalenci (p>0,05).
Secinājumi:. Darba pieredze programmēšanā nepalielina depresijas simptomu prevalenci. Vīriešiem programmētājiem depresijas simptomi novēroti biežāk. Darbs mazākos uzņēmumos palielina depresijas simptomu biežumu.

Aim of the study

The aim of this study was to determine if there is a correlation between work experience in programming and depression symptom prevalence and the potential risk factors that may influence the rates of symptoms associated with depression, like the female gender, age and the type of establishment the employees are working for.

Introduction

According to National Employment Agency of Latvia programmers are one of the most sought after professionals in the recent years and the demand for high qualified workers will continue to increase (Ministry of Economics of Latvia 2016).

Lifetime prevalence of depression varies widely, but in the majority of countries the number of people who may suffer from depression during their lifespan falls within 8 – 12% range (Kessler 2013).

Increased depression rates among programmers can be influenced because of countless factors. The biggest contributors being: self-critical behaviour, work related stress, residing and working in urban environment as well as isolation due to work with large quantities of data or job peculiarities (Haggerty 2016).

Individuals employed in computer technology fields, programming among those, note the constant change in technologies and software development, they experience the speed of evolution in these fields, and it may become a struggle and leave profound psychological and physiological damage (Khosrowpour, ~~and~~ Culpan 1989).

Studies suggest that there indeed is a link between depression and the related symptoms, and programmers. Evaluated by a semi structured interview pertaining 101 subjects, male software engineers, found that depression symptoms were the most frequent out of all mental health complaints. The study found that 32% of the subjects diagnosed as DSM-III, had depression symptoms (Shoji 1990).

Stress and anxiety comparison study done in 2014. including 100 professionals 50 software and 50 mechanical professionals of both sexes proved that software engineers had higher anxiety levels than that of mechanical professionals. Software field being relatively new therefore it is necessary to realize mental health hazards (Nayak 2014).

According to survey results, evidence consistently indicates that depression can adversely affect work productivity. Results of a survey and self-reported annual incomes of USA working population suggests that workers cost employers an estimated 44 billion dollars per year in lost productive time due to depression (Stewart 2003).

Materials and methods

A total of 90 programmers participated in the study, aged 22 to 54 (mean 29.17±5.53). The survey of programmers was performed using Patient Health Questionnaire – 9 (PHQ-) in two languages, English and a questionnaire validated in Latvian. In addition a survey consisting of questions about the age, gender, work experience in programming (in years), work experience with the recent programming languages used daily and the size and type of the establishment they currently work in. The PHQ-9 is the module tool for evaluating depression symptom severity,

which scores each of the 9 DSM-IV depression criteria as "0" (not at all) to "3" (nearly every day) over the last two weeks. Respondents answered the questions anonymously, using an online survey platform. Data was gathered from various Latvian software development companies and with the cooperation of Paris Graduate School of Digital Innovation - EPITECH post-graduates in France.

The data was gathered over the time span of 3 months (from December 2016 until February 2017). Statistical data interpretation and procession was performed with Microsoft Excel 2013 and IBM SPSS 20.0.

Mann – Whitney U test and Wilcoxon W test was used to determine the difference and the significance of the difference between two different groups of programmers. Correlation between two variables was tested using Spearman's rho nonparametric test. In this research threshold of significance was set at p=0,05.

Results

Out of 90 respondents 25,6% (n=23) were women and 74,4% (n=67) were men. Respondent evaluation using PHQ-9 revealed the following results: 61.11% (n=55) of all respondents did not score enough points (≥10) for diagnosis of depression. However 38.89% (n=35) had a total score ≥10 points, potentially requiring further evaluation and treatment from certified psychotherapist or a psychiatrist. Patient Health Questionnaire – 9 score ≥10 has sensitivity of 88% and a specificity of 88% for Major Depressive Disorder (Kroenke 2001).

Nonparametric measure of rank correlation, Spearman's rho, revealed that there was no significant correlation found between work experience and depression symptom prevalence in surveyed software engineers (p >0,05).

Between two groups of programmers where respondents were employed in smaller companies of less than 25 employees on average employed in a year, and larger companies where the average employee count employed per year was higher than 25, was statistically significant difference (p<0.05). Out of all programmers working in smaller companies, 47,61% of respondents had moderate or above moderate severity depression symptoms, whereas in larger establishments only 29,16% of programmers presented with moderate or above moderate severity symptoms.

In male group of the surveyed programmers 29,85% (n=20) had minimal depression symptoms (0-4 points in the PHQ-9 module), 25,37% (n=17) presented with mild depression symptoms (5-9 points in the PHQ-9), 35,82% (n=24) had moderate depression symptoms (10-14 points), 4,47% (n=5) of the respondents had moderately severe depression symptoms (15-19 points) and 1,49% (n=1) presented with severe depression symptoms (20-27 points).

In female group 34,78% (n=8) had minimal depression symptoms (0-4 points in the PHQ-9 module), 43,47% (n=10) presented with mild depression symptoms (5-9 points in the PHQ-9), 13,04% (n=3) had moderate depression symptoms (10-14 points), 4,3% (n=1) of the respondents

had moderately severe depression symptoms (15-19 points) and 4,3% (n=1) presented with severe depression symptoms (20-27 points).

Following the question in PHQ-9 survey, ‘’ If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?’’, ‘’Not difficult at all’’ answered 33,3% (n=30) of programmers, ‘’Somewhat difficult’’ answered 48,8% (n=44), ‘’Very difficult’’ accounted for 13,2% (n=12) of respondents and ‘’Extremely difficult’’ answered only 4,4% (n=4) of surveyed software engineers.

The most frequent symptoms among programmers were feeling tired and having no energy, different types of sleep disturbances and having little interest and pleasure in doing any type of activity. Of all programmers 88,9% reported feeling tired and having no energy at least once in the last two weeks. Trouble falling asleep, waking up during the night or sleeping too long was the second most common complaint, accounting for 81,2% of the respondents. Having little interest or pleasure in doing things was the third most common symptom of the surveyed programmers, consisting of 76,7% respondents.

Discussion

In this research there was no significant difference between the depression prevalence between genders, males having higher prevalence than females. As well as, smaller enterprise employees having significantly higher depression symptom prevalence when compared to programmers in larger corporations. The findings of this study indicate that the risk of acquiring depression symptoms during individual’s life span is higher than that of the general population.

Patient Health Questionnaire 9 is a highly useful screening tool, but it is not a stand-alone diagnostic test, therefor it cannot be used to diagnose depression without further testing (Manea, ~~and~~ Gilbody 2012).

A number limitations of this study must be emphasized. It is to be noted that the number of responding programmers was relatively small, furthermore the count of female software engineers was significantly lower than male the counterpart, increasing the likelihood of small sample bias. Additionally there is no way of checking misinterpretations by the respondents when answering different type of questions.

Data on research evaluating depression symptoms in programmers using PHQ-9 currently is scarce, further increasing the difficulties when comparing the data to this research. Although some studies suggest there is a link between depression and programming (Shoji 1990), the sample sizes are not large enough to be conclusive.

Conclusions

Work experience in programming does not increase the prevalence of depression symptoms. Prevalence of depression symptoms among programmers is higher in males compared to females.

Prevalence of depression symptoms is higher among software engineers employed in smaller enterprises.

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CHRONIC HEPATITIS C CLINICAL COURSE AND OUTCOME

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Abstract

Chronic hepatitis C clinical course and outcome

***Key words*:** *chronic hepatitis C (CHC), hepatitis C virus (HCV), stage of fibrosis, genotype, complications*

Introduction: The number of people infected with HCV increases by 3-4 million each year. It is important to diagnose the infection as soon as possible to prevent complications such as portal hypertension, liver cell insufficiency and hepatocellular carcinoma. In order to provide the best treatment possible, it is necessary to determine HCV genotype and stage of fibrosis.

Aim: To investigate clinical course and outcome of CHC by collecting and analyzing documented information about stage of fibrosis, genotype and common complications among CHC patients.

Materials and methods: The retrospective research was done by collecting and analyzing data of 137 CHC patients who were admitted to Riga East Clinical University Hospital during time period from January 2014 to December 2016. Statistical data was processed by IBM SPSS and Microsoft Excel.

Results: From 137 total cases 64.23% (n=88) were men from whom 23.86% (n=21) *exitus letalis* and 35.77% (n=49) were women - 18.37% (n=9) *exitus letalis*. Data of stage of fibrosis was available for 102 cases, from which 5.88% (n= 6) had stage 0; 34.31% (n=35) had stage 1; 9.80% (n=10) had stage 2; 5.88% (n=6) had stage 3 and 44.12% (n=45) had stage 4 (cirrhosis). Data of HCV genotype was available for 69 cases, from which genotype 1(undifferentiated) was determined in 17.39% (n=12), genotype 1a in 1.45% (n=1), genotype 1b in 55.07% (n=38), genotype 2 in 1.45% (n=1) and genotype 3 in 24.64% (n=17) cases. CHC complications were present in 78 cases and the commonest were – portal hypertension 84.62% (n=66), liver cell insufficiency 76.92% (n=60) and hepatocellular carcinoma 14.10% (n=11).

Conclusion: We can conclude that male patients were generally more represented in the research compared to female patients and had higher mortality rate. Almost half of the patients were diagnosed with CHC at the stage of cirrhosis. The most common was HCV genotype 1b, but the least common were - 2 and 1a. From all observed complications the most prevalent was portal hypertension.

Kopsavilkums

Hroniska vīrushepatīta C klīniskā gaita un iznākums

Atslēgvārdi: *hronisks C hepatīts (HCH), hepatīta C vīruss (HCV), fibrozes stadija, genotips, komplikācijas*

Ievads: Katru gadu ar HCV inficēto skaits pieaug par 3-4 miljoniem. Ir svarīgi diagnosticēt infekciju pēc iespējas agrīnāk, lai novērstu komplikāciju – portālās hipertensijas, aknu šūnu mazspējas un hepatocelulāras karcinomas attīstību. Lai nodrošinātu efektīvāko terapiju, ir nepieciešams noteikt HCV genotipu un fibrozes pakāpi.

Mērķis: Pētīt HCH klīnisko gaitu un iznākumu, ievācot un analizējot informāciju par fibrozes pakāpi, genotipu un biežākajām komplikācijām HCH pacientiem.

Materiāli un metodes: Tika veikts retrospektīvs pētījums, ievācot un analizējot datus par 137 HCH pacientiem, kas bijuši stacionēti Rīgas Austrumu klīniskās universitātes slimnīcā laika periodā no 2014.gada janvāra līdz 2016.gada decembrim. Datu statistiskā apstrāde tika veikta, izmantojot IBM SPSS un Microsoft Excel.

Rezultāti: No 137 kopējā gadījumu skaita 64.23% (n=88) bija vīrieši, no kuriem 23.86% (n=21) iestājās exitus letalis; 35.77% (n=49) bija sievietes, ko kurām 18.37% (n=9) iestājās exitus letalis. Dati par fibrozes pakāpi bija pieejami 102 gadījumos, no kuriem 5.88% (n= 6) bija 0 pakāpe; 34.31% (n=35) bija 1.pakāpe; 9.80% (n=10) bija 2.pakāpe; 5.88% (n=6) bija 3.pakāpe un 44.12% (n=45) bija 4.pakāpe (ciroze). Dati par HCV genotipu bija pieejami 69 gadījumos, no kuriem 17.39% (n=12) bija noteikts 1. (nediferencēts) genotips, 1.45% (n=1) – 1a genotips, 55.07% (n=38) – 1b genotips, 1.45% (n=1) – 2. genotips un 24.64% (n=17) tika noteikts 3.genotips. HCH komplikācijas bija attīstījušās 78 gadījumos un biežākās bija portālā hipertensija (84.62%(n=66)), aknu šūnu mazspēja (76.92% (n=60)) un hepatocelulārs vēzis (14.10% (n=11)).

Secinājumi: Es secinu, ka vīriešu dzimtas pacienti bija vairāk pārstāvēti šajā pētījumā salīdzinot ar sieviešu dzimtas pacientiem un vīriešiem bija arī augstāki mirstības rādītāji. Gandrīz pusē gadījumu HCH diagnosticēšanas brīdī bija attīstījusies aknu ciroze (4.fibrozes pakāpe). Biežākais genotips bija 1b, bet visretākie – 2 un 1a. No visām apskatītajām komplikācijām visbiežāk sastopamā bija portālā hipertensija.

Introduction

Hepatitis C is a liver infection caused by blood-borne Hepatitis C virus (HCV). Today most people become infected with the HCV by sharing needles or other equipment to inject drugs (cdc.gov). It is estimated that about 3% of the world's population (approximately 200 million

people) have been infected with HCV (Xiong 2016). In Latvia the incidence of CHC in 2016 is 1907 cases (96.9 cases per 100000 people) (spkc.gov.lv).

For some people, hepatitis C is a short-term illness but for 70%–85% of people who become infected with HCV, it becomes a long-term, chronic infection (Xiong 2016).

It is important to diagnose the infection as soon as possible to prevent complications such as portal hypertension, liver cell insufficiency and hepatocellular carcinoma. Despite highly effective direct-acting antiviral agents, the morbidity and incidence of liver-related complications of HCV is likely to persist in the near future (Goossens, Hoshida 2015).

Regarding complications it is known that CHC mostly leads to portal hypertension - progression of fibrosis contribute to increase in wedged hepatic venous pressure gradients. The correlations between pressures and morphological changes are maintained in all patients except those with cirrhosis (other factors such as revascularization and humoral factors are involved) (Leeuwen, Howe, Schener, Sherlock 1990).

Common complication of CHC is also malignancy. HCV is a leading etiology of hepatocellular carcinoma (HCC) (Goossens, Hoshida 2015). The risk of HCC, in chronic HCV infection, is associated with fibrosis stage. In cirrhotic subjects, the annual incidence of HCC is extremely high (1-7% per year), although HCC rarely develops in livers with less fibrosis (Yoshida, Shiratori, Moriyama, Arakawa, Ide, Sata 1999).

In order to provide the best treatment possible, it is necessary to determine HCV genotype and stage of fibrosis. Factors associated with successful therapy with interferon and ribavirin include genotypes other than 1, lower baseline viral levels, less fibrosis or inflammation on liver biopsy, and lower body weight or body surface area (Dhawan 2016). There are 6 major HCV genotypes and more than 50 minor subtypes. Genotype 1 HCV is the most common and is associated with a lower rate of response to treatment.

Persistent inflammation and hepatocellular injury lead to the fibrosis. Fibrosis is classified as 0-4 (staging is based on the extent of fibrosis), as follows:

- Stage 0: No fibrosis
- Stage 1: Fibrous portal expansion
- Stage 2: Periportal fibrous extension
- Stage 3: Fibrous septa formation, including portal-to-central bridging fibrosis
- Stage 4: Cirrhosis (Xiong 2016).

Materials and methods

The retrospective research was done to investigate clinical course and outcome of CHC by collecting and analyzing documented information about stage of fibrosis, genotype and common complications among 137 CHC patients who were admitted to Riga East Clinical University

Hospital during time period from January 2014 to December 2016. Statistical data was processed by Microsoft Excel.

Results

From 137 total cases of chronic HCV, 49 representatives were women and 88 were men, of which 9 women and 21 men deceased.

Data about stage of fibrosis at the time of discovery was available for 102 cases, from which stage 4, the final stage of fibrosis called cirrhosis was the dominant one with 44%, followed by stage 1 with 34%.

HCV genotype data was available for 69 cases, of which genotypes were ranked as follows in a descending order: genotype 1b 55 %, genotype 3 almost 25 %, genotype 1(undifferentiated) 17%, genotypes 2 and 1a 1,5% each. As you can see, the dominant is genotype 1, followed by genotype 3.

Further, we summarized the data about Chronic HCV infection complications – of total 78 cases, the most common were – portal hypertension with almost 85%, liver cell insufficiency with 77% and hepatocellular carcinoma with 14%.

Discussion

The findings of this study are supported by epidemiological data of HCV in Europe and similar studies that have been described in the international scientific literature.

Our results of HCV genotypes correspond to data from Latvian centre of Infectious diseases. In Latvia have been registered 68,80 % HCV patients with genotype 1b, in our study genotype 1b was found in 55% of patients. The second most common genotype that is registered in centre of Infectious diseases is type 3 – in 31,90 % of patients, in our study 25% of patients had this genotype. (LIHHASA 2015) Recently issued meta- analysis of HCV genotypes distribution in Europe shows the same order of genotype occurence - the predominant genotype is genotype 1 (64.4 %), followed by genotype 3 (25.5 %). (Petruzziello 2016)

In our study stage of fibrosis that was found in biopsy at the time of discovery in most cases was the final stage 4. In different sources of literature is written that final stage of fibrosis develops after about 20 years of infection, confirming that in 44% of cases in our study diagnosis was made very late. (Marcellin 2006) Delayed diagnosis of HCV favors the opinion of scientists that the incidence of complications of CHC will not decline over the next 10 years because most patients with CHC remain undiagnosed. (Petruzziello 2016). This is the problem we have encountered during the research – diagnosis of CHC was delayed.

Conclusion

In this retrospective research it was observed that male patients had higher mortality and were generally more represented in the research compared to female patients. This means that men have

more risk factors of developing CHC. Almost half of the patients were diagnosed with CHC at the stage of cirrhosis, which means that the diagnosis was delayed. The most common HCV genotype that was encountered in the acquired data from Clinical Center of Emergency Medicine "Gaiļezers" was 1b, as it is in Europe from the available data. And the least common were genotypes 2 and 1a. It is important to determine genotype to be able to provide the best treatment possible, because there are different therapy opportunities and medications for every genotype. From all observed complications the most prevalent was portal hypertension, which can be explained due to cirrhosis of liver and compression of portal vein.

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ENDOVASCULAR EMBOLIZATION IN PATIENTS WITH MASSIVE LARGE INTESTINE BLEEDING, EFFICIENCY, COMPLICATIONS AND ITS MANAGMENT. 5 YEARS DATA FROM SINGLE CENTER EXPERIENCE

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Abstract

Endovascular embolization in patients with massive large intestine bleeding, efficiency, complications and its management. 5 years data from single center experience

Key words: *LGIB, digital subtraction angiography (DSA), endovascular embolization (EVE)*

Introduction: Massive lower gastrointestinal bleeding usually leads to hospital admission with invasive diagnostic evaluations (Strate 2016). It is important for the interventional radiologist to be well versed in the endovascular therapeutic options (Navuluri 2012).

Aim: To find out clinical and laboratory results after EVE of LGIB and its complications in Riga East University Hospital, Interventional radiology department. Verify treatment technique and complications linked to embolization material. Identify frequency of surgical treatment application of complications.

Materials and methods: 21 patients, retrospective study. Patients had 2 following criteria - massive LGIB and DSA with or without EVE. EVE technique, Hgb levels before and after treatment, complications, treatment of complications were assessed. Allocation to 4 groups by EVE technique – coils, glue, microspheres, combine material. Data analysis: SPSS.

Results: 16 patients (76,2%) had EVE. Median Hgb rise with EVE - 3,39 g/dL. Median Hgb rise without EVE - 1,60 g/dL. Role of EVE is on the border of significance (p=0,050), EVE efficacy can be inferred clinically. EVE by coils n=4 (25%), showed no complications; Glue n=2 (12,5%), had 100% complications; Microspheres n=3 (18,75%), n=2 (66,7%) had complications; Combine n=7 (43,75%), n=2 (28,6%) had complications. There is no statistically significant dependence between specific EVE and summoned complication (p=0,070). Mortality n=1 (16,7%). Complication had n=6 (37,5%), n=2 (33,3%) had surgical treatment. There is no statistically significant dependence between EVE complications and surgical treatment (p=0,071).

Conclusion: EVE is effective treatment for patients with massive LGIB with clinical efficacy and increase of Hgb level. It shows tendency of lower complication rate for treatment technique using coils, without statistical significance.

Kopsavilkums

Masīvas resnās zarnas asiņošanas endovaskulārā embolizācija, efektivitāte, komplikācijas un komplikāciju ārstēšana. 5 gadu viena centra datu apkopojums

Atslēgvārdi: *Masīva resnās zarnas asiņošana (MRZA), digitālā subtrakcijas angiogrāfija (DSA), endovaskulārā embolizācija (EVE)*

Ievads: Masīva resnās zarnas asiņošana ir biežs stacionēšanas un endovazālās diagnostikas pielietošanas iemesls (Strate 2016). Invazīvam radiologam ir svarīgi labi orientēties endovaskulārās terapijas iespējās (Navuluri 2012).

Mērķis: Noskaidrot endovazālās embolizācijas klīniskus un laboratorus rezultātus pie masīvas resnās zarnas asiņošanas Rīgas Austrumu klīniskās universitātes slimnīcā, Invazīvās radioloģijas nodaļā. Izpētīt kāds embolizācijas materiāls retāk dod komplikācijas. Noskaidrot ķirurģiskas EVE komplikāciju koriģēšanas biežumu.

Materiāli un metodes: Restrospektīvs pētījums ar pētījuma grupu no 21 pacienta. Pacientu iekļaušanas kritērijs ir veikta DSA ar vai bez EVE. Tika izanalizēti EVE materiāls, Hgb līmeņi pirms un pēc ārstēšanas, komplikācijas, komplikāciju ārstēšana. Pacienti sadalīti četrās grupās pēc embolizācijas materiāla – koili, līme, mikrosfēras un materiālu kombinācija. Dati analizēti ar IBM SPSS programmu.

Rezultāti: 16 pacientiem (76,2%) tika veikta EVE. Vidējais Hgb pieaugums pacientiem ar veikto EVE ir 3,39 g/dL. Vidējais Hgb pieaugums pacientiem bez EVE ir 1,60 g/dL. Pacientiem ar EVE pielietojumu Hgb līmeņa pieaugums ir divreiz lielāks nekā pacientiem ārstētiem bez EVE, bez statistiskas ticamības (p=0.050). EVE ar koiliem ir veikta četriem pacientiem, nevienam neattīstījās komplikācijas. Līme tika pielietota diviem, un abiem komplicējās. Mikrosfēras pielietotās trijiem pacientiem, diviem no tiem attīstījās komplikācijas. Kombinētā EVE tika pielietota septiņiem pacientiem, diviem komplicējās. Statistiski nav ticamības atkarības starp EVE pielietojumu un komplikāciju attīstību (p=0,070). Mirstība pētījumā sastāda 6,25%, jeb viens pacients. Komplikācijas attīstījās sešiem pacientiem no

16, diviem no tiem tika pielietota ķirurģiskā komplikāciju korekcija. Starp EVE komplikācijām un ķirurģisko ārstēšanu statistiskas atkarības nepastāv (p=0,071).
Slēdzieni: EVE ir efektīva ārstēšanas metode masīvas resnas zarnas asiņošanas gadījumā, ar klīnisko efektivitāti un Hgb līmeņa pieaugumu. Visretāk komplikācijas dod EVE ar koiliem, bez statistiskas ticamības.

Introduction

Massive large intestine bleeding is rare, significant and expensive problem that requires methodical evaluation, management, and treatment. Intensive care unit use, blood transfusions, and invasive diagnostic tests are needed. Massive lower gastrointestinal bleeding (LGIB) usually leads to hospital admission with invasive diagnostic evaluations, and consumes significant medical resources (Strate 2016).

The annual incidence of LGIB is 20 to 30 cases per 100,000 in Westernized countries. Approximately 20% of them are massive bleeding cases. Massive bleeding requires more than 3 to 5 units of blood transfused in 24 hours. The mean cost per admission ranges from $9,700 to $11,800. (Tal Raphaeli 2012)

When medical management and endoscopic therapy are inadequate, endovascular intervention can be lifesaving in these emergent situations, it is important for the interventional radiologist to be well versed in the endovascular therapeutic options of LGIB (Navuluri 2012). Although interventional radiology only detects bleeding above a rate of 1 to 1.5 mL/min, colonic selective catheter angiography has 100% specificity and adds the benefit of being potentially therapeutic as well (Leander 2013).

There are two ways to treat this type of bleeding endovascularly: vasopressor infusions and embolization. Both aim to decrease perfusion to the site of vascular injury and accordingly allow for clot formation and subsequent endogenous repair of the injured vessel. A balance must be struck with respect to the extent of embolization or vasoconstriction to prevent total devascularization of the target area and consequent bowel necrosis. (Navuluri 2012).

Intraarterial vasopressin therapy for massive bleeding from the lower gastrointestinal tract involves leaving the angiographic catheter in the main trunk of the superior mesenteric artery or inferior mesenteric artery, depending on the site of bleeding. Infusion started at a rate of 0.2 U/min, and another angiogram is obtained 20-30 min later to evaluate the effectiveness of the infusion. If active hemorrhage is still detected, the infusion rate is increased, up to a maximum of 0.4 U/min; at rates higher than this, the potential complications associated with use of vasopressin, a potent vasoconstrictor, exceed the marginal benefit. (Zuckerman 1993).

Embolization has become a relatively safe option for treating LGI hemorrhage. Although embolization is more technically challenging, it has advantages of quicker completion of therapy, decreased recurrence of bleeding, and some decreased complications. The decision of whether to use embolization or vasopressin may come down to a matter of the availability of local expertise to

perform superselective catheterization. It is likely that, where the expertise exists, embolization will be used preferentially over vasopressin because embolization allows more rapid completion of therapy. (Darcy 2003).

The weaker anastamotic blood supply of the LGI tract, compared with the upper gastrointestinal system, is well known and predisposes the colon to a theoretically increased risk of postembolic ischemia. Although many cases of LGI embolization have been reported in the literature, the safety of this procedure has not been clearly defined. Several cases of postembolic colonic infarction were reported in the 1980s; but since then, newer catheter- based techniques have become available allowing more precise – superselective – hemostasis while preserving collateral blood flow to bowel mucosa. Therefore, it is necessary to redefine the postembolic infarction rate in terms of data from modern embolotherapy. This study presents the authors' experience with superselective LGI microcoil embolization for LGI hemorrhage with the goal of evaluating the safety and effectiveness of this treatment. Furthermore, a review of the literature for similar cases of LGI microcoil embolization is presented in an attempt to estimate the rate of major and minor ischemic complications from this modern transcatheter technique. (Kuo 2003).

William`s T. Kuo study in 2003, a retrospective review of LGI superselective microcoil embolization data for a 10-year period, showed that superselective microcoil embolization is a safe and effective treatment for LGI hemorrhage. During this research, twenty-two patients with evidence on angiography of LGI bleeding underwent superselective microcoil embolization. Immediate hemostasis was achieved in all 22 patients in this study. Complete clinical success was achieved in 86% of patients (19 of 22 patients). Rebleeding occurred in 14% of patients (3 of 22 patients) and each underwent colonoscopic intervention with success. (Kuo 2003).

Transcatheter arterial embolization (TAE) is effective for controlling acute gastrointestinal bleeding. Some studies have shown that TAE is safer than surgical intervention in the high-risk patient population and has a lower 30-d mortality rate. TAE is a viable option and temporizing measure in circumstances where endoscopic and/or surgical approach is not ideal. (Ramaswamy 2014).

The goal of TAE is super-selective embolization of bleeding vessels to reduce arterial perfusion pressure while maintaining adequate collateral blood flow to minimize the risk of bowel infarction. A 5 French angiographic catheter is used to access the celiac, superior mesenteric, or inferior mesenteric arteries depending on the suspected location of bleeding and its supplying vasculature. The type of embolic agent used is conventionally dependent on the interventional radiologist's experience and preference, etiology of bleeding, and availability of the agent. Embolic agents include coils, glue, onyx, Gelfoam, polyvinyl alcohol particles (PVA), and Amplatzer vascular plugs. The most commonly used embolic agents are coils and PVA. (Ramaswamy 2014).

Coils come in a variety of sizes and shapes, ranging from sub-millimeter to centimeters. Coils are composed of a metal component that acts as a physical occlusion and a fiber component that stimulates the thrombogenic process. Coils can be visualized under fluoroscopy after placement which is an important advantage when compared to Gelfoam or PVA. Newer types of embolization coils have an ability to be removed after deployment if the initial placement is felt to be unsatisfactory. (Ramaswamy 2014).

Gelfoam (absorbable compressed sponge) is a temporary agent made of subcutaneous porcine adipose tissue that remains effective for weeks to months before re-canalization occurs. For this reason, Gelfoam is not recommended as a single agent. Gelfoam can also be mixed with saline to form a slurry, which helps with delivery. Advantages of gelfoam include: widespread availability, cost-effectiveness, and allows future access to embolized vessels after resorption. Disadvantages include that the preparation of particles can be time consuming and recanalization of vessels is unpredictable. In addition, because Gelfoam is made of small particulates, it is difficult to control its placement and can be deployed more distally than intended, which can result in higher risk of bowel ischemia from embolization of nearby collateral vessels. (Ramaswamy 2014).

Several studies have shown that recurrent bleeding is more likely to occur when PVA particles, Gelfoam, or coils are used alone. Using coils with Gelfoam or PVA particles on both sides of the bleeding vessel is recommended to avoid “backdoor” bleeding and decrease the risk of recurrent bleeding. Some studies have shown that for upper GIB, which is commonly due to gastroduodenal ulcers, successful hemostasis can be achieved by embolizing the gastroduodenal artery or pancreaticoduodenal artery using coils alone, or using coils and Gelfoam together to embolize distally and proximally in the gastroduodenal arterial trunk. Clinical success rate of embolization for upper GIB have been cited to be around 44%-100%. (Ramaswamy 2014).

Aim

To find out clinical and laboratory results after endovascular embolization (EVE) of massive large intestine bleeding and its complications rate in Riga East University Hospital, Interventional radiology department. To verify treatment technique and complications linked to embolization material. To identify frequency of surgical treatment application of complications.

Materials and methods

This is a retrospective study, five-year data collection from the beginning of 2012 to the end of 2016, from the single center experience. Research took place in Riga East University Hospital, Interventional radiology department. Research group of 21 patients, who were hospitalized in Riga East University Hospital, were included in this retrospective study. All included patients had 2 following criteria - massive large intestine bleeding and digital subtraction angiography (DSA) with or without endovascular embolization. EVE material, hemoglobin (Hgb) levels before and after

treatment, complications of EVE, treatment of complications were assessed. Patients were allocated to 4 groups by EVE material – coils, glue, microspheres, combine material (coils with microspheres) and combine material (all three materials) to find out which material complicates less frequently. Hemoglobin level were analyzed at hospitalization day and discharging day after treatment. Complications were analyzed clinically by patient`s medical history - postprocedural abdominal pain, ischemic pain, peritoneal symptoms were assessed. Also, operative treatment rate of EVE complication as surgical colectomy were estimated. Data were analyzed using Statistical analysis software package (IBM SPSS) and Microsoft Excel programs.

Results

16 patients (76,2%) of 21 had EVE. Other five patients had no extravasation sign in DSA scan. All patients had hemoglobin level elevation after EVE. Median hemoglobin rise in patients with EVE were 3,39 g/dL. Median Hgb rise in patient without EVE were 1,60 g/dL (Fig.1, Fig.2). Research showed no statistically significant dependence between EVE use and Hgb elevation, but Mann-Whitney U test`s p-value (p=0,050) is on the border of statistical significance, so Hgb level rising can be inferred clinically. And clinically Hgb elevation using the EVE is two times better than without EVE.

Statistics

Hgb elevation

0 - without EVE	N	Valid	5
		Missing	0
	Mean		,6980
	Median		1,6000
	Std. Deviation		2,83787
	Minimum		-3,80
	Maximum		3,70
	Percentiles	25	-1,9000
		50	1,6000
		75	2,8450
1- With EVE	N	Valid	16
		Missing	0
	Mean		3,5281
	Median		3,3900
	Std. Deviation		1,94540
	Minimum		,67
	Maximum		7,08
	Percentiles	25	1,6875
		50	3,3900
		75	4,8850

Figure 1.

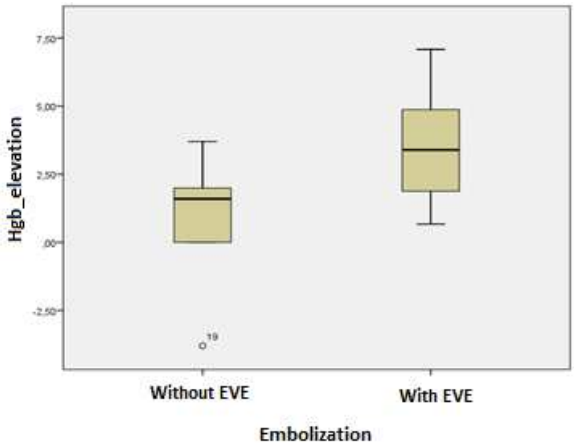

Figure 2.

16 patients of a group of 21, were treated by EVE. Six of them had complications. Coils alone were used 4 times with no complications; Glue alone was used twice and both cases were complicated with colonic ischemia; Microspheres alone were used three times and two of them were complicated; Five times were used combination of coils and microspheres and two of them were complicated; And finally, combination of all three materials were used twice with no complications (Fig.3). There is no statistically significant dependence between specific EVE material and summoned complication (Fisher`s Exact test 2-sided, p=0,070). Also, it shows tendency of lower complication rate for treatment using coils, without statistical significance.

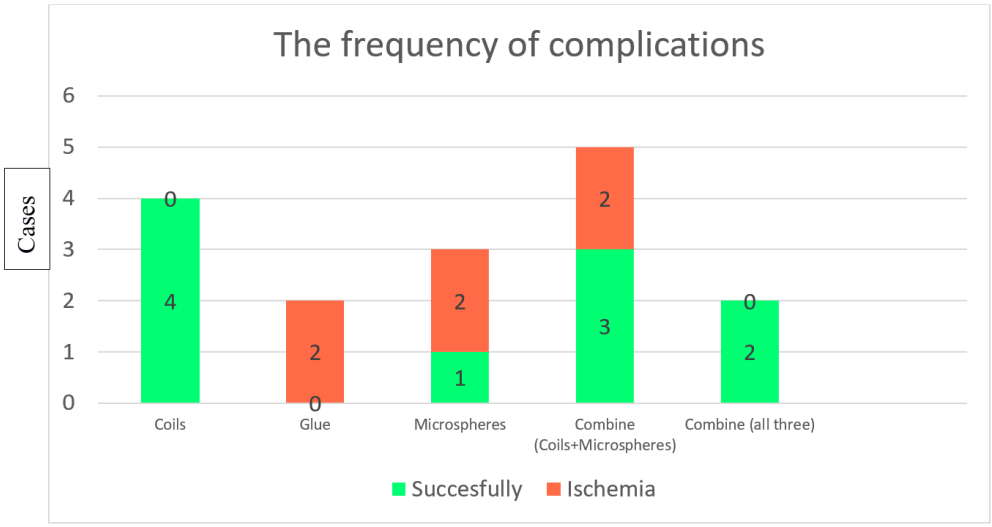

Figure 3.

Complication as peritoneal symptoms had n=6 (37,5%) of a group of 16 who had endovascular embolization. Surgical treatment was indicated for three of them. Two of this group were successfully operated. One patient 92 years old female died after EVE with ischemic complications, due to family rejection for surgical treatment. Mortality in this study is 1/16 or 6,25%. There is no statistically significant dependence between EVE complications and surgical treatment necessity (Fisher`s exact test 2-sided, p=0,071).

Discussion

Large intestine massive hemorrhage is a challenging problem. Literature-based protocols should be established to ensure fast and effective resuscitation, diagnosis, and treatment of these patients. Colonoscopy is the initial diagnostic modality of choice for most institutions, and it can be therapeutic in some patients. Diagnostic studies should be used thoughtfully. Most patients with colonic hemorrhage will not need surgery. Some patients will have their bleeding source localized and a segmental colon resection performed. In an unstable patient with unlocalized colonic hemorrhage, total abdominal colectomy is still the procedure of choice. A primary anastomosis should be considered in most patients. Although interventional radiology only detects bleeding above a rate of 1 to 1.5 mL/min, colonic selective catheter angiography has 100% specificity and also adds the potential benefit of being potentially therapeutic as well (Leander 2013).

Conclusions

Endovascular embolization is effective treatment for patients with massive large intestine bleeding with clinical efficacy and increase of hemoglobin level. It shows tendency of lower complication rate for endovascular embolization treatment using coils, without statistical significance.

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ANTIBACTERIAL THERAPY TRENDS IN PATIENTS WITH ULCERATIVE COLITIS IN RIGA EAST CLINICAL UNIVERSITY HOSPITAL

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Abstract

Antibacterial therapy trends in patients with ulcerative colitis in Riga East Clinical University Hospital

Key words: *inflammatory bowel disease, antibacterial therapy, ulcerative colitis*

Introduction. Ulcerative colitis (UC) is one of the most frequent forms of inflammatory bowel disease (IBD). Antibacterial therapy is frequently used in UC treatment in cases of complications. Unjustified use of antibiotics leads to increased microbial resistance.

Methods and materials. We reviewed all IBD hospitalization cases in time period 2010 – 2015. 416 were identified as UC cases. We analysed the compliance of antibacterial therapy to the European Crohn's and Colitis organisation (ECCO) guidelines. Collected data was analysed using programme SPSS ver. 23.0.

Results. 700 cases of admission to the hospital were examined. There were 416 (59.4%) UC cases; 221(59.8%) were female and 195(62.7%) were male patients; average age 47,1(SD=19,8 years). 329 (79.0%) patients were urgently admitted to the hospital with exacerbation of the disease, while 11 (2.64%) patients were admitted in order to have their diagnosis clarified. IBD was detected for 76 (18.2%) patients as a cooccurring diagnosis. Average number of days spent in hospital: 8.7 (SD = 7.4). Metronidazole was most often used in 133 (79,64%) cases. Ciprofloxacin and Ceftriaxone were used equally often: in 62 (14.9%) cases.

Conclusions. Metronidazole was the most frequently used antibiotic corresponding to the ECCO IBD therapy guidelines**.** Ceftriaxone was the second most commonly used antibiotic and its use does not correspond to the guidelines. Antibacterial therapy was applied for almost a half of the patients.

Kopsavilkums

Antibakteriālas terapijas pielietošanas tendencies ulceratīvā kolīta pacientiem Rīgas Austrumu Klīniskās Universitātes slimnīcā.

Atslēgas vārdi: *iekaisīgās zarnu slimības, antobakteriālā terapija, ulceratīvais kolīts*

Ievads: Ulceratīvais kolīts ir viena no biežāk sastopamajām iekaisīgo zarnu slimības formām(IZS). Antibakteriālo līdzekļu pielietošana ir neatņemama sastāvdaļa ulceratīvā kolīta komplikāciju ārstēšanā. Nepamatota antibakteriālas terapijas pielietošana veicina mikroorganismu rezistences attīstību pret antibiotikām.

Materiāli un metodes: Tika analīzēti visi IZS hospitalizācijas gadījumi no 2010. līdz 2015. gadam. Kopā identificēti 416 ulceroza kolīta pacienti. Pētījumā analizēta antibakteriālās Terapijas pielietošanas atbilstība ECCO (European Crohn's and collitis organisation) vadlīnijām. Iegūtie dati tika apstrādāti izmantojot statistikas programmatūru SPSS.23.

Rezultāti: Kopā tika reģistrēti 700 iekaisīgo zarnu slimības pacientu vēstures. No tiem 416 (59.4%) bija ulceroza kolīta gadījumi. No tiem 221(59.8%) bija sievietes un 195(62.7%) vīrieši, vidējais vecums 47.1(SD=19.8 gadi). 329(79%) pacienti tika hospitalizēti ar slimības paasinājumu, 11(2.64%) pacienti, lai precizētu diagnozi. 76(18.2%) pacientiem IZS tika diagnosticēta kā blakusdiagnoze. Vidējais pavadītais dienu skiats slimnīcā bijis 8.7(SD=7.4). No antibakteriāliem līdzekļiem Metronidazol tika pielietots 133(79.64%) gadījumos. Ciprofloxacin un Ceftriaxone tika pielietots 62(14.9%) gadījumos.

Secinājums: Viens no biežāk pielietotiem antibakteriāliem līdzekļiem bija Metronidazol, kas atbilst ECCO iekaisīgo zarnu slimību ārstēšanas vadlīnijām. Ceftriaxone bija otrs biežāk pielietotais antobakteriālais līdzeklis, kas neatbilst ārstēšanas vadlīnijām. Antibikateriālā terapija tika pielietota gandrīz pusei no visiem pacientiem.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) (Dignass et al 2010) are the most frequent IBD forms, while such forms as microscopic colitis (collagenous colitis and lymphocytic colitis) are of rare occurrence (Axel Dignas set al 2012*)*. The data about the most frequent IBD form, respectively, UC, was dealt within the research. UC is a disease which affects the mucuous membrane of the colon. Like in the case of CD, etiology is unknown. The symptoms of the disease

are chronic diarrhea with or without blood admixture, discomfort and pain in the area of stomach. Exacerbations are possible during which severe diarrhea (more than 10 times per day) and stomach ache are typical. The disease may become complicated due to intestinal perforation and bleeding, toxic dilatation of the colon and venous thrombosis (://www.ccfa.org/resources/antibiotics. html?referrer=). Like in the case of CD, the therapy plan depends on the severity degree of the disease. Antibacterial therapy is indicated only in the cases, when there is suspicion of infectious complications, or when immediate surgery is assigned for the patient (Daniel et al 2003).

Unjustified use of antibiotics leads to increased microbial resistance to antibacterial treatment. Often in cases of colitis, antibacterial therapy is unnecessarily implemented without proper investigation of the severeness of the illness and its course, causing additional complications and problems with choosing adequate therapy.

Aim of the research

Aim of the research was to analyse and evaluate the applied antibacterial therapy in patients with UC, and evaluate its conformity with the latest European Crohn's and Colitis organisation (ECCO) IBD therapy guidelines, thereby concluding for the conformity of its application.

Materials and methods

The design of the research – retrospective research.

Clinical documentation of the medical archive was analysed in the research regarding the patients who had been admitted to Riga East Clinical university hospital "Gaiļezers" with the diagnosis K51 (SSK-10), within the period from 2010 to 2015 included. The patients' selection was performed by means of the computer program "Physicians' office". The inclusion criteria were as follows:

- Gender: women and men
- Patients with confirmed IBD (ulcerative colitis)

The exclusion criteria were as follows:

- Patients with the suspicion of IBD (indeterminate colitis)
- Patients with Crohn's disease

On the basis of the relevant medical documentation the following aspects were analyzed: age and gender of the patients, duration of the hospital stay, the form of IBD: UC, CD; the phase of the disease, the length of IBD, as well as the co-occurring disorders which might be related to the application of the antibacterial therapy for therapeutic or health control purposes. The interventions performed during the hospital stay were dealth with, as well. The applied antibacterial therapy and combinations of these medications were analysed.

An original research protocol and data base were established. The data were summarized and statistically processed by using nonparametrical tests with SPSS ver 23.0.

Results

700 cases of admission to the hospital were examined, out of which 389 (55.6%) were women and 311 (44.4%) men (the average age 47±19.7 years). There were 416 (59.4%) UC and 199 (28.4%) CD cases; the rest refer to IBD *suspecta* and were not analysed further. Out of all UC patients 329 (79.08%) were urgently admitted to the hospital with exacerbation of the disease, while 11 (2.64%) patients were admitted in order to have their diagnosis specified. Inflammatory bowel disease was detected for 276 (18.26%) patients as a co-occurring diagnosis, respectively, the patients were admitted to the hospital due to the co-occurring disorders. The average number of days spent at the hospital constituted 8.7 days (SD = 7.345). 6.9 years was the average length of IBD. Interventions were performed for 52 (7.4%) patients during their stay at the hospital in connection with IBD (abscess drainage, fistula surgery, establishment of anastomoses, establishment or closing of stomas).

The results of our research indicate that women and men are most often admitted to the hospital due to UC. It was more common for men to have UC than women: out of all hospitalised women 221 (59.8%) had UC but out of all hospitalised men 195 (62.7 %) had UC.

In the case of UC, Metronidazole was the most commonly used antibacterial medication, respectively, in 133 (19.0 %) cases. Ciprofloxacin and Ceftriaxone were used equally often: in 62 (37.12 %) cases. In 94 (22.59 %) cases combinations of antibiotics were used. Most common combinations were Ciprofloxacine and Metronidazole used in 46 (11.1 %) cases; Ceftriaxone and Metronidazole used in 34 (8.2 %) cases and Ciprofloxacine, Metronidazole and Ceftriaxone all together in 5 (1.2 %) cases. In 9 (2.16 %) cases other antibiotic combinations were used.

Discussion

The literature data indicate that there are 1.6 million CD patients in Europe and 2.1 million people with UC (Burischa et al 2013). The World Gastroenterology Organisation (Kaser et al 2010) recommends to apply antibacterial therapy for the CD patients in cases of complications, for example, in the case of fistulas, abscesses, bacterial proliferation syndrome and intestinal strictures. It was statistically credibly approved in the research (Khurram J Khan et al 2011) that the antibacterial therapy applied during the exacerbation of CD and UC considerably improves the patients' condition in comparison to placebo (Khurram J Khan et al 2011). Similarly, in the case of CD complications (fistulas), by using ciprofloxacin or metronidazole, statistically credible data have been obtained about efficient treatment, namely, the possibility of fistulas closure increases (Sutherlanet al 1991). Taking into account the aforementioned information, it may be concluded that it is important to clarify the clinical activity of IBD and evaluate the existence of complications in the patient who has been admitted to the hospital, and decide upon the usefulness of the antibacterial therapy application afterwards. It follows from our research that the disease phase was

established only for 349 out of 700 patients. Perhaps, the physicians were not informed about the necessity to determine the IBD form.

Ceftriaxone is the second most frequently used antibacterial medication in our research, which was applied for IBD patients. It contradicts the ECCO guidelines, respectively, the ECCO IBD therapy guidelines do not recommend the use of this antibacterial medication for IBD patients. No research has been carried out on the treatment effect of ceftriaxone in IBD patients. There is one description of the case (Mattis et al.; Lederman et al 2004) in pediatrics, where autoimmune hemolytic anemia caused by ceftriaxone to a 9 years old CD patient is presented. The use of ceftriaxone for the IBD patients would be justified only due to co-occurring disorders, for example, the treatment of severe pneumonia, in the case of enterocolitis caused by *Salmonella spp.* or in case of systemic disease, skin infection caused by *Nocardia spp.,* or in case of systemic disease (Arias-Loste et al 2012, Mattis et al 2004, Longmore et al 2014). In order to interpret correctly, why the ceftriaxone therapy was applied to 148 IBD patients - 60 CD patients and 62 UC patients in our research, it would be important to clarify, whether these patients had any co-occurring diagnosis, while being admitted to the hospital, which the attending physician considered as important enough to start the ceftriaxone therapy irrespective of IBD. Taking into account that the medical documentation of the hospital was completed only partially, we experienced difficulties in order to establish the necessity of the use of ceftriaxone.

The use of metronidazole for IBD patients is recommended according to the ECCO guidelines, and its positive treatment effect has been also confirmed in several studies for IBD patients with infection caused by *C. difficile* (Arias-Loste et al 2012), for patients of Crohn's disease after small intestine resection (Rutgeerts et al 1995, Rahier et al 2009). Metronidazole may be used also for UC patients after IPAA (ileal pouch–anal anastomosis) and in the case of anastomosis inflammation (Siegmund B et al 2004). In our research metronidazole was used in 262 cases: 133 UC and 90 CD cases, consequently it is the most often used medication.

The ECCO guidelines support the use of a combination of metronidazole and ciprofloxacin especially for CD patients with perianal fistulas. A statistically positive treatment trend was observed in several studies within the active period of the Crohn's disease, by using this medication combination especially in the cases, when the colon was involved in the pathological process (Greenbloom et al 1998). In the case of the ulcerative colitis, no advantages of the combination of metronidazole and ciprofloxacin are mentioned in the ECCO guidelines, therefore it may be concluded that it does not have a significant treatment advantage as compared to metronidazole in monotherapy.

Taking into account the completion shortcomings of the medical documentation, it is impossible to explain the fact why in 12 cases all the three antibacterial medications – ceftriaxone, metronidazole and ciprofloxacin were used. Neither in the ECCO guidelines, nor in other sources,

any information was found on the combined application of the said medications. It would be important to specify, whether these medications have been given simultaneously to or instead of the prescribed therapy.

Conclusions

1. Metronidazole is the most frequently used antibacterial medication in the case of UC, which corresponds to the ECCO IBD therapy guidelines.
2. Ceftriaxone is the second most often used antibacterial medication, however, its use does not correspond to the ECCO IBD therapy guidelines, and the use of this medication for these patients has not been justified properly in the medical documentation.
3. Antibacterial therapy was applied for almost a half of the patients admitted to the hospital in order to specify the diagnosis which may not be explained with the health control and treatment indications, and therefore indicates certain methodological problems.

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PREGNANCY YOGA CLASSES – POTENTIAL BENEFITS FOR MOTHER HEALTH

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Abstract

Pregnancy yoga classes-potential benefits for mother health

Key words: *Yoga, physical activity, pregnancy, labour outcome*

Introduction: A regular moderate intensity physical activity during pregnancy is recommended by international guidelines. Health benefits include reduced risk of excessive gestational weight gain and conditions such as gestational diabetes and preeclampsia. Psychological benefits of physical activity during pregnancy include reduced stress, as well as improved well-being and satisfaction with the childbirth experience.
Aim: To find out how yoga practice affects the course of pregnancy and childbirth outcomes compared pregnant women who attend yoga with a control group - pregnant women who do not attend yoga.
Materials and methods: Study was conducted in 3 yoga studios in Riga. Women who attended "Prenatal yoga" were surveyed. The second part of survey was carried out after the childbirth. The control group consisted of women in postpartum period, who do not attended yoga.
Results: A total of 58 women (29 in yoga group and 29 in control group) participated in a study. Women in yoga group had less weight gain than control group - mean 14.55 ±2.68 kg vs. 17.03 ±3.61 kg. The rate of Caesarean section was 6.9% (n=2) vs. 20.7 % (n=6), using of epidural anaesthesia – 34.5 % (n=10) vs. 20.7 % (n=6), labour complications - perineal tears – 20.7 % (n=6) vs. 37.9 % (n=11). Psychological aspects-satisfaction with the childbirth experience, which was rated from 1-5, shows mean 4.45 vs. 4.03. Rating about how labour proceeded according to expectations shows mean 3.97 vs. 3.38.
Conclusion: Prenatal yoga has positive role on pregnancy course and labour. Women, who practiced yoga, had better results in psychological aspects, physical conditions and partly in perinatal outcomes.

Kopsavilkums

Joga grūtniecības laikā- potenciālie ieguvumi mātes veselībai

Atslēgas vārdi: *Joga, fiziskās aktivitātes, grūtniecība, dzemdību iznākums*

Ievads: Regulāras mērenas intensitātes fiziskās aktivitātes grūtniecības laikā tiek rekomendētas starptautiskajās vadlīnijās. Ieguvumi no fiziskajām aktivitātēm grūtniecības laikā ietver samazinātu risku pārmērīgam svara pieaugumam, kā arī gestācijas diabētam, preeklampsijai un priekšlaicīgām dzemdībām. Psiholoģiskie ieguvumi ir mazāks stresa un noguruma līmenis, kā arī augstāka labsajūta un apmierinātība ar dzemdību pieredzi.
Mērķis: Noskaidrot, kā jogas nodarbību apmeklēšana ietekmē grūtniecības gaitu un dzemdību iznākumu, salīdzinot grūtnieces, kas apmeklē jogu, ar kontroles grupu – grūtniecēm, kas neapmeklē jogu.
Materiāli un metodes: Pētījums norisinājās 3 jogas studijās Rīgā. Grūtnieces, kuras apmeklēja jogas nodarbības, tika aptaujātas. Aptaujas otrā daļa notika pēc dzemdībām. Kontroles grupā tika aptaujātas sievietes, kas neapmeklēja grūtnieču jogu.
Rezultāti: Kopā 58 sievietes (29 jogas grupā un 29 kontroles grupā) piedalījās pētījumā.
Grūtniecēm jogas grupā bija mazāks svara pieaugums nekā kontroles grupā -vidēji 14.55 ±2.68 kg vs. 17.03 ±3,61 kg. Tika salīdzināti dati par dzemdību iznākumu : Ķeizargriezienu operāciju daudzums – 6.9% (n=2) jogas grupā un 20.7 % (n=6) kontroles grupā, epidurālās anestēzijas lietošana – 34.5 % (n=10) vs. 20.7 % (n=6), stimulācija ar oksitocīnu – 10.3 % (n=3) vs. 37.9 % (n=11), dzemdību komplikācija- starpenes plīsumi – 20.7 % (n=6) vs. 37.9 % (n=11). Tika salīdzināti arī psiholoģiskie faktori. Apmierinātība ar dzemdību norisi, kura tika vērtēta skalā 1-5, parādīja rezultātu vidēji 4.45 vs. 4,03. Vērtējums par to, vai dzemdības atbilda tam, kā bija iecerēts, atspoguļo vidējo rādītāju 3.97 vs. 3.38.
Secinājumi: Jogai grūtniecības laikā ir pozitīva ietekme uz grūtniecības gaitu un dzemdībām. Sievietēm, kuras apmeklēja grūtnieču jogu, bija labāki vidējie rādītāji psiholoģiskajos aspektos, fiziskajos rādītājos (mazāks svara pieaugums) un daļēji dzemdību iznākumos.

Introduction

Physical activity is important in all stages of human life. It maintains and improves cardiorespiratory fitness, reduces the risk of obesity and associated comorbidities, and results in greater longevity. "Women who begin their pregnancy with a healthy lifestyle (for example,

exercise, good nutrition, nonsmoking) should be encouraged to maintain those healthy habits. Those who do not have healthy lifestyles should be encouraged to view the preconception period and pregnancy as opportunities to embrace healthier routines. Exercise, defined as physical activity consisting of planned, structured, and repetitive bodily movements done to improve one or more components of physical fitness, is an essential element of a healthy lifestyle, and obstetrician–gynaecologists and other obstetric care providers should encourage their patients to continue or to commence exercise as an important component of optimal health" (ACOG 2015).

A regular moderate intensity physical activity during pregnancy is recommended by international guidelines. "Health benefits of physical activity during pregnancy include reduced risk of excessive gestational weight gain and conditions such as gestational diabetes, preeclampsia, preterm birth, varicose veins, and deep vein thrombosis. There is some evidence that physical activity during pregnancy is associated with a reduced length of labour and delivery complications. However, vigorous leisure activity is associated with reduced birth weight. Psychological benefits to physical activity during pregnancy include reduced fatigue, stress, anxiety, and depression, as well as improved well-being. From a public health perspective, women who are active during pregnancy are more likely to continue physical activity during postpartum" (Kelly *et al*. 2015).

"Physiologic responses to exercise, such as changes in heart rate, cardiac output, ventilation, and energy expenditure, are all greater during pregnancy than prepregnancy, and may become more pronounced as pregnancy progresses. Hormonal changes increase joint laxity that may place a woman at increased risk for injury. Adaptations to physical activity are needed to reduce the risk of injury for both the mother and baby". (Kelly et al., 2015) Prenatal yoga classes are one of options, which provide moderate intensity physical activity and are available for pregnant women in Latvia. "Much like other types of childbirth-preparation classes, prenatal yoga is a multifaceted approach to exercise that encourages stretching, mental centering and focused breathing. Research suggests that prenatal yoga is safe and can have many benefits for pregnant women and their babies. Research suggests that prenatal yoga can: improve sleep, reduce stress and anxiety, increase the strength, flexibility and endurance of muscles needed for childbirth, decrease lower back pain, nausea, carpal tunnel syndrome symptoms, headaches and shortness of breath" (Mayo clinic 2015).

There are no national guidelines about physical activities during pregnancy in Latvia. Also there are few information sources and studies about physical activity impact and forms for pregnant women and antenatal care specialists. The aim of this study is to find out how yoga practice affects the course of pregnancy and childbirth outcomes compared pregnant women who attend yoga with a control group - pregnant women who do not attend yoga.

Materials and methods

Prospective study was conducted in 3 yoga studios in Riga from January 2016 to January 2017. Women who attended "Prenatal yoga" classes and women from control group were surveyed. The second part of survey was carried out after the childbirth. The questionnaire included questions about their basic medical history, weight and height, lifestyle factors, pregnancy course, habits of physical activity and prenatal yoga, childbirth outcome and psychological aspects. "Prenatal yoga" classes are specialized yoga trainings with breathing and stretching exercises, usually 1 hour long. The control group consisted of randomly selected women with similar age and parity in postpartum period, who did not attend prenatal yoga. Analysis and summary of information acquired with Microsoft Excel 2010 and IBM SPSS 20 programs. Mean values of the women age, body mass index and other mean parameters were calculated with standard deviation values according to the format: mean ± SD. The results were considered statistically significant if $p < 0.05$. The distribution of data was assessed using *Shapiro – Wilk* test and normally distributed data were described using mean value and standard deviation (SD), data that didn't have normal distribution were described using median value and interquartile range (IQR).

Results

A total of 58 women (29 in yoga group and 29 in control group) participated in a study. Mean age was 31.59 ± 4.14 in yoga group. The age distribution reflects the normal distribution curve (*Shapiro-Wilk test*, p=0.369). The minimum value – 24 years, the maximum value – 40 years. The mean age in control group was 29.83 ± 5.31. The age distribution reflects the normal distribution curve (*Shapiro-Wilk test*, p=0.272). The minimum value– 23 years, the maximum value – 40 years.

The mean body mass index (BMI) before pregnancy in yoga group was 20.93 ±1.51. The minimum value – 17.2, the maximum value – 24.2. The mean BMI before pregnancy in control group was 23.16 ± 2.62. The minimum value– 17.9, the maximum value – 29.7.

The questionnaire included also questions about medical and gynaecological history. For approximately half of women in each group this was the first pregnancy, for other half – second or third. Parity is compared in Figure 1.

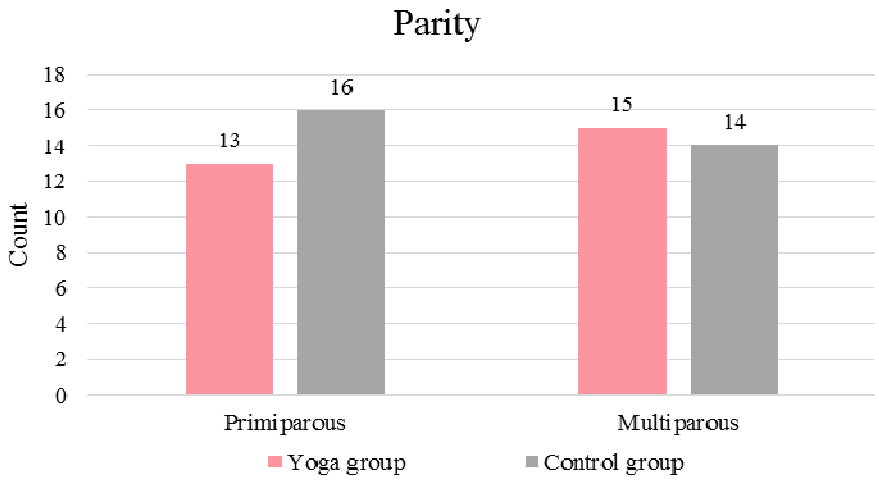

Figure 1. **Parity**

Women in yoga group had less weight gain during pregnancy than in control group - mean 14.55 ± 2.68 kilograms vs. 17.03 ± 3.61 kilograms. Analysing the weight gain with the *Mann-Whitney U test*, it was found that in the yoga group weight gain is statistically significantly less than in control group (p = 0.006).

Following data about labour outcome had compared: the rate of Caesarean section was 6.9% (n=2) in yoga group and 20.7% (n=6) in control group. Analysing the number of Caesarean sections with *Chi-square test*, in the yoga group number of Caesarean section is in lower percentage, but there was no statistically significant difference (p = 0.128).

As the subsequent factors, that were compared in yoga group and control group, were the need for epidural anaesthesia use and the need for birth stimulation with oxytocin. Epidural anaesthesia was used in 34.5 % (n=10) cases in yoga group and in 20.7 % (n=6) cases control group (p = 0.062). Stimulation with oxytocin frequency was 10.3 % (n=3) in yoga group and 37.9 % (n=11) in control group (p = 0.134).

Labour complications are compared in Figure 2. Perineal tears were more often in control group – in 37.9 % (n=11) cases, compared with 20.7 % (n=6) in yoga group (p = 0.074). Labour disorders also were more often in control group.

	Yoga group	**Control group**
Labour disorders	2 (6.9%)	6 (20.7%)
Perineal tears	6 (20.7%)	11 (37.9%)
Others	1 (3.4%)	1 (3.4%)

Figure 2. **Labour complications**

New-born's weight and height were also compared. There are no statistically significant differences between new-born's weight and height in the yoga group and in the control group (p = 0.669 and p = 0.612). The average new-born's weight (median(IQR)) was 3.595 (3.360-3.920) kilograms in yoga group and 3.573 (3.131-4.025) kg in control group, average height – 53.52 (53-54) centimetres in yoga group and 53.24 (52-54.5) centimetres in control group.

Also psychological aspects were compared. Satisfaction with the childbirth experience, which was rated from 1 to 5, shows mean 4.45 ± 0.87 in yoga group and 4.03 ± 0.94 in control group (p=0,069). Rating about how labour proceeded according to expectations, rated from 1 to 5, shows mean 3.97 ± 1.05 in yoga group and 3.38 ± 1.35 in control group (p=0,091).

Habits of attendance of yoga classes are shown in Figure 3. Yoga classes are attended once a week (52%) or two to three times a week (48%).

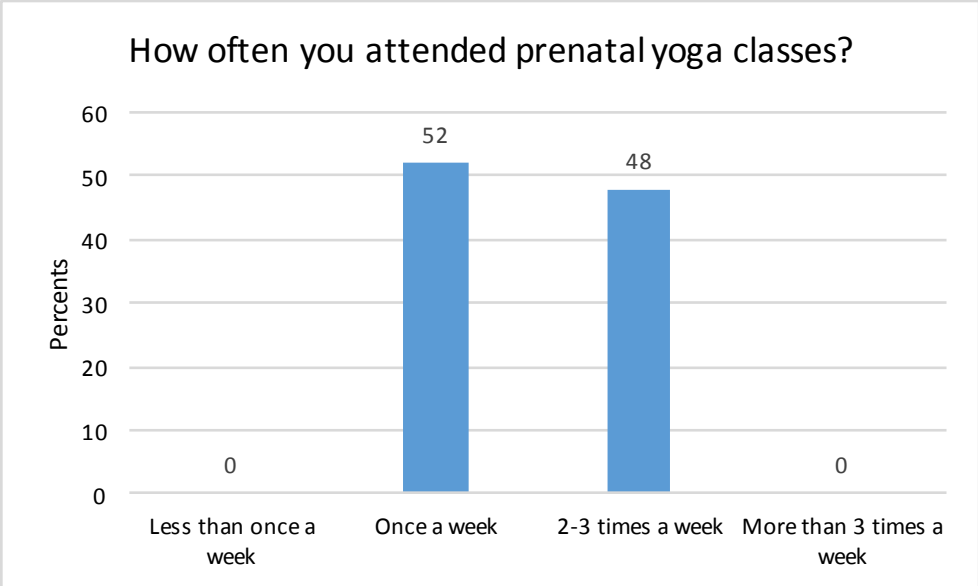

Figure 3. **Frequency of prenatal yoga classes attendance**

Yoga group participants were asked to respond to a question about the benefits of yoga attendance. Almost all (27 members) said that it helped to feel emotionally well during pregnancy. None of the survey participants mentioned that it has no effect. Other answers and the frequency are reflected in Figure 4.

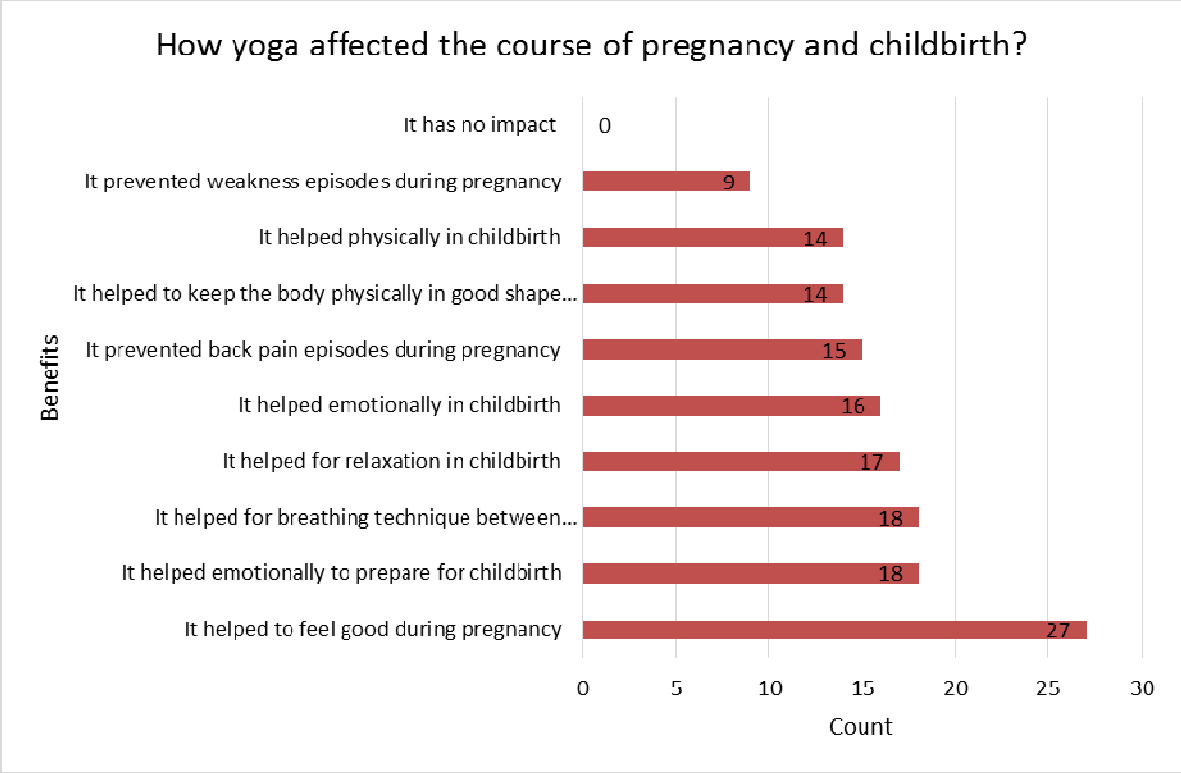

Figure 4. **Benefits of prenatal yoga**

Discussions

Prenatal yoga has different benefits for mother health. According to this study, women who attended pregnancy yoga classes have better results in psychological and emotional aspects. Looking at others sources and studies, many authors emphasize the importance of yoga in mental health and well-being. In a study, where twice during pregnancy, yoga group participants reported on affect and provided a saliva sample before and after a 90-min prenatal Hatha yoga session, cortisol was lower and positive affect higher on yoga compared to usual activity days. Negative affect and contentment improved more in response to the yoga session. Yoga group participants showed fewer postpartum but not antepartum depressive symptoms than control group participants. Findings indicate that prenatal Hatha yoga may improve current mood and may be effective in reducing postpartum depressive symptoms (Bershadsky *et al*. 2014). Other studies approve that prenatal yoga has benefits also for physical conditions and perinatal outcomes. The findings suggest that prenatal yoga may help reduce pelvic pain. It may also improve mental condition (stress, depression, anxiety, etc.), physical condition (pain and pleasure at the delivery, etc.), and perinatal outcomes - obstetrical complications and delivery time (Kawanishi *et al.* 2015). Other group, where prenatal yoga has benefits, is high risk pregnancies. The results of study of yoga in high-risk pregnancy suggest that guided yogic practices and visualization can improve the intrauterine fetal growth and the utero-fetal-placental circulation (Rakhshani *et al*. 2015).

Conclusions

Prenatal yoga has positive role on pregnancy course and labour. Pregnant women who attended yoga have less childbirth complications, less stimulation with oxytocin frequency and lower incidence of Caesarean section. Pregnant women who attended yoga have statistically significantly lower weight gain during pregnancy than in control group.

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VITAMINS AND MICRO NUTRIENT SUPPLEMENTS DURING PREGNANCY

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Abstract

Vitamins and micro nutrient supplements during pregnancy

Key words: *pregnancy, anemia, vitamins, micronutrient supplements, iron, folic acid*

Introduction: A lot of studies evaluate the essential vitamins, microelements and macroelements effects on the pregnancy and its outcome. In some countries, e.g. Canada, guidelines have been developed for pregnant women, which included recommendations about certain dietary supplements and vitamin use.

Aim: To clarify the vitamins and nutritional supplements usage habits among pregnant women and assess how does it conforms with international recommendations.

Material and methods: the survey was carried out in Maternal and child care unit in Riga Maternity hospital. 100 randomly selected women in postpartum period were surveyed and their medical data were collected.

Results: 100% (n=100) of research participants were using vitamins or nutrition supplements during pregnancy. 66% (n=66) were using special complex vitamins for pregnant women. 69% (n=69) were using any of microelement separately (iron, calcium, magnesium, B6 and D vitamin, folic acid, iodine). Analyzing use of separate nutrition supplement, the most used is iron supplements - 38% (n=38), MgB6 - 28% (n=28), folic acid 25% (n=25). Assessing compound of complex vitamins elements and nutrition supplements, most pregnant women provided themselves with these elements: 96 % (n=96) iron, 82% (n=82) folic acid, 82% (n=82) MgB6, 65% (n=65) calcium and 65% (n=65) D vitamin.

Conclusions: The most used nutrition supplement is iron, which can be explained with the widespread distribution of anemia during pregnancy. There are required additional knowledge and understanding of certain vitamins, macro- and microelements role and use during the pregnancy for both antenatal care specialists and pregnant women.

Kopsavilkums

Vitamīni un mikroelementu uzturvielu bagātinātāji grūtniecības laikā

Atslēgas vārdi: *grūtniecība, anēmija, vitamīni, mikroelementi, dzelzs, folskābe*

Ievads: Pētījumi apliecina būtisku vitamīnu, mikroelementu un makroelementu ietekmi uz grūtniecības norisi un iznākumu. Atsevišķās valstīs, piemēram, Kanādā, ir izstrādātas vadlīnijas grūtniecēm , kurās rekomendēta atsevišķu uztura bagātinātāju un vitamīnu lietošana

Mērķis: Noskaidrot vitamīnu un uztura bagātinātāju lietošanas paradumus grūtnieču vidū un izvērtēt , kā to lietošana atbilst starptautiskām rekomendācijām.

Materiāli un metodes: tika veikta 100 nejauši izvēlētu nedēļnieču aptauja un iegūti dati no medicīniskās dokumentācijas Rīgas Dzemdību namā, Mātes un bērna aprūpes centrā.

Rezultāti: 100% (n=100) pētījuma dalībnieču grūtniecības laikā lietoja vitamīnus vai uztura bagātinātājus. 66% (n=66) lietoja specializētos grūtnieču kompleksos vitamīnus. 69% (n=69) lietoja kādu no mikroelementiem atsevišķi (dzelzs, Ca, Mg, B6, D vitamīns, folskābe). Analizējot atsevišķu uztura bagātinātāju lietošanu, visvairāk lietoja dzelzi saturošus preparātus - 38% (n=38), MgB6 - 28% (n=28), folskābi 25% (n=25). Izvērtējot komplekso vitamīnu sastāvā esošo elementu un atsevišķo preparātu sastāvu, visvairāk grūtnieces nodrošināja sevi ar šādiem elementiem - 96 % (n=96) dzelzs, 82% (n=82) folskābe, 82% (n=82) MgB6, 65% (n=65) kalcijs un 65% (n=65) D vitamīns.

Secinājumi: Visbiežāk lietotais ir dzelzs preparāts, ko var skaidrot ar grūtnieču anēmijas plašo izplatību. Nepieciešamas papildus zināšanas un izpratne par noteiktu vitamīnu, mikroelementu un makroelementu nozīmi un lietošanu grūtniecības laikā gan antenatālās aprūpes speciālistu, gan grūtnieču vidū.

Introduction

A balanced diet with adequate energy intake usually provides an adequate supply of the essential micronutrients. Although a balanced diet is generally accessible for the European population, specific groups have inadequate vitamin and mineral intakes, especially with regards to iron, iodide, folic acid, vitamin D and vitamin B_{12}. Micronutrient malnutrition represents an important challenge for public health worldwide, particularly in vulnerable population groups such as pregnant women (Berti *et al.* 2011).

Nutritional supplements, which are recommended for pregnant women, are folic acid, iron, calcium, vitamin D, iodine, magnesium and vitamin B6. It is recommended that all women of childbearing age consume 0.4 mg (400 micrograms) of folic acid daily to prevent two common and serious birth defects, spina bifida and anencephaly (CDC 2016). Folate needs increase substantially in pregnancy owing to the enlargement of the uterus, the development of the placenta, and the increasing red cell volume of the mother, as well as the growth of the developing fetus. There is consistent scientific evidence that folic acid is of critical importance both pre- and prericonceptionally in protecting the fetus from neural tube defects (Berti *et al.* 2011).

Iron supplements are important for pregnant women. In settings where anemia in pregnant women is a severe public health problem (i.e. where at least 40% of pregnant women have a blood hemoglobin [Hb] concentration < 110 g/L), a daily dose of 60 mg of elemental iron is preferred over a lower dose. In the first and third trimesters, the Hb threshold for diagnosing anemia is 110 g/L; in the second trimester, the threshold is 105 g/L. If a woman is diagnosed with anemia during pregnancy, her daily elemental iron should be increased to 120 mg until her Hb concentration rises to normal (Hb 110 g/L or higher). Thereafter, she can resume the standard daily antenatal iron dose (60 mg) to prevent recurrence of anemia (WHO 2012).

In populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of preeclampsia among pregnant women, particularly among those at higher risk of hypertension. A suggested scheme for supplementation in pregnant women is 1.5–2.0 g elemental calcium per day, from 20 weeks' gestation until the end of pregnancy, daily, with the total daily dosage divided into three doses, preferably taken at mealtimes (WHO 2013).

Vitamin D, a lipid-soluble vitamin and prohormone, is known to play an important role in bone metabolism through regulation of calcium and phosphate homeostasis. Although relatively few countries have nationally representative data available on the vitamin D status of their population, vitamin D deficiency is suspected to be a public health problem in many parts of the world. Vitamin D deficiency in pregnancy has been associated with an increased risk of pre-eclampsia, gestational diabetes mellitus, preterm birth, small-for-gestational age infants, impaired fetal skeletal formation causing infant rickets (softening of bones commonly leading to deformities and/or fractures) and reduced bone mass, as well as other tissue-specific conditions. Immune dysfunction, placental implantation, angiogenesis (abnormal growth of new blood vessels from pre-existing vessels), excessive inflammation and hypertension in the mother have also been associated with vitamin D deficiency, although the underlying pathogenic mechanisms are not well understood. In cases of documented deficiency, vitamin D supplements may be given in dose- 5 μg (200 IU) per day. Vitamin D may be given alone or as part of a multiple micronutrient supplement,

to improve maternal serum vitamin D concentrations (WHO 2012) A recent study found women taking 4,000 IU of vitamin D daily had the greatest benefits in preventing preterm labor/births and infections (American Pregnancy Association, 2017).

Iodine is an essential nutrient required for the biosynthesis of thyroid hormones, which are responsible for regulating growth, development and metabolism. Iodine requirements increase substantially during pregnancy and breastfeeding. If requirements are not met during these periods, the production of thyroid hormones may decrease and be inadequate for maternal, fetal and infant needs. The provision of iodine supplements may help meet the increased iodine needs during pregnancy and the postpartum period and prevent or correct iodine deficiency and its consequences. In case of iodine deficiency there is increased possibility of undeveloped thyroid gland, developmental delay, deafness, cretinism, and perinatal mortality. It is 150 μg recommended iodine per day (Harding *et al.* 2017).

Magnesium is an essential mineral required for regulation of body temperature, nucleic acid and protein synthesis and in maintaining nerve and muscle cell electrical potentials. Many women, especially those from disadvantaged backgrounds, have low intakes of magnesium. Magnesium supplementation during pregnancy may be able to reduce fetal growth restriction and preeclampsia, and increase birth weight. Recommended maximum dose per day is 350 mg of magnesium (Makrides *et al.* 2014).

Vitamin B_6 is important for several metabolic processes, as well as development and functioning of the nervous system, primarily through the biosynthesis of neurotransmitters. Recommended dose of vitamin B_6 is 1.9 -2 mg (WHO 2016).

According to the World Health Organization (WHO) and the *National Institute of Clinical Excellence* (NICE) guidelines in the United Kingdom the following is recommended to pregnant women: 1,5-2g calcium, 200-2000IU (5-50 μg) vitamin D, 30-60 mg iron (in anaemia case - 120 mg), 0.4 mg folic acid (5 mg when there is risk factors), 1.9 -2 mg of vitamin B_6, 350mg of magnesium maximum and 150 μg iodine per day.

The aim of this study is to clarify the vitamins and nutritional supplements usage habits among pregnant women and assess how does it conforms with international recommendations.

Materials and methods

The survey was carried out in Maternal and child care unit in Riga Maternity hospital. 100 randomly selected women in postpartum period were surveyed and their medical data were collected. The questionnaire included questions about their basic medical history, lifestyle factors, pregnancy course, habits of using vitamins and micro nutrient supplements and childbirth outcome. All the data obtained were processed with Microsoft Excel 2010 program. The composition of

vitamins and supplements was analysed and compared with the World Health Organization (WHO) and the National Institute of Clinical Excellence (NICE) guideline recommendations.

Results

Characteristics of the study group.

Age distribution in study group is following: 5% of women are under 20 years old, 14% in group from 21 to 25 years old, 39% in group 26-30 years old, 25% are from 31 to 35 years old, 15% of women are from 36 – 40 years old and 2% - from 41 to 45 years.

Almost a half of all women have higher education (43%, n=43), incomplete higher 11% (n=11), secondary vocational 13% (n=13), general secondary 19% (n=19), and 14% (n=14) – primary education.

This childbirth to women was first in 44% of cases (n=44), second in 43% (n=43), third in 11% (n=11), fourth and sixth in 1% each. In 17 cases (17%) previous pregnancy was less than one year before this one, and in 83% (n=83) previous pregnancy was more than one year before.

Outcomes of pregnancy.

12% of women had preterm delivery (until 36 weeks and 6 days of gestation), other 88% had term delivery, of whom 28% (n=28) delivery was in 37-39 weeks of gestation, 44% (n=44) in 40 weeks of gestation and 16% (n=16) in 41-42 weeks of gestation.

Newborn weight was divided into following groups: under 2600 grams (8%; n=8), from 2600 grams till 4000 grams (74%; n=74), and over 4000 grams (18%; n=18). 48% of newborns are girls, and 52% of newborns are boys.

Habits of using vitamins and nutrition supplements.

All of research participants (n=100) were using vitamins or nutrition supplements during pregnancy. 66% of them (n=66) were using complex vitamins for pregnant women, 69% (n=69) were using any of microelements separately. The most common microelements used separately are: iron (38%; n=38), magnesium in combination with B_6 vitamin (28%; n=28), folic acid (25%; n=25), calcium (11%; n=11), D vitamin (7%; n=7).

After assessing compound of vitamins and nutrition supplements used by women in study group, most pregnant women provided themselves: 96% (n=96) iron, 82% (n=82) folic acid, 82% (n=82) magnesium in combination with B_6 vitamin, 65% (n=65) calcium and 65% (n=65) D vitamin, 40% (n=40) iodine (fig.1, blue columns).

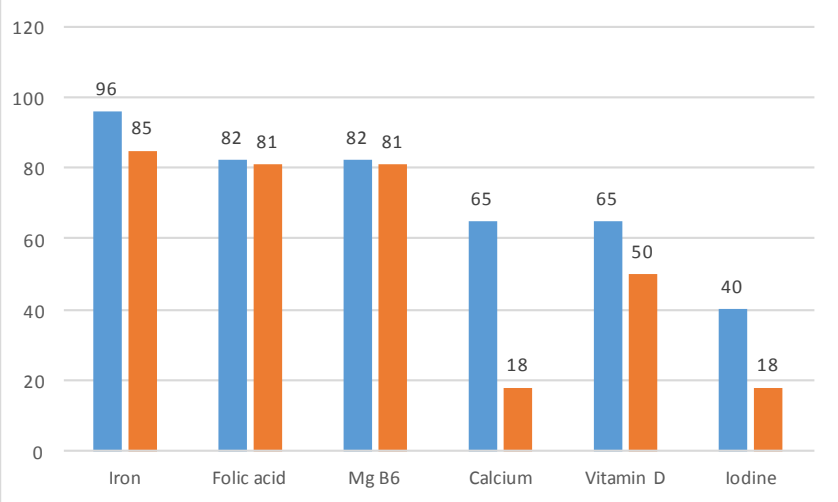

Figure 1. **The rate of pregnant women provided themselves with vitamins and nutrition supplements and the rate of pregnant women provided themselves with recommended amount of vitamins and nutrition supplements by WHO and NICE**

Comparing the amount of vitamins and microelements with WHO and NICE recommendations (fig. 1, orange columns), 85% (n=85) with iron, 81% (n=81) with folic acid and magnesium in combination with B_6 vitamin, 50% (n=50) with D vitamin, 29% (n=29) with iodine and 18% (n=18) with calcium of pregnant women provided themselves with necessary amount of vitamins and microelements.

Research participants started to use vitamins and microelements at different moment of pregnancy: 48% (n=48) started in the beginning of pregnancy, 16% (n=16) in mid-pregnancy, 21% (n=21) used a part in the beginning and a part later, 5% (n=5) in last weeks of pregnancy and 10% (n=10) used only when analyses showed decreased indicators.

In 58% of cases (n=58) gynaecologist, obstetrician or GP (general practitioner) advised to use vitamins and microelements, in 38% (n=38) pregnant women has chosen to use it by her own and in 4% of cases (n=4) – other.

Discussions

There are no united guidelines in Latvia about diet, use of vitamins and nutrition supplements for pregnant women. It will be very important to have recommendations, because some elements deficiency, for example, iodine deficiency in Latvia is quite common.

Results of the research shows that the most common nutrition supplement used is iron, what can be explained with widespread distribution of iron deficiency anaemia among pregnant women. Almost all pregnant women in study group provided themselves with necessary amount of iron. The level of haemoglobin in blood should be taken in account while prescribing iron supplements. In case of iron deficiency anaemia higher amount of iron daily should be prescribed to cover the loss of this microelement (WHO 2012).

There is no single point of view about effect of calcium on iron absorption in intestines. There is negative effect on iron absorption both by dairy products and calcium supplements on haem and non-haem iron. But still most of information suggest that changes in the calcium content have a small effect on iron absorption (Lynch 2000). Studies on human subjects long time suggested that calcium inhibits iron absorption in small intestines, regardless if it was taken in calcium salts or in dairy products. But recent reviews of studies in which calcium intake was substantially increased for long periods have showed no changes in haematological measures or indicators of iron status (Lonnerdal 2010).

As was mentioned, folic acid has metabolic effects that prevent two common and serious birth defects, spina bifida and anencephaly (CDC 2016). Pregnant women should intake 0,4 mg folate daily despite with folate rich diet. But if there are congenital central nervous system defects in family anamnesis or diabetes, the intake of folate during pregnancy should be increased to 5 mg daily. There is no need to use folic acid during all pregnancy, because neural tube closes approximately in 12 week of gestation, so it is recommended to use folate supplements one month before conception and in first three months of pregnancy. The use of folate after first pregnancy trimester does not have any effect on central nervous system diseases prevention.

There is a need in additional iodine intake in the situation of widespread iodine deficiency in Latvia. Study shows that only 29% of research participants provided themselves with necessary recommended amount of iodine.

Conclusions

All of research participants were using vitamins or nutrition supplements during pregnancy. Most women provided themselves with recommended amount of iron (85%), folates (81%) and magnesium in combination with B6 vitamins (81%).

None of the complex vitamins and nutrition supplements, which were used in the study group, contains all of these components in WHO and NICE recommended amount.

Three most important nutrition supplements during pregnancy are iron, folates and iodine, which intake is extremely necessary. It is difficult to access the real daily amount of vitamins and microelements that are consumed, because of variety of products containing these elements. May be a situation where pregnant women provided herself with necessary vitamins and microelements using diet only.

Additional knowledge and understanding of certain vitamins, macro- and microelements role and use during the pregnancy for both antenatal care specialists and pregnant women are required.

Acknowledgements

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RADIOLOGICAL ASSESSMENT OF FEMOROACETABULAR IMPINGEMENT IN HIP OSTEOARTHRITS PATIENTS

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Abstract

Radiological Assessment of Femoroacetabular Impingement in Hip Osteoarthritis Patients

Key words: *femoroacetabular impingement, hip, osteoarthritis, statistical shape modelling*

Femoroacetabular impingement (FAI) has been recognized as a risk factor for hip osteoarthritis (OA) development. Various radiological parameters and statistical shape analyses have been developed for the assessment of FAI. Aim of the study was to determine the prevalence and characteristics of FAI in patients with and without radiological signs of hip OA.

50 pelvic radiographs of unilateral hip OA patients and 50 patient radiographs with no definite signs of OA were retrospectively analysed. In both groups, alpha angle, lateral centre edge angle, neck shaft angle, acetabular depth, coverage was measured and the presence/absence of pistol grip deformity and crossover sign was assessed using the *Impax-Orthopaedic-Tools 3.0.2.3* program. SSMs were created using the *Bone Finder 1.2.0* program, which automatically sets 65 landmark points on the contour of the proximal femur.

In the Arthritis group there were significantly more cases of pathological alpha angles (>50^o) 66% vs. 28% (P<0.001), pistol grip deformities 56% vs. 12% (P<0.001) and acetabular protrusion 30% vs. 10% (P=0.02) comparing to Control group. There were significantly more cases with at least two signs of FAI in the Arthritis group – 74% vs. 34%. (P<0.001). Two of eight proximal femoral modes (mode 2, mode 4) were associated with hip OA characteristics (P=0.002; P=0.03).

Mixed-type femoroacetabular impingement is the most common impingement form and correlates with radiographic signs of OA. SSM can be used as a diagnostic tool and a radiographic biomarker for the risk assessment of subsequent OA development.

Kopsavilkums

Femoroacetabulārās atdures radioloģiskais izvērtējums gūžas locītavas osteoartrīta pacientiem

Atslēgvārdi: *femoroacetabulārā atdure, gūžas locītava, osteoartrīts, formu statistiskā modelēšana*

Femoroacetabulārā atdure ir arvien vairāk tiek atzīta kā gūžas locītavas osteoartrīta (OA) attīstības riska faktors. Mūsdienās ir noteikti vairāki rentgenoloģiskie parametri un statistiskās gūžas locītavas formas analīžu metodes femoroacetabulārās atdures izvērtēšanai. Pētījuma mērķis bija noteikt femoroacetabulārās atdures prevalenci un īpatnības pacientiem ar un bez rentgenoloģiskām OA pazīmēm.

Retrospektīvi tika analizētas 50 vienpusēja OA un 50 pacientu bez OA pazīmēm iegurņa rentgenogrammas. Abās grupās tika mērīts alfa leņķis, laterālais centra malas leņķis, kakla-ķermeņa leņķis, *acetabulum* dziļums, nosegums un izvērtēta pistoles tvēriema deformācija un krusteniskā pazīme *Impax-Orthopaedic-Tools 3.0.2.3* programmā. Statistiskie formas modeļi tika izveidoti ar *Bone Finder 1.2.0* programmu, kas automātiski izvieto 65 punktus ap ārējo proksimālā ciskas kaula kontūru.

Artrīta grupā statistiski ticami vairāk tika konstatēts patoloģiski paaugstināts alfa leņķis (>50^o) (66% pret 28%, P<0.001), pistoles tvēriena deformācija (56% pret 12%, P<0.001) un *acetabulum* protrūzija (30% pret 10%, P=0.02), salīdzinot ar kontroles grupu. Atrīta grupā vairākumā gadījumu pacientiem bija vismaz divas femoroacetabulārās atdures pazīmes (74% pret 34%, P<0.001). Divi no astoņiem formas modeļiem (otrais un ceturtais) pozitīvi korelēja ar OA rentgenoloģiskajām pazīmēm (P=0.002; P=0.03).

Jaukta tipa femoroacetabulārā atdure ir visbiežākais atdures veids un korelē ar rentgenoloģiskajām OA pazīmēm. Statistiskā formas modelēšana var tikt izmantota kā rentgenoloģiskais marķieris OA tālākas attīstīšanās riska izvērtēšanai.

Introduction

Osteoarthritis (OA) is the most common joint disorder and the most frequent cause of musculoskeletal disability in developed countries (Andrianakos *et. al*. 2006). The incidence of hip OA varies between different populations. In general, radiograohic signs of hip OA can be found in

8 % of the world population (Dagenais *et. al.* 2008). The prevalence of hip OA is increasing due to the aging population.

The pathogenesis of osteoarthritis still remains unclear. Nowadays there is a hypothesis, that most cases of OA develop secondarily because of morphological and anatomical abnormalities of the hip joint. One of the most frequent pathologies that is characterised by morphological abnormalities of the proximal femur and/or acetabulum is femoroacetabular impingement (FAI). For the first time FAI was recognised as a possible precursor of hip OA more than 50 years ago when Murray described the pistol grip deformity (Murray 1965). FAI is caused by repetitive contact between a widened femoral neck and a decreased offset at the head- neck junction (Beaule *et. al.* 2005). There are three types of FAI: cam-type, pincer-type and mixed-type (Ganz *et. al.* 2003).

In cam-type impingement (CTI) there is a nonspherical portion of the femoral head which is abutting against the acetabular rim. This causes outside-in abrasion of the acetabular cartilage, avulsion from the *labrum* and subchondral bone, leading to early onset of OA development (Ito *et. al.* 2001). Radiographic signs specific to CTI seen in AP pelvic radiographs are alpha angle more than 50^{o}, pistol grip deformity and *coxa vara*.

In pincer-type impingement (PTI) there is repeated contact between an over covered acetabular rim and the femoral head neck junction. The repeated contact causes labral degeneration, ossification of the acetabular rim, and deepening of the acetabulum (Beck *et. al.* 2005). Radiographic signs specific to CTI seen in AP pelvic radiographs are centre edge angle more than 39^{o}, crossover sign, *coxa profunda* and acetabular protrusion.

The most common form of impingement is the mixed- type. This is due to the fact that CTI and PTI are rarely found in isolation (Purnajyoti *et. al.* 2011). In a study by Beck *et. al.* (2005) 149 patient hips were evaluated preoperatively and during operation- only 26 hips had an isolated aspheric femoral head and 16 hips- isolated *coxa profunda*, the remaining hips had mixed-type FAI.

Since increasing evidence suggests that hip shape has a causative role in the development of OA and subsequent need for hip arthroplasty (Agricola *et. al.* 2013), various diagnostic methods have been developed for assessment of FAI. This pathology can be evaluated using radiographic measurements in AP, Dunn and cross-table lateral view pelvic radiographs. Statistical shape modelling (SSM) is a technique that recognizes all independent shape variants in the study group and describes them quantitatively (Agricola *et. al.* 2015). With SSM it is possible to identify specific shape variants at risk of developing OA. In year 2013 a fully automatic shape model matching system called *Bonefinder* was presented to derive statistical shape models of the proximal femur from AP pelvic radiographs (Linder *et. al.* 2013).

Material and methods

100 patient AP pelvic radiographs who were hospitalized in Latvian state Hospital of Traumatology and Orthopaedics from year 2014 to 2015 were retrospectively analysed. Patients were divided into two equal groups- Arthritis (50) and Control (50) group.

OA was defined by radiographic signs included in *Kellgren-Lawrence* classification- joint space narrowing, subchondral sclerosis and osteophytes (Kellgren *et. al.* 1957). The stage of OA was defined by *Tonnis* classification (Tonnis *et. al.* 1999): 0 stage- no signs of OA; I stage (mild) - increased sclerosis, slight narrowing of the joint space, no or slight loss of head sphericity; II stage (moderate) - small cysts, moderate narrowing of the joint space, moderate loss of head sphericity; III stage (severe) – large cysts, severe narrowing or obliteration of the joint space, severe deformity of the head.

The inclusion criteria in the Arthritis group were:

1. Unilateral hip arthroplasty due to OA
2. OA grade I/II on the contralateral hip

The inclusion criteria in the Control group were:

1. Bilaterally no or mild signs of OA (grade 0/I)
2. Patients aged atleast 65 years or older

The exclusion criteria were:

1. OA grade III (by *Tönnis*) on the contralateral hip in the Arthritis group
2. OA grade II, III (by *Tönnis*) in the Control group
3. Data about posttraumatic OA

Patients with OA grade III were not included in the study due to the severe deformity of the hip joint. If there is obliteration of the joint space, the radiographic parameters cannot be precisely measured.

The age limit in the Control group was determined because of the fact that after 65 years incidence of OA noticeably decreases (Zhang *et. al.* 2006). If the patient has no or mild arthritic changes in the hip there is little chance that OA will develop in further life. In both groups, alpha angle, lateral centre edge angle, neck shaft angle, acetabular depth, coverage was measured and the presence/absence of pistol grip deformity and crossover sign was assessed using the *Impax-Orthopaedic-Tools 3.0.2.3* program.

Proximal femoral shape was analysed using the *BoneFinder 1.2.0* program, which automatically sets 65 landmark points on the contour of the proximal femur. The program automatically generates statistical shape models which describe every shape by the sum of a mean shape and a linear combination of a number of shape modes where the shape mode values vary between subjects (Linder *et. al.* 2013).

The obtained date were analysed using IBM SPSS Statistics 23.0 program. Kolmogorov-Smirnow test was used for assessing normally distributed data. Radiographic parameters were compared between the two groups using Pearson's Chi-square Test, Independent Samples t Test and Mann-Whitney U test. P value equal or less than 0.05 was considered statistically significant.

Results

The mean age in both groups significantly differed- 67.40±11.78 (42-89) vs. 82.04±7.53 (65-94) years (P<0.001) due to inclusion criteria in Control group (age ≥65 years).

Table 1. **Radiographic parameters of femoroacetabular impingement**

Rentgenographic parameter	Arthritis group	Control group	P value
Pistol grip deformity	56%	12%	<0.001
α angle >50^{o}	66%	28%	<0.001
α angle >50^{o} and pistol grip deformity	54%	10%	<0.001
Crossover sign	40%	30%	0.40
Centre-edge angle >39^{o}	42%	34%	0.53
Coxa valga	6%	14%	0.31
Coxa vara	10%	8%	1.00
Coxa profunda	30%	38%	0.52
Acetabular protrusion	30%	10%	0.02

As seen in Table 1 in the Arthritis group there were significantly more cases of pathological alpha angles (>50^{o}), pistol grip deformities and acetabular protrusion comparing to Control group. Radiographic parameters characteristic for PTI (crossover sign and centre-edge angle >39^{o}) did not significantly differ between both groups. However acetabular protrusion which is a contributing factor for PTI was more frequent in Arthritis group. Pathological alpha angle (OR 4.99; 95% CI 3.13-11.68), pistol grip deformity (OR 9.33; 95% CI 2.13-11.68) and acetabular protrusion (OR 3.85 95% CI 1.28-11.64) has a positive correlation with radiographic characteristics of OA. By assessing the prevalence of pathological alpha angle between male and female patients it was significantly more prevalent in male patients (62.5% vs 39.7%, P=0.03). Centre-edge angle more than 39^{o} was equally frequent in male and female patients (37.5% vs 38.2%, P=0.94).

The most common sign of CTI was pathological alpha angle in 66% of OA and 28% of control group patients and the most frequent sign of PTI was centre-edge angle more than 39^{o} (42% and 34%). Mixed-type FAI was significantly more frequent in the Arthritis group compared to Control group- 32% vs. 0% (P<0.001). There were significantly more cases with at least two signs of FAI in the Arthritis group - 68.50% vs. 31.50%. (P<0.001) comparing to Control group. Presence of at least two signs of FAI has a positive correlation with radiographic characteristics of OA.

The shape variation of both groups was explained by eight modes. Two modes (Mode 2, Mode 4) showed a statistically significant correlation with radiographic characteristics of OA (for Mode 2- P=0.002, for Mode 4- P=0.03).

Discussion

There is growing evidence about FAI as a causative factor of hip OA. Radiographic signs of CTI (alpha angle >50^{o}, pistol grip deformity) were more prevalent in the Arthritis group which correlates with literature data (Khanna *et. al.* 2014). CTI is more frequently found in men which also was confirmed in our study. Nicholls *et. al.* (2011) identified that there was a 5.8% increased risk of requiring a total hip arthroplasty for every degree of increased alpha angle.

Pistol grip deformity had a strong correlation with the presence of radiographic signs of OA (OR 9.33; 95% CI 2.13-11.68). Doherty *et. al.* (2008) compared 1007 cases with advanced hip OA and 1123 controls without hip OA, and identified a smaller association- OR of 6.95 (95% CI 4.6–10.4) of developing OA if a pistol grip deformity was determined. This suggests that pistol grip deformity is a specific sign of CTI and an indicator of future OA development and need for hip arthroplasty

PTI can result from global (CEA >39° or acetabular protrusion) or localized acetabular over coverage of the femur. PTI is usually found more frequently in women but the prevalence between genders in our study was almost similar (37.5% vs 38.2%). From all parameters specific to PTI only acetabular protrusion showed a positive correlation with radiographic signs of OA. Gosvig *et. al.* (2010) determined that individuals with a deepened acetabular socket have 2.4 times higher chance of developing OA. The presence of α angle >50^{o} (28%) and centre-edge angle >39^{o} (34%) in patients without radiographic signs of OA suggests that there must be cofactors such as genetic predisposition, mixed-type FAI, high fizical activites, sublte trauma etc. that in combination with CTI and PTI cause articular damage and subsequent developement of OA. This is supported by the fact that mixed-type FAI was significantly more frequent in the Arthritis group compared to Control group- 32% vs. 0% (P<0.001; OR 2.47 95% CI 1.90-3.20).

As mentioned above SSM can be used to quantitatively describe the total variation of the proximal femoral shape to determine the association between specific modes and OA. By analysing the 100 AP pelvic radiographs eight shape modes were created to describe the overall proximal femoral shape variation in the study population. Two of which (Mode 2, Mode 4) shoved positive correlation with radiographic signs of OA. Mode 2 describes a wide femoral neck with a prominent, large greater trochanter and enlarged femoral head and Mode 4- a wide and short femoral neck with a non-spherical femoral head. Worldwide various subtle shape variants of the proximal femur and/or pelvis have been reported to be associated with OA (Agricola *et. al.* 2013; 2015). The development of automatic hip shape assessing systems using SSM is widely used to study the association between the hip shape and the risk of developing OA.

Conclusions

1. Alpha angle more than 50^{o} is the most common radiographic sign of cam-type impingement seen in anteroposterior pelvic radiographs.
2. Centre edge angle more than 39^{o} is the most common radiographic sign of pincer-type impingement seen in anteroposterior pelvic radiographs.
3. Mixed-type femoroacetabular impingement is the most common impingement form and correlates with radiographic signs of osteoarthritis.
4. Since cam and pincer type impingement is more common in arthritic patients but also present in some cases of non-arthritic joints, cofactors may have an important role in the development of osteoarthritis associated with femoroacetabular impingement.
5. Wide and short femoral neck with a prominent, large greater trochanter and enlarged non-spherical femoral head correlates with radiographic signs of osteoarthritis and may play a role in the hip joint degeneration.
6. Statistical shape modelling can be used as a diagnostic tool and a radiographic biomarker for the risk assessment of subsequent osteoarthritis development.

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COMPARISON OF THE EFFICACY OF INTRA-ARTICULAR PLATELET-RICH PLASMA AND CORTICOSTEROIDS IN THE TREATMENT OF MODERATE KNEE OSTEOARTHRITIS

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Abstract

Comparison of the efficacy of intra-articular platelet-rich plasma and corticosteroids in the treatment of moderate knee osteoarthritis

Key words: *platelet-rich plasma, corticosteroid, knee osteoarthritis, Kellgren - Lawrence classification, VAS, IKDC, KSS*

Introduction: Osteoarthritis is the most prevalent type of arthritis, which significantly impacts patients mobility and quality of life. The present interventions including intra-articular corticosteroid (CS) injections showed the lack of beneficial long-term outcomes. However, new approach in osteoarthritis management has emerged. Platelet-rich plasma (PRP) is an autologous blood product that has unique ability to promote tissue regeneration. PRP injections are widespread used by specialists in the treatment of knee osteoarthritis due to its high efficacy and safety.

Aim, Material and Methods: The aim of this study was to compare the efficacy and safety ofintra-articular platelet-rich plasma and corticosteroids in the treatment of knee osteoarthritis. 30 patients, with symptomatic radiologically confirmed (II-III grade by Kellgren-Lawrence classification) knee osteoarthritis, were enrolled in a prospective randomized study within the period from April 2016 to January 2017. Exclusion criteria were any history of previous knee surgical procedures and use of nonsteroidal anti-inflammatory drugs during 10 days prior the injection. Two groups were created by random selection: patients in PRP group (n=15) received intra-articularly 8 cc of PRP, patients in CS group (n=15) received intra-articulary 1 cc of 40mg/mL of triamcinolone acetonide and 5 cc of 2% of lidocaine. The severity of pain and the function of the affected knee were evaluated by International Knee Documentation Committee (IKDC) scale, by Visual Analogue Scale (VAS) for pain and by Knee society score (KSS) after one week (W1), one month (M1), three months (M3) and six months (M6).

Results: Data of 30 patients with mean age 68±9 years were analyzed. There were no significant differences between the two groups across age, sex, Kellgren-Lawrence grade for osteoarthritis, or laterality. VAS initial values in both PRP and CS groups were equal (mean ± standard error [SE] 6±1) and improved at W1 identically (mean±SE, 3±2). However, a significant interaction between time and treatment was identified comparing the VAS score of both groups. There was a statistically lower VAS score in the PRP group versus the CS group at M3 (mean±SE, 1±1 vs. 4±2, respectively, $p<0.001$) as well as at M6 (mean±SE, 1±2 vs. 5±2, respectively, $p<0.001$). A similar effect (the same primary outcomes and considerably different secondary outcomes) was observed evaluating IKDC score for comparison between PRP and CS groups at W1 (mean ± SE, 66±15 vs. 64±14, respectively, $p<0.003$) and at final follow-up (mean±SE, 81±16 vs. 54±20, respectively, $p<0.003$). In addition, linear contrasts identified a higher KSS score in the PRP group compared with the CS group at M6 follow-up (mean±SE, 90±14 vs. 72±15, respectively, $p<0.006$). No complications were recorded in the CS group, mild synovitis was observed in 11 patients (73%) in PRP group after W1, however it absorbed spontaneously till M1.

Conclusions: Short-term results were similar of both intra-articular PRP and CS injections at W1. Nonetheless, PRP demonstrated a statistically significant improvement over CS at M3 and M6. Furthermore, complications of PRP injections were insignificant and self - limited.

Kopsavilkums

Trombocītiem bagātinātas plazmas un hormonālo preparātu intraartikulāras terapijas salīdzinājums pacientiem ar ceļa locītavas mērenu osteoartītu

Atslēgasvārdi: *trombocītiem bagātināta plazma, hormonāls preparāts, ceļa locītavas osteoartrīts, Kellgren - Lawrence klasifikācija, VAS, IKDC, KSS*

Ievads: Pēdējā gadu desmitē īpaša uzmanība tiek pievērsta jaunai ārstēšanas metodei - trombocītiem bagātinātās plazmas (PRP - *platelet-rich plasma*) intraartikulārām injekcijām pacientiem ar ceļa locītavas osteoartrītu. Intraartikulārai terapijai ir augsta efektivitāte un drošība, kas ir pamatkritēriji speciālistu izvēlē pētīt PRP ārstēšanas metodi un pielietot to ikdienas darbā.

Darba mērķis: Salīdzināt trombocītiem bagātinātās plazmas (PRP) un hormonālā preperāta (HP) intraartikulārās terapijas efektivitāti un drošību pie ceļa locītavas II - III pakāpes osteoartrīta.

Materiāls un metodes: Laika posmā no 2016.gada aprīļa līdz 2017.gada janvārīm prospektīvā randomizētā pētījumā tika iekļauti 30 pacienti ar primāru ceļa locītavas II – III pakāpes osteoartrītu, pēc *Kellgren – Lawrence* klasifikācijas. Iekļaušanas kritēriji: sāpes un/vai kustību ierobežojumi ceļa locītavā, agrāk nav bijušas veiktas invazīvas manipulācijas ceļa locītavai; pēdējo 10 dienu laikā nav lietoti nesteroīdie pretiekaisuma līdzekļi (NSPL). Randomizācijai izmantoja "*Randomizer for Clinical Trial*" datorprogrammu, veidojot PRP un HP grupas. Pacientiem HP grupā (n = 15) inraartikulāri ievadīja Sol. Triamcinolone acetonide 40mg un Sol. Lidocaini 2% - 5 ml, PRP grupā (n = 15) ievadīja 8 ml PRP. Sāpju, funkcionalitātes un terapijas efektivitātes izvērtēšanai dinamikā, 1 nedēļu (N1), 1 mēnesi (M1), 3 mēnešus (M3) un 6 mēnešus (M6) kopš injekcijas veikšanas, tika izmantotas Vizuālā Analoga Sāpju skala (VAS), *Knee society score* skala (KSS) un *International Knee Documentation Committee* skala (IKDC). datu apkopojums veikts izmantojot SPSS un Excel programmas.
Rezultāti: Pētījumā iekļauti 30 pacienti ar vidējo vecumu 68 ± 9gadi.Terapijas efektivitātes izvērtējums:
Izvērtējot pēc VAS skalas, sākotnējās vērtības gan PRP gan HP grupās bija vienādas (vidējais ± SK 6 ± 1), rezultāti uzlabojās N1 laika posmā līdzvērtīgi (vidējais ± SK, 3 ± 2). Periodā M3, PRP grupa salīdzinot ar HP grupu, VAS punktu skaits bija statistiski ticami mazāks (vidējais ± SK, 1 ± 1 vs. 4 ± 2, attiecīgi, p <0,001), attiecīgi M6 (vidējais ± SE, 1 ± 2 vs 5 ± 2, attiecīgi, p <0,001). Līdzīgs rezultāts tiek novērots, izvērtējot IKDC punktu skaitu, salīdzinājumā starp PRP un HP grupām N1 laika periodā (vidējais ± SE, 66 ± 15 vs 64 ± 14, attiecīgi, p <0,003) un M6 (vidējais ± SE, 81 ± 16 vs 54 ± 20, attiecīgi, p <0,003). N1 laika periodā KSS punktu skaits (vidējais ± SE, 79 ± 25 vs 78 ± 23, attiecīgi, p <0,005), M6 laika period identificēts augsts KSS punktu skaits PRP grupā, salīdzinot ar HP grupu (vidējais ± SE, 90 ± 14 vs 72 ± 15, attiecīgi, p <0,006). Pacientiem HP grupā netika novērotas komplikācijas. PRP grupā 11 pacientiem (73%) N1 laika posmā konstatēja nelielu sinovītu, kurš sponāti uzsūcās3 nedēļas pēc injekcijas.
Secinājumi: PRP un HP intraartikulāro injekciju terapijas efektīvitāte N1 laika periodā ir līdzvērtīga. Bet PRP kā terapijas metode demonstrē statistiski ticamus rezultātus ilgtermiņā, salīdzinot ar HP M3 un M6 laika periodā. PRP terapijas blakusparādības un komplikācijas bieži ir klīniski nenozīmīgas un pašlimitējošas.

Introduction

Osteoarthritis (OA) is a slowly progressive chronic disease characterized by pathological changes in the entire joint organ including cartilage, subchondral bone, synovium, ligaments, and menisci. In the recent past, OA was considered as a normal sign of aging and was described as a degenerative disorder which mainly causes cartilage degradation. (Haq 2003: 377; Jordan 2003: 1145)

However, more recent studies have determined that OA occurs and evolves due to the interaction of multiple risk factors and affects the whole joint. (Creamer 1997: 503)

OA is the most common type of arthritis, whereas more than 100 different types of arthritis are identified in medicine. The disease most commonly affects the middle-aged and elderly; nevertheless, it may appear earlier as a result of trauma, overuse or interaction of various risk factors. Local inflammation, mechanical forces, cellular and biochemical changes present significant role in the pathogenesis of OA. (Lane 2011: 478) OA may affect all joints, although predominantly involves the weight-bearing joints such as knees, hips, and spine. Other commonly affected joints include wrists, elbow and shoulder joints.

Knee OA is likely to become the fourth most important global cause of disability in women and eighth most important in men. According to some expert opinions, radiographic evidence of knee OA in men and women over 65 is found in 30% of patients. Knee OA is a greater factor in limiting activity than heart disease, hypertension, blindness, or diabetes. (Jordan 2003: 1151)

Pathophysiology

The earliest pathological changes usually can be visible on cartilage surface with the greatest amount of load. Due to the structural imbalance of the collagen network caused by overloading,

collagen is not capable of preventing proteoglycans attraction with water that completes in cartilage swelling. Chondrocytes are the only cells that can be found in cartilage, which restore cartilage through normal metabolic (anabolic/catabolic) processes. These metabolic processes accelerate dramatically due to the OA progression and the loss of the matrix; chondrocytes proliferate rapidly and form clusters. At least a part of the chondrocyte cells experiences a phenotypic switch to a hypertrophic chondrocyte which is analogous to cells found in the hypertrophy zone of the growth plate that produce type X collagen and MMP-13. Significant matrix degradation and loss progress due to the continuous production of proteases, stimulated by proinflammatory cytokines and fragments of matrix proteins. Chondrocytes in an autocrine and paracrine manner produce more cytokines and proteases as a feedback to previous biochemical interaction. As a result, damage of matrix and destruction of chondrocytes lead to matrix areas devoid of cells. (Hunter 2016: 1)

Subchondral bone sclerosis is caused by the production of improperly mineralized collagen. Osteophytes occur at the joint margins, mainly at the insertion site of tendons or ligaments. Bone cysts and bone erosion may develop in some cases with disease progression.

Synovitis is observed in the majority of the patients with symptomatic disease course. (Loeuille 2005: 3492) However, the synovitis in the case of OA is not initiating a cause of inflammation in comparison with other forms of so-called inflammatory arthritis. Although synovitis significantly increases the pain and contributes disease progression through cartilage destruction caused by the production of inflammatory factors and proteins referred to as damage-associated molecular patterns (DAMPs - damage-associated molecular patterns), including the alarmins. (Liu-Bryan 2015: 35)

Soft-tissue components of the joint, including ligaments, the joint capsule, the menisci, are commonly affected by OA. Damage occurs due to loss of cells and extracellular matrix disruption in soft-tissue structures. Joint enlargement occurs due to thickening of the joint capsule and osteophyte formation, whereas tears in ligaments and menisci can be found in patients with advanced OA without previous history of trauma. (Loeser 2013: 108)

Classic cellular inflammation is not typical in OA, where the number of leukocytes in the joint fluid is usually low, and seldom exceeds 1000 to 2000 cells per milliliter. In contrast with other forms of inflammatory arthritis, for instance, rheumatoid arthritis, where the number of synovial fluid leukocytes frequently exceeds 2000 cells per milliliter, and besides, commonly leukocyte infiltration and fibroblast proliferation are more aggressive.

The damage of joint tissues in OA is stimulated by a range of proteases including particular matrix metalloproteinases, cysteine proteinases including cathepsin K, and serine proteinases. (Troeberg. 2012: 133)

The biochemical activity of these proteinases results in degradation of cartilage extracellular matrix proteins. Aggrecan is the large proteoglycan that provides a great proportion of the resiliency

of cartilage, which degradation begins in the initial stages of OA by members of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family referred to as aggrecanases (ADAMTS-4 and -5). Furthermore, collagen consists of approximately 50% of collagen type II that is responsible for the tensile strength of cartilage. Type II collagen is degraded by collagenases, which, like aggrecanases, are matrix metalloproteinases. MMP-13 is considered to be the leading collagenase responsible for cartilage degradation in OA. (Troeberg 2012: 133)

Osteoarthritis is routinely diagnosed on the basis of clinical findings. However, radiological investigation methods may not only confirm the disease but also determine the degree of damage, establish the development of complications, show the progression of the disease and effectiveness of therapy, exclude other musculoskeletal disorders. (Doherty 2017: 1; Kadiša 2011: 46)

The Kellgren and Lawrence system is a method for classifying the severity of knee osteoarthritis. This classification was proposed by Kellgren in 1957 and later accepted by WHO in 1961. (Pai Vivek 2015: 1)

Classification:
Grade 0: no radiographic features of OA are present
Grade I: doubtful joint space narrowing and possible osteophytic lipping
Grade II: definite osteophytes and possible joint space narrowing on anteroposterior weight-bearing radiograph
Grade III: multiple osteophytes, definite joint space narrowing, sclerosis, possible bony deformity
Grade IV: large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity

Figure 1. **OA of the knee, grading by Kellgren and Lawrence system** (Ryu 2012:1)

Aim, material, and methods

The aim of this study was to compare the efficacy and safety of intra-articular platelet-rich plasma and corticosteroids in the treatment of knee osteoarthritis. 30 patients (23 females and 7 males), with symptomatic radiologically confirmed (II-III grade by Kellgren-Lawrence

classification) knee osteoarthritis, were enrolled in a prospective randomized study within the period from April 2016 to January 2017. Two groups were created by random selection: platelet-rich plasma (PRP) group and corticosteroid (CS) group with 15 patients in each group.

Patient selection criteria: patients older than 55 years with a history of chronic pain, swelling and/or reduced range of motion in the knee joint. Confirmation of pathological changes (Kellgren - Lawrence grades II-III) to the knee joint was verified by assessing X-Ray images in anteroposterior and lateral projections. Exclusion criteria: pregnancy, breastfeeding, oncological diseases, endocrine diseases (gout, diabetes), autoimmune diseases (rheumatoid arthritis) acute/chronic infectious disease, blood clotting disorders (thrombocytopenia, coagulopathy), patients with previous interventions on the knee joint (punctures, blockades, arthroscopy, etc.), patients, who received consistent hormonal therapy or non-steroidal anti-inflammatory drugs (NSAIDs) within 10 days.

Full blood count and platelet-rich plasma test were performed in PRP group patients in PRP administration day. 18 cc of peripheral blood and 2 cc of anticoagulant were mixed and placed in fractionation and concentration device adapter OMNIGRAFTER / DUOGRAFTER to prepare PRP injection. 8 ml PRP solution were obtained and used in patients in PRP group, whereas patients in CS group received 1 cc of 40mg/mL of triamcinolone acetonide and 5 cc of 2% of lidocaine. The severity of pain and the function of the affected knee were evaluated by International Knee Documentation Committee (IKDC) scale, by Visual Analogue Scale (VAS) for pain and by Knee Society score (KSS) after one week (W1), one month (M1), three months (M3) and six months (M6).

Data processing was performed using software «Randomizer for Clinical Trial», SPSS 20, Microsoft excel.

Platelet-rich plasma is an autologous product that concentrates a large number of platelets in a small volume of plasma. PRP has a unique ability to promote wound healing and osteogenesis. That ability substantially distinguishes PRP from fibrin glue which possesses only haemostatic and sealing properties. PRS functions as a prompt hemostatic substance that is biocompatible and safe. Moreover, PRP facilitates endothelial, epithelial and epidermal tissue regeneration, stimulates angiogenesis, improves collagen synthesis, promotes soft tissue healing, diminish scar tissue formation. PRP preparations with high leukocyte concentration have additional anti-bacterial properties. (Smith 2007: 73)

PRR is defined as platelet sequestration and concentration in autologous blood plasma. PRP beneficial properties are based on the acceleration of the tissue regeneration process, which is caused by degranulation of the alpha granules in platelets and releasing of growth factors and cytokines in great number. Platelets do not contain nuclei, though its cytoplasm is rich in

organelles - mitochondria and granules. Alfa granules contain more than 30 biologically active proteins that ensure haemostasis and tissue regeneration, provide cell migration, differentiation and proliferation. Each platelet contains approximately 50 to 80 alpha granules; the mean platelet count fluctuates from 150,000 to 300,000 in one ml of blood. In order to achieve PRP definition criteria (1,000,000 / ml), the platelet concentration in a blood sample has to increase three to five times in comparison with baseline concentration.

Treatment with platelet-rich plasma injections is a safe method, side effects and complications are rare, often clinically insignificant. The explanation includes several factors:

- PRP injection administration is a minimally invasive approach;
- performs without anaesthesia;
- due to the use of patient homologous blood products the possibility of sensibilization and allergic reactions are highly low, besides it carries no risk of transmitting infectious disease.

Contraindications of PRP are given in Table 1.

Table 1. **Contraindications of PRP administration**

Absolute contraindications	Relative contraindications
• Sepsis • Septic arthritis • Osteomyelitis at treatment site • Local infection at the site of the procedure • Hemodynamic instability • Critical thrombocytopenia • Autoimmune inflammatory tendinitis, tenosynovitis, enthesitis, fasciitis, arthritis	• Recent fever or illness • Cancer- especially hematopoietic or of bone • HGB < 10 g/dl • Platelet count < 105/ul • Consistent use of NSAIDs within 48 hours of procedure • Corticosteroid injection at treatment site within 1 month • Consistent systemic use of corticosteroid within 2 weeks of procedure • Avascular bone necrosis

Results

30 patients (7 (23%) men and 23 (77%) with knee OA were enrolled in an open prospective randomised study within the period from April 2016 to January 2017. All patients were randomised into two groups: PRP group (n = 15), and CS group (n = 15). The mean patient age was 68 ± 9 years, the mean age in PRP and CS groups were 65 ± 8 and 71 ± 10 years respectively (p = 0.07).

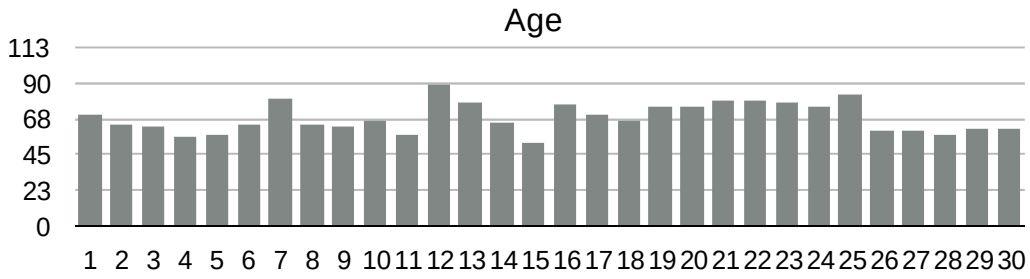

Figure 2. **Age distribution in patients with OA**

Regarding OA distribution by Kellgren-Lawrence classification, 9 patients had radiographically confirmed II grade of OA and 21 patients III grade of OA.

Pain evaluation over time (VAS): the initial values for both PRP and CS groups were similar (mean ± SE, 6 ± 1), the improvement of results over W1 period were equivalent (mean ± SE, 3 ± 2, p <0.001). Compared PRP and CS groups over M1 period, VAS values were slightly lower in PRP group (mean ± SE, 2± 2 vs. 3 ± 2, respectively, p <0.007). Over M3 period, PRP group presented statistically significantly less VAS scores in comparison with CS group (mean ± SE, 1 ± 1 vs. 4 ± 2, respectively, p <0.001), whereas over M6 period (mean ± SE, 1 ± 2 vs 5 ± 2, respectively, p <0.001).

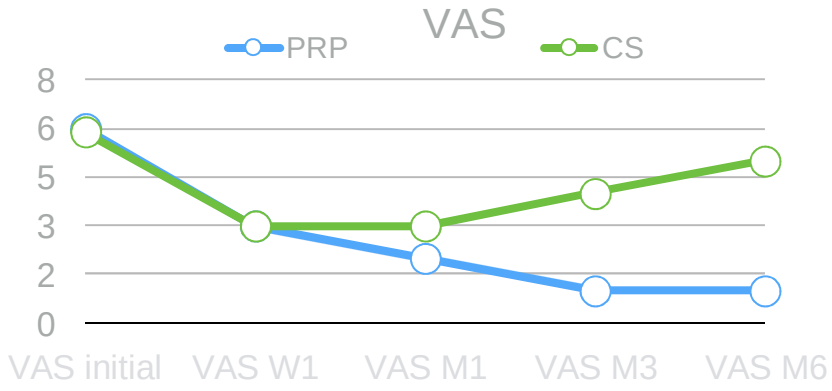

Figure 3. **Evaluation of pain according to VAS over time**

Evaluation of subjective state over time (IKDC): the initial values for both PRP and CS groups were very similar (mean ± SE, 34 ± 10 vs. 27 ± 7, respectively, p <0.045); in comparison the values of PRP and CS groups over W1 period were (mean ± SE, 66 ± 15 vs. 64 ± 14, respectively, p <0.003), over M1 period (mean ± SE, 70 ± 17 vs. 61 ± 17, respectively, p <0.055), over M3 period (mean ± SE, 77 ± 14 vs. 59 ± 18, respectively, p <0.025), and over M6 period (mean ± SE, 81 ± 16 vs. 54 ± 20, respectively, p <0.003); the difference occurs after 3 month follow-up because IKDC scores in CS group began to decrease.

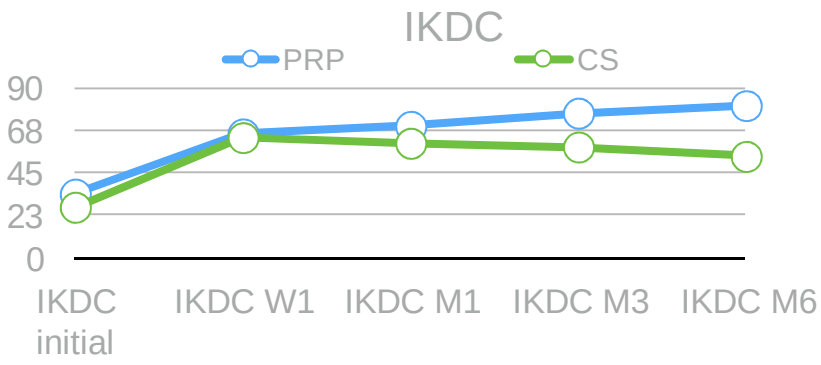

Figure 4. **Evaluation of subjective state according to IKDC over time**

Evaluation of objective state over time (KSS): the initial and W1 values for both PRP and CS groups were relatively similar (initial mean ± SE, 60 ± 6 vs. 51 ± 7, respectively, p <0.001; over W1, mean ± SE, 79 ± 25 vs. 78 ± 23, respectively, p <0.005); over M1 period KSS scores were insignificantly lower in PRP group in comparison with CS group (mean ± SE, 88 ± 10 vs. 80 ± 11, respectively, p <0.04). Over M3 (mean ± SE, 91 ± 8 vs. 75 ± 14, respectively, p <0.002) and M6 (mean ± SE, 90 ± 14 vs. 72 ± 15, respectively, p <0.006) periods a substantial difference was identified in scores between PRP and CS groups in advantage for former.

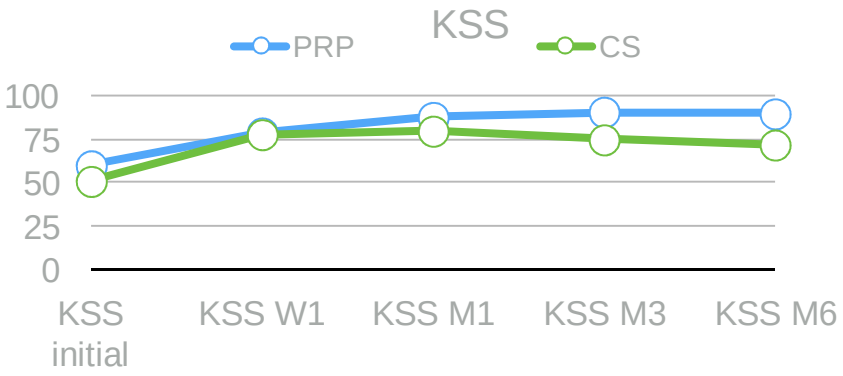

Figure 5. **Evaluation of objective state according to KSS over time**.

Detailed mean results are presented in the table below.

Table 2. **Detailed mean results with standard errors in total and for both groups separately over time**

Scale/Follow-up	Total mean score ± SD	Mean score ± SD in PRP group	Mean score ± SD in CS group	p
IKDC initial	31 ± 9	34 ±10	27 ± 7	0.045
KSS initial	56 ± 8	60 ± 6	51 ± 7	0.001
VAS intial	6 ± 1	6 ± 1	6 ± 1	0.7
IKDC N1	64 ± 15	66 ± 15	64 ± 14	0.003
KSS N1	79 ± 24	79 ± 25	78 ± 23	0.005
VAS N1	3 ± 2	3 ± 2	3 ± 2	0.001
IKDC M1	66 ± 17	70 ± 17	61 ± 17	0.055
KSS M1	84 ± 11	88 ± 10	80 ± 11	0.04
VAS M1	2 ± 2	2 ± 2	3 ± 1	0.007
IKDC M3	68 ± 18	77 ± 14	59 ± 18	0.025
KSS M3	83 ± 14	91 ± 8	75 ± 14	0.002
VAS M3	3 ± 2	1 ± 1	4 ± 2	0.001
IKDC M6	67 ± 23	81 ± 16	54 ± 20	0.003
KSS M6	81 ± 17	90 ± 14	72 ± 15	0.006
VAS M6	3 ± 3	1 ± 2	5 ± 2	0.001

No complications were recorded in the CS group, mild synovitis was observed in 11 patients (73%) in PRP group after W1, however, it absorbed spontaneously within 3 weeks.

Despite the fact that OA is the most common type of arthritis, which significantly affects the quality of life and causes the physical disability, the available medical interventions to cease the disease progress are still limited. Traditional and accepted methods of OA treatment such as pharmacological therapy and intra-articular injections have not been providing impressive results to decelerate the progress of disease or completely cease it. Mostly now available methods are considered to affect subjective complaints, for instance, pain and range of motions, in a short-term period. The relatively new strategy of treatment of OA is an application of cell elements and tissue growth factors. Regarding this strategy, PRP has been proposed as a perspective method of treatment, which improves not only clinical but also structural signs, due to enhancing and remodelling the damaged cartilage caused by the activity of growth factors in a high concentration.

PRP efficacy and safety were proved in both in vitro and in vivo studies in comparison with placebo, CS or hyaluronic acid. In this study, the results coincided with other studies results conducted in the world, although the short-term results of PRP and other treatment options present the same improvement, however, after 3 and 6 months PRP therapy provides a significant advantage. In addition, PRP intra-articular injections are well tolerated, the most common side effect is synovitis, which usually is absorbed within a few weeks. In this study, synovitis was also observed in patients in PRP group, whereas no systemic reactions, such as nausea or dizziness were documented. In comparison with other treatment methods, PRP injections similarly perform better results in patients with lower OA stage. PRS efficiency at last OA stages is a controversial question since most researchers do not include such patients in their studies.

Conclusion

1. Short-term results in patients with II - III grade OA by Kellgren - Lawrence classification were equivalent in both PRP and CS groups.
2. PRP injections have demonstrated statistically reliable and better results after three and six months compared to the CS injections.
3. PRP intra-articular treatment side effects and complications are often clinically insignificant and self-limited. Synovitis was the only observed complication.
4. Following steps should be performed to precisely define length and strength of PRP effects: the number of patients and duration of observation should be increased; the effectiveness of PRP should be compared with other treatment methods, for example, hyaluronic acid injections.

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PROGNOSTIC BIOMARKERS IN PATIENTS WITH ISCHEMIC STROKE WHO RECEIVED THROMBOLYTIC THERAPY

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Abstract
Key words: *ischemic stroke, thrombolytic therapy, effectiveness, clinical outcome, biomarkers*
Introduction. Ischemic stroke is one of the most common cause of death and functional disability across the world. Endovascular mechanical thrombectomy and intravenous thrombolysis with alteplase are the only effective treatment approaches for acute ischemic stroke. Brain ischemia is a complicated biochemical process. Several biomarkers are released during ischemic stroke and they are associated with direct cell damage, blood-brain barrier disruption and inflammatory response. Serum biomarkers evaluation may provide information about stroke severity, pathogenesis and therapeutic benefits.
Aim. The aim of the research was to evaluate the association between C-Reactive protein (CRP), troponin I, d-dimer, creatinine, glucose, glomerular filtration rate (GFR) and low density lipoprotein cholesterol (LDL-C) levels at the admission and the results of thrombolytic therapy.
Materials and methods. 113 patients who underwent thrombolytic therapy for acute ischemic stroke in Pauls Stradins Clinical University Hospital from 01.01.2015 till 01.01.2016 were studied retrospecively. Blood samples were collected in the emergency department. Neurological status was estimated using the National Institute of Health Stroke Scale (NIHSS). The efficacy of thrombolytic therapy was assessed by comparing NIHSS score at the admission and after treatment. Afterward all patients were divided into three groups – the major improvement (NIHSS>4), minor improvement (NIHSS ≤4) and without any clinical effect.
Results. Only the median levels of GFR were significantly (p=0.015) lower in patients who didn't have any clinical improvements after thrombolytic therapy as compared to patients with the major or minor improvements (60.0, interquartile range [IQR] 42.4-72.3 ml/min/1.73m^2; 83.2, IQR 65.3-98.3 ml/min/1.73m^2 and 75.9, IQR 59.2-94.6 ml/min/1.73m^2). Based on the receiver operating characteristic (ROC) curve, the optimal cut-off value of GFR level as an indicator for prediction of worsen clinical outcome after thrombolytic therapy was projected to be 61.65 ml/min/1.73m^2, which yielded a sensitivity of 71.4% and a specificity of 24.5%, the area under the curve was 0.788 (95% confidence interval [CI], 0.648-0.928). According Spearman rank correlation test was founded statistically significant indirect correlation between GFR level and NIHSS score after treatment (r=- 0.410, p=0.020) in patients with severe stroke (NIHSS >14).
Conclusion. GFR level lower than 61.65 ml/min/1.73m^2 at the admission could be predict a worse outcome, especially in patients with severe stroke.

Kopsavilkums
Atslēgvārdi: *išēmisks insults, trombolītiska terapija, klīnisks iznākums, biomarķieri, efektivitāte*
Ievads. Išēmisks insults ir viens no vadošajiem nāves un invaliditātes cēloņiem pasaulē. Vienīga efektīvā insulta ārstēšana ir reperfūzijas terapija, izmantojot intravenozo trombolīzi ar alteplāzi pirmo 4.5 stundu laikā vai arī endovaskulāru trombektomiju. Galvas smadzeņu išēmija ir komplicēts bioķīmisks process. Išēmijas laikā izdalās vairāki biomarķieri, kas ir saistīti ar tiešu šūnu bojājumu, hematoencefāliskās barjeras bojājumu un iekaisuma reakciju. Šo biomarķieru noteikšana dod iespēju noteikt insulta smagumu, patoģenēzi, kā arī paredzēt trombolītiskās terapijas ieguvumu.
Mērķis. Pētījuma mērķis bija novērtēt C-reaktīva olbaltuma (CRO), troponīna I, d-dimēru, kreatinīna, glikozes, glomerulāras filtrācijas ātruma (GFĀ) un zema blīvuma lipoporoteīnu holesterīna (ZBLH) līmeņa saistību ar trombolītiskas terapijas efektivitāti.
Materiāli un metodes. Pētījumā kopumā tika iekļauti 113 pacienti, kuri saņēma intravenozas trombolīzes terapiju Paula Stradiņa klīniskas universitātes slimnīcā (PSKUS) neiroloģijas nodaļā laika periodā no 01.01.2015 līdz 01.01.2016. Asins analīzes tika paņemtas uzņemšanas nodaļā. Pacientu neiroloģisks statuss tika novērtēts, izmantojot Nacionālas Veselības Institūta Insulta Skalu (National Institute of Health Stroke scale – NIHSS). Trombolīzes efektivitāte tika noteikta salīdzīnot NIHSS vērtību pirms un pēc saņemtas trombolītiskas terapijas. Atbilstoši klīniskam efektam visi pacienti tika sadalīti trīs grupās – pacienti ar būtisku uzlabošanās (NIHSS>4), ar minimālu uzlabošanās (NIHSS≤4) un pacienti bez jebkāda klīniska efekta.
Rezultāti. Veicot datu statistisku analīzi, tika noteikts, ka GFĀ mediānas vērtība bija nozīmīgi mazāka pacientiem, kuriem pēc intravenozas trombolīzes nenovēroja nekādu klīnisku efektu, salīdzīnot ar tiem pacientiem, kuriem novēroja būtisku vai minimālu uzlabošanās (60.0, starpkvartiļu izklede [SKI] 42.4-72.3 ml/min/1.73m^2; 83.2, SKI 65.3-98.3 ml/min/1.73m^2 un 75.9, SKI 59.2-94.6 ml/min/1.73m^{2,} p<0.05). Pamatojoties uz ROC līknes analīzi GFĀ <61.65 ml/min/1.73m^2 iestāšanās brīdī ar 71.4% jutīgumu un 24.5% specifiskumu norāda uz samazinātu trombolīzes terapijas

efektivitāti. Atbilstoši Spīrmena rangu korelācijas analīzi tika atrasta statistiski nozīmīga korelācija starp GFĀ līmeni un NIHSS vērtību pēc saņemtas trombolīzes (r=-0.410, p=0.020) pacientiem ar smagu išēmisku insultu (NIHSS>14).
Secinājumi. GFĀ <61.65 ml/min/1.73m^2 iestāšanās brīdī varētu būt izmantojams kā slikts prognostisks rādītājs pirms trombolītiskas terapijas, it īpaši pacientiem ar smagu išēmisku insultu.

Introduction

The current World Health Organization definition of stroke is “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” (Aho et al. 1980). There are two types of stroke, hemorrhagic and ischemic. Ischemic stroke occur far more common than the hemorrhagic. Despite of effective treatment approaches such as endovascular thrombectomy or intravenous thrombolysis with alteplase, ischemic stroke has remained on of the leading cause of death and functional dissability across the world. The mortality rate in ischemic stroke patients were achieved 87.7 deaths per 100, 000 persons according to latvian CDPC statistical data for 2014 year. Clinical outcome of the ischemic stroke may dependent on several factors such as advanced age, stroke severity, medical complications or comorbidities (Andersen et al. 2011). The most frequent serious medical complications include pneumonia, congestive heart failure, cardiac arrest, deep vein thrombosis, pulmonary embolism and urinary tract infection. Hemorrhagic transformation is an important complication of ischemic stroke, especially after thrombolytic therapy. There are several factors which might be used as predictors of hemorrhagic transformation. Massive cerebral infarction, grey matter infarction, atrial fibrillation, hyperglycemia, lower total cholesterol and low-density lipoprotein cholesterol (LDL-C) , lower platelet count, poor collateral vessels, elevated globulin level, radiological predictors (early computed tomography (CT) signs, hyperdense middle cerebral artery sign), micro- and macro-albuminuria might be associated with increased hemorrhagic transformation risk (Zhang et al. 2014). A host of prestroke comorbid conditions are associated with an increased risk of poor outcome following ischemic stroke. Atrial fibrillation, diabetes mellitus, heart failure, renal dysfunction or cancer might negatively influence the treatment efficiacy (Saposnik et al. 2011; Dessiles et al. 2013; McGrath et al. 2013). Moreover a recently conducted meta-analysis showed strong statistically significant relationship between having an anemia and worse clinical outcome in patients with ischemic stroke (Barlas et al. 2016). Apart from common comorbidities, sickle cell trait also were associated with poor prognosis (Olowoyo et al. 2016). Olowoyo et al. were observed increased 30-day mortality rate among the patients with sickle cell trait than the controls.

The aim of the research was to evaluate the association between C-Reactive protein (CRP), troponin I, d-dimer, creatinine, glucose, glomerular filtration rate (GFR) and LDL-C levels at the admission and the results of thrombolytic therapy.

Material and methods

This study had a reptrospective design. Nine hundred forty-five patients admitted to the Stroke Unit at the department of Neurology of the Pauls Stradins Clinical University Hospital of Riga from 01.01.2015 till 01.01.2016 were enrolled in this study. The inclusion criteria were: (a) diagnosis of ischemic stroke based on history, neurological examination and multimodal CT evaluation (noncontrast CT, CT-angiography and perfusion CT), (b) eliglibity for intravenous thrombolytic therapy with alteplase 0.9 mg/kg according to current guidelines. The exclusion criteria were: (a) admission to the hospital later than 4.5 hours of the onset of neurological focal symptoms, (b) suspicion of acute coronary syndrome (hystory, ECG changes, elevated cardiac troponin levels or creatine kinase isoenzyme MB (CK-MB) levels), (c) suspicion of acute bacterial infection based on clinical examination and history, (d) fatal outcome during hospitalization. There were 832 patients that were excluded due to the mentioned factors. The final study group consisted of 113 patients, 67 women and 46 men.

The following variables were collected for all patients: age, gender, initial stroke severity as assessed using the National Institute of Health Stroke Scale (NIHSS), NIHSS score on the second day after thrombolytic therapy, initial CRP, troponin I, d-dimer, creatinine, glucoce, GFR and LDL-C levels in blood serum and stroke etiology according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria. Treatment effectiveness was assessed by comparing NIHSS score at the admision and 24 hours after thrombolytic therapy. Afterward all patients were divided into three groups - the major improvement, minor improvement, and without any clinical effect. Early neurological improvement corresponding to an increase of more than 4 point from the baseline NIHSS score was classified as the major improvement, consequently minor improvement was classified as increasing of not more than 4 points. Any patient with neurological deterioration after received thrombolytic therapy was classified into group - without any clinical effect. In the emergency department before treatment were collected venous blood samples and were done multimodal CT examination.

Statistical analysis was performed using IBM SPSS software (version 22.0 for Windows). The level of significance was set at $p < 0.05$. Continuous variables were presented as median with interquartile range (IQR). Group comparisons of continuous variables were performed using Kruskal - Wallis H and Mann - Whitney U tests for independent samples. The chi-square test was used for categorical comparisons of data. The relationship between GFR level at the admission and NIHSS score 24 hours after thrombolytic therapy was determined using Spearman rank corelation coefficient. Receiver operating characteristic (ROC) curves were utilized to evaluate the accuracy of GFR to predict worse outcome. Area under the curve (AUC) was calculated as measurements of the accuracy of the test.

Results

Among the 113 patients with acute ischemic stroke, the major improvement after received thrombolytic therapy was determined in 54 patients, minor improvement in 52 patients, and only 7 patients did not had any clinical effect. The baseline characteristics of 113 patients are described in Table 1.

Table 1. **Baseline characteristics of acute ischemic stroke patients according to clinical outcome**

Patients data	Effectiveness of treatment			p[a]
	Major improvement NIHSS >4 (n=54)	Minor improvement NIHSS≤4 (n=52)	Without any clinical effect (n=7)	
Age, mean (min., max.)	67.15 (32,88)	73.23 (43,92)	78.86 (71,94)	0.007
Gender, no. (%): Female (n=67) Male (n=46)	 33 (49.3%) 21 (45.7%)	 27 (40.3%) 25 (54.3%)	 7 (10.4%) 0 (0%)	0.049
Stroke severity, median NIHSS score (IQR)	12 (8-16)	8 (6-11)	10 (7-18)	0.001
Stroke etiology, no. (%) Atherothrombotic stroke (n=28) Cardioembolic stroke (n=75) Undetermined etiology (n=10)	 13 (46.4%) 36 (48.0%) 5 (50.0%)	 14 (50.0%) 34 (45.3%) 4 (40.0%)	 1 (3.6%) 5 (6.7%) 1 (10.0%)	0.942
IQR - interquartile range; [a]p for gender and stroke etiology was assessed using Kruskal-Wallis test, but for stroke severity and age using $\chi 2$ test.				

Advanced age was associated with reduced effectiveness of intravenous thrombolysis ($p<0.05$). The mean age of patients who had significant neurological improvement was 67.15 years, simultaneously the mean age of patients who had not any clinical effect was 78.86 years. Gender and stroke severity also had influence on thrombolysis ($p<0.05$). More severe stroke on admission surprisingly was associated with better effect of thrombolytic therapy. Median NIHSS score in patients with the major improvement was significantly higher as compared to patients with minor improvement and without any clinical effect (12, interquartile range [IQR] 8-16; 8, IQR 6-11; 10, IQR 7-18, $p<0.05$). Stroke etiology was not associated with any clinical outcome after thrombolytic therapy ($p>0.05$).

A significant difference in the median GFR values on admission was observed between groups with different clinical effect of thrombolysis ($p<0.05$) (see Fig.1). Serum GFR levels on admission were lower in patients who did not have any clinical improvements after thrombolytic therapy as compared to patients with the major or minor improvements (60.0, IQR 42.4-72.3 ml/min/1.73m^2; 83.2, IQR 65.3-98.3 ml/min/1.73m^2 and 75.9, IQR 59.2-94.6 ml/min/1.73m^2). The relationships between serum biomarkers and effect of thrombolysis was shown in Table 2.

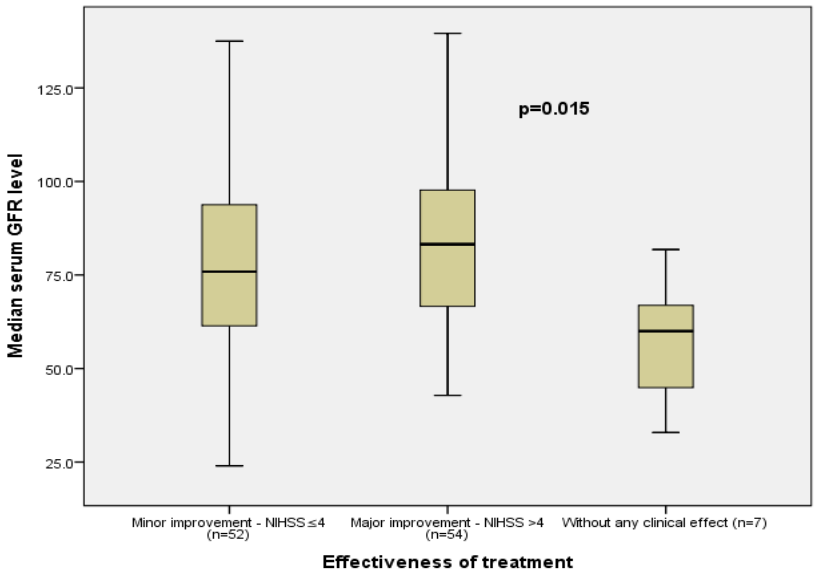

Figure 1. **Serum GFR level on admission in different clinical outcome after thrombolytic therapy**

Table 2. **Serum biomarkers levels on admission according to clinical outcome**

Laboratory findings (median, IQR)	Effectiveness of treatment			p[a]
	Major improvement NIHSS >4 (n=54)	Minor improvement NIHSS≤4 (n=52)	Without any clinical effect (n=7)	
CRP (mg/L)	3.0 (1.5-8.8)	2.5 (0.9-7.0)	3.4 (2.7-9.4)	0.296
LDL-C (mmol/L)	2.68 (2.15-3.27)	2.43 (1.83-2.93)	2.19 (1.75-2.98)	0.128
D-dimer (mg/L)	900 (360-1678)	1000 (650 -1950)	1240 (710-2650)	0.300
Troponin I (ng/L)	11 (6-33)	14 (10-30)	17 (10-40)	0.349
GFR (ml/min/1.73m^2)	83.2 (65.3-98.3)	75.9 (59.2-94.6)	60.0 (42.4-72.3)	0.015
Creatinine (µmol/L)	76 (61-88)	77 (68-99)	85 (73-111)	0.100
Glucose (mmol/L)	6.35 (5.70-7.40)	6.15 (5.25-7.28)	7.30 (6.30-8.30)	0.078

IQR- interquartile range, CRP- C reactive protein, LDL-C low density lipoprotein cholesterol, GFR- glomerular filtration rate
[a]p value was assessed using Kruskal-Wallis test

Based on the receiver operating characteristic (ROC) curve, the optimal cut-off value of GFR level as an indicator for prediction of worsen clinical outcome after thrombolytic therapy was projected to be 61.65 ml/min/1.73m^2, which yielded a sensitivity of 71.4% and a specificity of 24.5%, the area under the curve was 0.788 (95% confidence interval [CI], 0.648-0.928) (see Fig. 2).

There were not found any significant correlation between GFR levels and NIHSS score after thrombolytic therapy. Nevertheless in patients with severe ischemic stroke, which defined on admission as 14 and more points according to NIHSS scale, were found statistically significant indirect correlation between GFR level and NIHSS score after treatment (r=-0.410, p=0.020) (see Fig. 3).

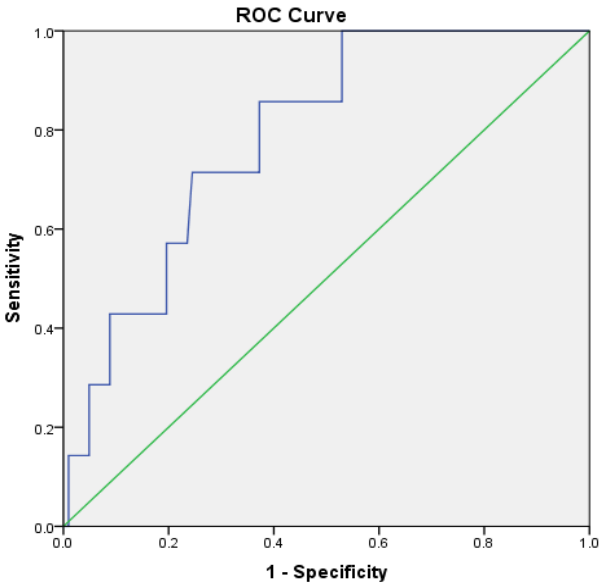

Figure 2. **Receiver operating characteristic (ROC) curves were utilized to evaluate the accuracy of GFR levels to predict worse outcome in patients who underwent thrombolysis**

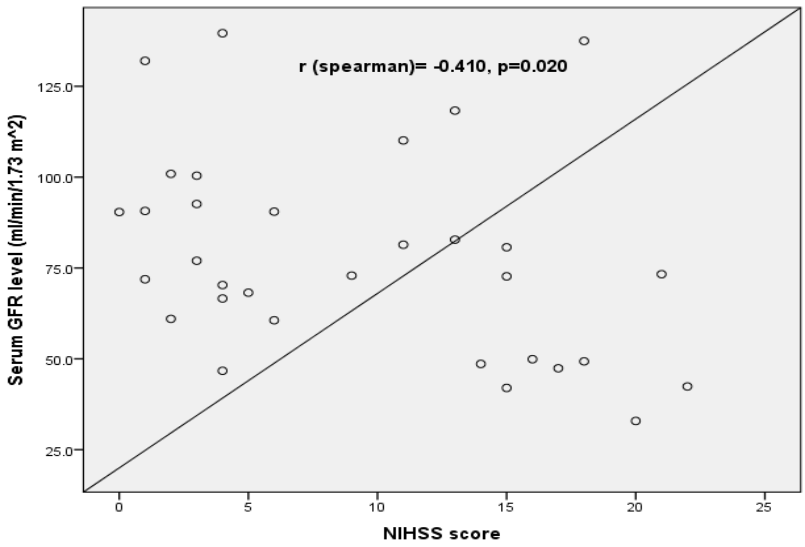

Figure 3. **Correlation between serum GFR level on admission and the National Institutes of Health Stroke Scale (NIHSS) score after thrombolytic therapy in patients with severe stroke (NIHSS>14)**

Discussion

In this study were found that renal impairment may impact on thrombolytic therapy efficacy. Moreover GFR value, which measure level of kidney function and determine stage of kidney disease, could be used as predictor for thrombolytic therapy effectiveness. In this study GFR level lower than 61.65 ml/min before treatment was determined as a poor prognostic biomarker especially in patients with severe stroke (NIHSS >14). In previous studies GFR level lower than 60 ml/min mostly was used as the definition of renal dysfunction (Power et al. 2013; Naganuma et al. 2011; Gensicke et al. 2013; Hsieh et al. 2014; Agrawal et al. 2010; Fabbian et al. 2015; Lee et al. 2013). Furthermore GFR <30 ml/min strongly was associated with a poor outcome. In several

studies were observed increased risk of hemorrhagic complications after received thrombolytic therapy in patients with renal dysfunction (Tütüncü et al. 2013; Fabbian et al. 2015; Naganuma et al. 2011; Lee et al. 2013). However Power et al. did not found any significant association between renal impairment and higher rate of symptomatic intracerebral hemorrhage (sICH). Nevertheless in the same study renal impairment was associated with reduced efficacy of thrombolysis. However recently a meta-analysis done by Hao et al. showed that renal dysfunction did not increase the risk of poor outcome and sICH in patients who underwent intravenous thrombolysis.

The pathological mechanism whereby renal impairment could impact on thrombolytic therapy effectiveness remains unclear. There are several suggested mechanisms which could explain association between renal dysfunction and poor clinical outcome in patients with ischemic stroke. The safety of intravenous thrombolysis could diminished by increased risk of hemorrhagic complications. Meanwhile patients with renal impairment are indeed at an increased risk of sICH. The underlying mechanisms might be endothelial and platelet dysfunction. Furthermore patients with renal impairment have more severe white matter disease, which may facilitate sICH after thrombolytic treatment as well (Neumann-Haefelin et al. 2006; Khatri et al. 2007). Another mechanism which could explain reduced intravenous thrombolysis efficacy is associated with altered fibrin clot properties and structure in patients with renal impairment. (Sjøland et al. 2007). Sjøland et al observed that in patients who had end-stage renal disease was reduced plasma fibrin clot permeability and susceptibility to lysis.

This study has some limitations. Firstly, patients did not have CT control examination after received thrombolytic therapy for identifying any hemorrhagic complication. Therefore association between renal dysfunction and icreased risk of sICH could not be determined. Secondly, this was a retrospective study and neurological examination of the same patient on admission and 24 hours after thrombolytic therapy was performed by different neurologists. Thirdly, the sample size was relatively small.

Conclusion

In this study were observed that low GFR level on admission could impact on intravenous thrombolytic therapy. GFR level lower than 61.65 ml/min/1.73m^2 at the admission could be predict a worse outcome, especially in patients with severe stroke. Thereby in patients with history of kidney disease or abnormal creatinine or GFR levels on admission the risks and benefits of thrombolytic therapy should be assessed in particularly.

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OPPORTUNISTIC INFECTIONS IN FATAL HIV/AIDS CASES IN LATVIA

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Abstract

Opportunistic infections in fatal HIV/AIDS cases in Latvia

Key words: *HIV, opportunistic infections*

Number of HIV infected individuals in Latvia is rising and is among some of the highest in Europe, while antiretroviral therapy coverage level is one of the lowest. The most common reason for hospitalization among HIV/AIDS patients in Latvia are opportunistic infections (Seikals K., Sture G., 2016). HIV/AIDS epidemic in Latvia is confined predominantly to intravenous drug abusers and their sexual partners. Such individuals don't follow up their medical conditions and almost as a rule present to the medical care terminally ill, thus despite advanced approach clinical investigation is limited by patient poor condition and time (L.Vīksna 2016, G.Stūre et al., 2017). In such cases autopsy is the only option for establishing the diagnosis. The aim of our study was to evaluate the spectrum, prevalence and morphology of opportunistic infections (OI) in lethal HIV/AIDS cases in Latvia for time period 2010.-2016. We retrospectively reviewed HIV/AIDS patient autopsy protocols for demographic data, pathological diagnosis, actual clinical diagnosis at the time of death and gross and microscopic organ descriptions. In 455 HIV/AIDS patients we identified 71 Pneumocystis jiroveci pneumonia, 40 disseminated cytomegalovirus diseases, 114 Candidiasis, 47 Cryptococcosis, 27 cerebral toxoplasmosis, 10 atypical mycobacteriosis, 5 Aspergillosis cases and various combinations of OI, causing predominantly pneumonia (74%) and brain (34%) lesions. We conclude that numbers of deaths among HIV/AIDS patients related to OI (28%) as well as tuberculosis (23%) and bacterial pneumonia (27%) and advanced lesions produced by these diseases at the time of death indicate that HIV/AIDS epidemic in Latvia is not controlled.

Kopsavilkums

Oportūnistisko infekciju analīze letālos HIV/AIDS gadījumos Latvijā

Atslēgas vārdi: *HIV, oportūnistiskās infeckijas*

HIV inficēto pacientu daudzums Latvijā pieaug un ir viens no augstākajiem rādītājiem Eiropā, savukārt antiretrovīrālās terapijas uzņemšanas līmenis HIV/AIDS pacientu vidū ir viens no zemākajiem. Biežākais HIV/AIDS pacientu hospitalizācijas iemesls Latvijā ir oportūnistiskās infekcijas (Seikals K., Sture G., 2016). HIV/AIDS epidēmija Latvijā izplatās pārsvarā starp intravenozo narkotiku lietotājiem un viņu seksuāliem partneriem. Bieži šādi indivīdi nerūpējas par savu veselības stāvokli un tiek nogādāti slimnīcās terminālās stadijās un, kaut gan HIV/AIDS pacientu klīniskā izmeklēšana ir augstā līmenī, adekvātā izmeklēšana ir limitēta pacientu smagā stāvokļa un laika trūkuma dēļ. Gadījumos, kad iestājās pacienta nāve, bet klīniskā diagnoze ir neskaidra, pacienti tiek nosūtīti uz patologanatomisko izmeklēšanu. Pētījuma mērķis bija novērtēt oportunistisko infekciju (OI) izplatību un morfogologiju letālos HIV/AIDS gadījumos Latvijā laika periodā no 2010. līdz 2016. gadam. Tika retrospektīvi analizēti HIV/AIDS pacientu autopsiju protokoli izvēlētājām laika periodam. Tika ievākti demogrāfiskie dati, patoloģiskā un klīniskā diagnoze nāves iestāšanās brīdī, makro- un mikroskopiski orgānu apraksti. Pētījumā tika iekļauti 455 HIV/AIDS pacienti, kuru vidū tika identificēti 71 Pneumocystis jiroveci pneimonijas, 40 diseminētā citomegalovīrusa infekcijas, 144 kandidozes, 47 kriptokokozes, 27 cerebrālās toksoplazmozes, 10 diseminētas atipiskās mikobakteriozes kā arī 5 plaušu aspergilozes gadījumi. Visbiežāk izolētās vai kombinētās OI izraisīja plaušu (74%) un smadzeņu (34%) bojājumus. Secinājums: OI ir svarīgs letalitātes faktors HIV/AIDS pacientu vidū Latvijā (28%). Letālo OI, tuberkulozes (23%) un bakteriālās pneumonijas (27%) saistīto HIV/AIDS gadījumu skaits kā arī šo slīmību smaga gaita norāda uz zemu ārstēšanas līmeni un sliktu HIV/AIDS epidēmijas kontroli Latvijā.

Introduction

According to the official statistical data at the present decade rates of the new HIV diagnoses in Latvia are among the highest in Europe with a mean of 300 new HIV cases being registered each year. Rates of progression to AIDS and AIDS-related mortality rates are also high. In European Union (EU) Eastern Region including all Baltic States the main HIV transmission routes are heterosexual contacts and intravenous drug use (ECDC 2015). In the most of developed world hiv/aids population is expanding and aging since highly active antiretroviral therapy (HAART)

introduction and mortality profile is shifting towards non HIV/AIDS associated age related degenerative diseases and non AIDS defining cancers however due to poor antiretroviral therapy coverage (Viksna et al., 2016) rates of AIDS related deaths are still high in Latvia (ECDC 2015).

According to previous studies among HIV/AIDS patients in Latvia, the most common cause of hospital admission are opportunistic infections (Seikals, Sture 2016). HIV/AIDS associated infections encountered in the WHO European Region include tuberculosis, bacterial infections, Pneumocystis jiroveci pneumonia, herpes infections (herpes zoster, cytomegalovirus, herpes simplex virus 1, 2), Candida oesophagitis, Cryptococcal meningitis, toxoplasmosis, Mycobacterium avium complex disease (https://aidsinfo.nih.gov/guidelines). Clinical investigation of HIV/AIDS patients in Latvia is advanced however limited by compliance of these patients. It is known that HIV/AIDS epidemic in Latvia is confined predominantly to intravenous drug users and their sexual partners. Due to poor socioeconomic status health neglect is almost universal among this population therefore typical presentation to healthcare is in terminal stages. Adequate investigation options in case of late presentations are limited because invasive investigations with tissue sampling are impossible due to poor patient condition. Tissue specimen collection however is very useful in HIV/AIDS patients because not always it is possible to differentiate colonization from infection by laboratorial analysis alone, and infection can be proven only when tissue invasion is identified on histology. Time till lethal outcome is frequently a matter of hours or days and also limits diagnostic possibilities. In cases of unclear clinical diagnosis autopsy helps to establish final diagnosis and either confirms, elaborates or disputes the clinical diagnosis. According to Latvian legislation all patients dying from dangerous infectious diseases including HIV have to undergo autopsy (https://likumi.lv/).

Aim. To analyze the spectrum, prevalence and morphology of opportunistic infections in lethal HIV/AIDS cases in Latvia for the time period 2010 - 2016.

Materials and methods

Review of medical autopsy protocols in the RECUH Pathology Centre for time period 2010.-2016. Selection of HIV positive patients who died in different medical centers in Riga district during time period encompassed by study. Our study is representative of mortality trends among Latvian HIV/AIDS population in general due to the fact that mostly these patients are treated in large medical centers in Riga district and all patients dying in these centers are referred for medical autopsies in the RECUH Pathology Centre. In autopsy protocols we analyzed patient demographic data, pathological and clinical diagnoses including main diagnosis, complications and comorbidities. We analyzed also organ macroscopic appearance at autopsy as well as histological slide descriptions for lethal cases of opportunistic infections. Presence of combinations of opportunistic infections (OI) in patients who died from them, as well as prevalence of OI at the time

of death in patients dying from other diseases were also analyzed. All data was collected and processed by Microsoft Excel and IBM SPSS 21.0 software.

Results

We found that a mean of 60 HIV/AIDS patient autopsies are performed in the RECUH Centre of Pathology each year. Our study included 455 HIV/AIDS patients with 69% (n=314) males and 31% (n=141) females. Mean age at the time of death was 40 (±9 SD) years with no statistically significant difference between genders (p=0,953 as calculated by Spearman correlation test). 72% were unemployed at the time of death, 9% died in the prison hospital, 9% were disabled and only 10% reported being occupied although the whole study population was in the working age. According to clinical data 94% (n=429) of patients were in the AIDS stage at the time of death. Of them 90% (n=388) were in C3, 5% (n=20) in B3, and 5% (n=21) in A3 stages. In the majority of cases potential risk factors for HIV transmission were not reported. Among the identified risk factors intravenous drug use (IVDU) and heterosexual contacts were the only ones reported.

Conditions leading to death were opportunistic infections (28%), tuberculosis (23%), malignancy (11%), end stage liver disease (11%), wasting syndrome complicated by nonspecific bacterial pneumonia, sepsis and miscellaneous conditions (27%).

Of patients who died from opportunistic infections (OI), 23% had more than one potentially lethal OI infection at the time of death. We identified cases where OI were present at autopsy but were not the cause of death as well as cases where certain isolated OI has led to fatal outcomes.

Of 71 case of Pneumocystic (PC) pneumonia 43 were fatal. In fatal cases it was almost invariably bilateral totally disseminated throughout lungs and on microscopy diffuse alveolar filling with eosinophilic foamy exudates (pathognomonic of PC pneumonia) and intense interstitial inflammatory infiltration were present. In 15 cases PC pneumonia was associated with Cytomegalovirus (CMV) pneumonitis. All these patients had a clinical diagnosis of disseminated CMV infection prior to death. Microscopic changes characteristic for active CMV infection are interstitial and intraalveolar macrophages with intranuclear inclusions surrounded by halo as well as intracytoplasmatic inclusions which reflects active new virus particle production.

Of 47 Cryptococcosis cases 23 were fatal. We identified cases of isolated pulmonary (n=10), isolated CNS (n=12) as well as disseminated Cryptococcosis (n=25). Initially Cryptococcus causes pulmonary disease as it spreads by spore inhalation. In cases of pulmonary Cryptococcosis microscopically fungal masses were identified within intraalveolar spaces and interstitial tissues. Cryptococcus is neurotropic and in case of extrapulmonary dissemination Cryptococcal meningoencephalitis is a common finding. Extensive extrapulmonary disease with multiple organ involvement was also identified in a few cases. Besides lungs, meninges and brain, liver, kidneys and bone marrow were involved most frequently. Grossly Cryptococcal lesions in parenchymatous

organs appear as gelatinous soft areas due to high content of polysaccharides in fungal capsules, and Cryptococcal meningitis appears as diffuse leptomeningitis with mucinous fluid around meninges. On microscopy Cryptococcal lesions in all organs are also similar; they consist of masses of round-oval fungal cells surrounded by clear spaces that are capsule not staining on routine hematoxylin and eosin preparations.

Cerebral toxoplasmosis was identified in 27 where 17 of them were fatal. Gross lesions in fatal cases are areas of cerebromalacia or abscesses in cerebral or cerebellar hemispheres, localized most commonly on the white-grey border, or in basal ganglia. On microscopy lesions reveal diffuse tissue necrosis surrounded by ruptured toxoplasma cysts with free parasites within brain tissues.

Of 10 cases of disseminated atypical mycobacteriosis 6 were fatal. Involved organs were liver, spleen, kidneys, intestines, lymph nodes, bone marrow and lungs. White yellowish 0.5-1cm lesions were identified in these organs in gross examination. On microscopy nonnecrotizing granulomas, scarce or absent multinucleated Langhans giant cells were considered diagnostic in cases where atypical mycobacteria infection was also proven clinically.

Candidiasis was the most common identified OI at the time of death overall, however majority of the Candida spp. induced lesion were not fatal. We identified 114 cases of Candidiasis including isolated oral (n=65), isolated esophageal (n=13), oroesophageal (n=14) as well as invasive candidiasis in organs other than esophagus (n=8) including tracheobronchial and intestinal Candidiasis, Candida pneumonia and disseminated Candidiasis with Candidaemia. In most of the cases where invasive Candidiasis was present it was associated with other HIV/AIDS associated or non related fatalities. 5 cases of fatal isolated Candida pneumonia were identified. On gross autopsy examination of these patient lungs lesions were described as multiple diffuse whitish infiltrates in different lobes which is characteristic for hematogenous spread and consistent with the fact that all these patients had Candidaemia prior to death as documented in clinical charts. Diagnoses were confirmed by microscopically identifying fungi within these lesions.

In 6 cases where disseminated candidiasis was suspected clinically prior to death, it turned out to be disseminated tuberculosis in 5 and disseminated atypical mycobacteriosis in one case.

We found that 40 patients had disseminated Cytomegalovirus (CMV) disease at the time of death as documented in clinical records. CMV disease diagnosis is established by clinicians when invasive CMV disease and viremia or viremia alone is proven. On autopsy, CMV was found in association with variable pulmonary pathogens, most frequently Pneumocystis jiroveci as mentioned before. Only two lethal outcomes were directly related to CMV disease. In one case patient died from CMV encephalitis which was histologically proven following autopsy and in the second case patient had clinically proven CMV colitis, developed dehydration followed by lower extremity thrombophlebitis and died from pulmonary artery thromboembolism.

Pulmonary aspergillosis was identified in 5 cases, 3 of them were aspergillomas and 2 were pneumonias. Only one case of aspergillus pneumonia was isolated and has lead to patients' death. Diagnosis was proven histologically by identifying narrow dichotomously branching at an acute angle septate hyphae and angioinvasion.

25% of study population (n=112) had tuberculosis (TB) at the time of death. In 93% (n=104) of cases where TB was present at autopsy it was considered as a cause of death by pathologist. In 21% of lethal TB cases it was isolated pulmonary and in 79% it was disseminated. Extrapulmonary disease was found most frequently in liver, spleen, kidneys, CNS, intestines. On gross examination pulmonary TB was almost invariably bilateral military disseminated and multiple monomorphic lesions were found in affected organs in cases of extrapulmonary dissemination. There was a statistically significant correlation between tendency to develop disseminated TB and presence of at least one OI that typically develops at CD4 count below 200 cells/µl ($p=0,01$ as calculated by Spearman's rank-order correlation test). Overall prevalence of potentially lethal OI at the time of death in patients dying from TB was 26%.

27% of study population died from wasting syndrome complicated by nonspecific bacterial pneumonia and sepsis. Bacterial pneumonia is not specific for AIDS as well as is tuberculosis and can develop at any CD4 count however both are more severe in AIDS patients than in general population. On gross examination pneumonias were most frequently bilateral and extensive. Such findings as abscess, pleuritis and empyema were not uncommon. Nonspecific bacterial pneumonia is a common final pathway of AIDS patients dying with wasting syndrome and other AIDS associated conditions especially neurological due to impaired pulmonary ventilation because such patients are in prostration and immobile in the last days – weeks of life.

Prevalence of OI in patients dying from malignancies was 15% and in patients dying from end stage liver disease 8%.

Discussion

Numbers of new HIV cases in Latvia are high not due to active HIV testing policy as it is in our neighbor country Estonia where HIV tests are preformed not only among risk populations but in all individuals of reproductive age. Numbers of new HIV cases are high in Latvia because many HIV tests are performed when patients are admitted with AIDS defining diseases. On the other hand, numbers of performed HIV tests in Lithuania are low. Therefore dynamics of the new HIV diagnoses rates are different among Baltic States. While numbers of new HIV cases decrease in Estonia they are rising in Latvia and Lithuania (ECDC 2015).

Rapid lethal outcomes following admission and advanced lesions produced by opportunistic infections (OI) that typically develop at CD4 count below 200 cell/µl identified at autopsy indicate that HIV/AIDS patients are not receiving antiretroviral therapy and turn to healthcare institutions

late. High prevalence of OI among patients who died from tuberculosis indicates that this study population group is characterized by the most profound immunosuppression added also the fact that tuberculosis was disseminated at the time of death in most of the cases where it was present.

Mean age at the time of death in our study population is equal to that of HIV diagnosis in EU in general (ECDC 2015) which means that HIV in Latvia is diagnosed late. This is consistent with the fact that HIV/AIDS patients are frequently in extremis on admission to the hospital whether the cause of disease is HIV/AIDS related or not (non AIDS defining malignancies, end stage liver disease, miscellaneous).

Conclusions

Numbers of AIDS related lethal outcomes among HIV/AIDS patients in 2010.-2016. in Latvia were high and comprised 94% which accounts for OI, tuberculosis, wasting syndrome and bacterial pneumonia and AIDS defining malignancies. In coupe with advanced stages of opportunistic diseases (including OI) and HIV/AIDS non related diseases at the time of death this indicates that HIV/AIDS epidemic in Latvia is not controlled in comparison to EU in general where HIV/AIDS patient mortality trends are shifting towards non HIV/AIDS related conditions. Active HIV testing and treating policies among risk populations as well as social education need to be employed to overcome HIV/AIDS epidemic.

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BIRTH WITH DOULA – FASHION OR NECESSITY?

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Abstract

Birth with doula - fashion or necessity?

Key words: *Doula, labors, giving birth women, support*

Introduction: Recently it's becoming more popular among women in the European countries to give birth with doula. In most cases doula is a woman who have no medical education that supports the other woman during pregnancy and labor (Meadow 2014). Primarily, doulas work includes informing and explaining to women about parturition and supporting women physically and emotionally (Meadow 2014). In surveys made by doulas good pregnancy results and higher level of women satisfaction have been discovered (Hodnett *et al.* 2012; Papagni *et al.* 2006). However, despite the popularity of this movement, professional medical research in Latvia on this topic are still not existent.

Aim: To analyze the data in Riga maternity hospital (RMh) of women giving birth in 2014, 2015, 2016, who chose doula services as support for their births and compare this data with women giving birth without such services, who gave birth in a normal physiological manner in due time.

Materials and methods: 18129 birth histories were viewed, 125 of which were deliveries with doulas. A control group was also recruited for the study - 127 women who gave birth in a normal physiological way and in due time. The average age, the number of births and number of pregnancies coincides with a group of women giving birth to doulas. The data was collected and statistically processed using the IBM SPSS 24.0 program.

Results: From 125 labors given with the help of doulas - 43 (34,4%) were in 2014, 39 (31,2%) in 2015 and 43 (34,4%) in 2016. Doula services were chosen by women with the average age of 31,5. 63 (50.4%) of women were Latvians, 95 (76%) women were married, 97 (77.6%) women had a higher education and 109 (87.2%) women had an official job. Most of doulas services were provided to women who had their first labor - 62 (49.6%) cases. In 33 (26.4%) cases with doulas service there were prolonged pregnancies. In 30 (24%) cases women had complications such as dysfunction of the uterus. Comparing births supported by doulas with the births that occurred in the control group, it was established that such complications as the rupture of the labia and fetal distress were less common in the group of women which were supported by doulas, which is a statistically significant result ($p < 0.034$; $p < 0.034$). However, it is also noted that in the group of women which were supported by doulas the perineal rupture (59.6%) is statistically more frequent in comparison with the control group (45%), where $p < 0,038$. It was found that the indices on the Apgar scale in newborns in the first minute are higher in the research group than in the control group, which is a statistically significant result, $p < 0.001$. It was also shown that epidural anesthesia in the research group was performed significantly less than in the control group ($p < 0.01$) and that the use of oxytocin for birth stimulation in women in the research group was lower, and this is a statistically significant difference, where $p < 0.001$.

Conclusions: For the past 3 years the tendency to give birth with doulas in the Riga Maternity Hospital has not changed. Services provided by doulas are preferred by women with higher education, stable income and a relationship status during their first labor. In general, deliveries with doulas are significant support for women. The results suggest that participation of doulas during labor have good potential benefits. It is necessary to collect more data and to continue the research covering the situation throughout Latvia towards doula service.

Kopsavilkums

Dzemdības ar dūlām – modes lieta vai nepieciešamais pakalpojums?

Atslēgvārdi: *Dūlas, dzemdības, dzemdētājas, atbalsts*

Ievads. Pēdējo gadu laikā Eiropas valstīs pieaug popularitāte dzemdēt ar dūlas atbalstu. Dūlas galvenokārt ir sievietes, kuras atbalsta otru sievieti grūtniecības laikā, dzemdībās un pēcdzemdību periodā, bez medicīniskās izglītības (Meadow 2014). Dūlas galvenajos pienākumos ietilpst informēt un skaidrot sievietēm par dzemdību norisi, kā arī atbalstīt sievietes fiziski un emocionāli (Meadow 2014). Dūlu veiktās aptaujas liecina par labākiem grūtniecības iznākumiem un augstāku sievietes apmierinātības līmeni, ja tiek izmantoti viņu pakalpojumi (Hodnett *et al.* 2012; Papagni *et al.* 2006). Taču, neskatoties uz šī brīža dūlu kustības popularitātes vilni, Latvijā joprojām nav bijis medicīnas profesionāļu veikta pētījuma par to, vai tiešām dūlu ietekme uz grūtniecību un dzemdību gaitu ir tik pozitīva.

Mērķis. Analizēt datus par Rīgas Dzemdību namā (RDzN) 2014., 2015., 2016. gadā dzemdējošām sievietēm, kuras izvēlējušās dūlas sniegtos pakalpojumus dzemdību laikā, un salīdzināt šādas dzemdības ar fizioloģiskām laicīgām dzemdībām, kas norisinājās bez dūlas atbalsta.

Materiāli un metodes. Tika analizētas 18129 dzemdētāju vēstures, no kurām atlasīja 125 vēstures – dzemdības, kurās piedalījās dūlas. Pētījumam tika atlasīta arī nejauša kontroles grupa - 127 sievietes ar fizioloģiskām laicīgām dzemdībām, kuru vidējais vecums, dzemdību un grūtniecību skaits ir līdzīgi, kā tas ir sievietēm no pētījuma grupas.

Dati tika apkopoti un statistiski apstrādāti ar IBM SPSS 24.0. datorprogrammas piedāvātām histogrammām un analīzes metodēm.
Rezultāti. Starp 125 dzemdībām, kuras norisinājās RDzN ar dūlu atbalstu: 43 (34,4%) notika 2014. gadā, 39 (31,2%) 2015. gadā un 43 (34,4%) 2016. gadā. Sieviešu, kas izvēlējās dūlas pakalpojumus dzemdībās vidējais vecums - 31,5 gadi, 63 (50,4%) sievietes pēc tautības - latvietes, 95 (76%) sievietēm ģimenes statuss ir reģistrēta laulība, 97 (77,6%) sievietēm ir augstākā izglītība, 109 (87,2%) ir sievietes ar oficiālu darba vietu, no kurām 16 (12,8%) ir vadītāju amatos. Visbiežāk dūlas sniegtos pakalpojumu izmanto sievietes pirmdzemdētājas - 62 (49,6%) gadījumi. 33 (26,4%) gadījumos ar dūlām dzemdējošās sievietes bija grūtniecību pārnēsājušas (>41 nedēļas).
Salīdzinot dzemdības, kurās piedalījušās dūlas (turpmāk- pētījuma grupa), ar kontroles grupu, kaunuma lūpu plīsums un augļa distress ir novērotas statistiski nozīmīgi retāk (p <0,034; p <0,034). Taču pētījuma grupā starpenes plīsums sievietēm ir novērots statistiski nozīmīgi biežāk (59,6%), nekā kontroles grupā (45%), kur p < 0,038. Konstatēts, ka Apgares skalas rādītāji jaundzimušajiem pirmajā minūtē pētījuma grupā ir augstāki, nekā šie paši rādītāji kontroles grupā, kas ir statistiski nozīmīgi rezultāti, kur p < 0,001. Tika pierādīts arī, ka epidurālo anestēziju pētījuma grupā veic statistiski nozīmīgi retāk, nekā kontroles grupā (p < 0,01). Un, ka oksitocīna pielietošana stimulācijas nolūkos sievietēm pētījuma grupā ir mazāka, un šī ir statistiski nozīmīga atšķirība, jo p < 0,001.
Secinājumi. Tendence dzemdēt ar dūlām RDzN pēdējo trīs gadu laikā nav mainījusies.
Dzemdības, kurās savu atbalstu sniedz dūlas lielākoties izvēlās sievietes ar augstāko izglītību, stabiliem ienākumiem, noslēgtām laulībām, un pirmo grūtniecību.
Iegūtie rezultāti liecina, ka dūlu līdzdalībai dzemdībās ir potenciāli labvēlīgi ieguvumi. Ir nepieciešami vairāki dati un pētījumi, lai izvērtētu kopēju tendenci un situāciju dzemdībās ar dūlām visā Latvijā.

Introduction

For the last few years it's becoming more popular among women to dive birth with doula (Rezeberga et al. 2016). Doula is a person, who brings physical, social and emotional individual support for women during their pregnancies, labors, and postnatal period (Meadow 2014). But in most cases doula have no medical education. Primarily, doulas work includes informing and explaining to women about parturition. Doula care about women, take part in her labor and execute all women personal preferences, which related to the birth process. With such activities doula try to promote positive birth outcomes and well-being in labor.

Nowadays, not uncommon to believe that the good is that which is natural. In 21st century living women become more and more appreciated not only by the medical professional assistance, but also for additional emotional support in their labor. Which could be provided by doula.

Data which were collected about doulas support in 2016 shows, that doulas have bring their support for 16 women or families, who have planned babies, supported nearly 500 pregnant women, take part in 206 deliveries, in which 32 were home deliveries, and take care about 400 women in postnatal period (http://www.dulas.lv/atbalsts/nodarbibas/params/post/1111071/marta-latvija-notiks-dulu-nedela-ar-vadmotivu-dulas-atbalsts-visai-gimenei).

Some studies shows that support binged by doula helps women to initiate timely lacto genesis within 72 hours in post-partum period (Nommsen-Rivers et al. 2009), reduce anxiety in women during the postnatal period (Akbarzadehen et al. 2015), and tends to decrease the duration of labors (Campbell et al. 2006).

However, despite the popularity of this movement, professional medical researches in Latvia on this topic are still not existent. It's an actual find out whether birth with doula support is just a fashion thing or profit opportunity in medicine, or really need individualized service for woman in her birth.

Material and methods

It was in 2016-2017 years made retrospective study which included data from Riga Maternity hospital birth histories during the period from January 2014 to December 2016. Totally 18129 birth histories were viewed, 125 of which were deliveries with doulas. A control group was also recruited for the study - 127 women who gave birth in a normal physiological way and in due time. The average age, the number of births and number of pregnancies coincides with a group of women giving birth to doulas.

The study was made by respecting the provisions of the Helsinki Declaration and the Human Rights Convention. The permission of the Riga Stradiņš University Ethics Committee and Riga Maternity hospital was received. The data was collected and statistically processed using the IBM SPSS 24.0 program.

The study used descriptive statistics - the standard deviation methods and cross tabulations. And to determine the differences between the signs used: “Cross tables” “Mann-Whitney U” test, “Chi-Squer” and “Fisher's Exact” tests. Statistical hypothesis truth level - $p < 0.05$ was the basis for the “zero” hypothesis rejection and for alternative hypothesis adoption.

Results

This survey shows that from 125 labors given in RMh with the help of doulas - 43 (34,4%) were in 2014, 39 (31,2%) in 2015 and 43 (34,4%) in 2016. Doula services were chosen by women with the average age of 31,5. 63 (50.4%) of women were Latvians, 95 (76%) women were married, 97 (77.6%) women had a higher education and 109 (87.2%) women had an official job.

Women who given birth by doula support in 48% of cases choose family childbirth, and in 26.4% cases the only support person is doula. However, it is interesting that 9.6% of cases women made an agreement with midwife (or doctor) and doula in their labors and patients relatives are also participating in such kind of labors. Comparing such labors for three years, it was established that a common trend for women to choose doula as the support person for their labors doesn’t change.

Most of doulas services were provided to women who had their first labor - 62 (49.6%) cases. In 33 (26.4%) cases with doulas service there were prolonged pregnancies. In 30 (24%) cases women who had choose labors binged by doulas support had complications such as dysfunction of the uterus and in this cases stimulation with oxytocin were done.

The control group are randomly selected 127 women who gave birth in a normal physiological way and in due time. The average age, the number of births and number of pregnancies coincides with a group of women giving birth to doulas.

To compare spontaneous birth results, from the research (doulas) group were excluded 13 patients who had their birth with caesarean sections.

Comparing births supported by doulas with the births that occurred in the control group, it was established that such complications as the rupture of the labia (7.4%; 17.4%) and fetal distress (3.2%; 11%) were less common in the group of women which were supported by doulas, which is a statistically significant result ($p < 0.034$; $p < 0.034$). However, it is also noted that in the group of women which were supported by doulas the perineal rupture (59.6%) is statistically more frequent in comparison with the control group (45%), where $p < 0{,}038$. It was found that the indices on the Apgar scale in newborns in the first minute are higher in the research group than in the control group, which is a statistically significant result, $p < 0.001$.

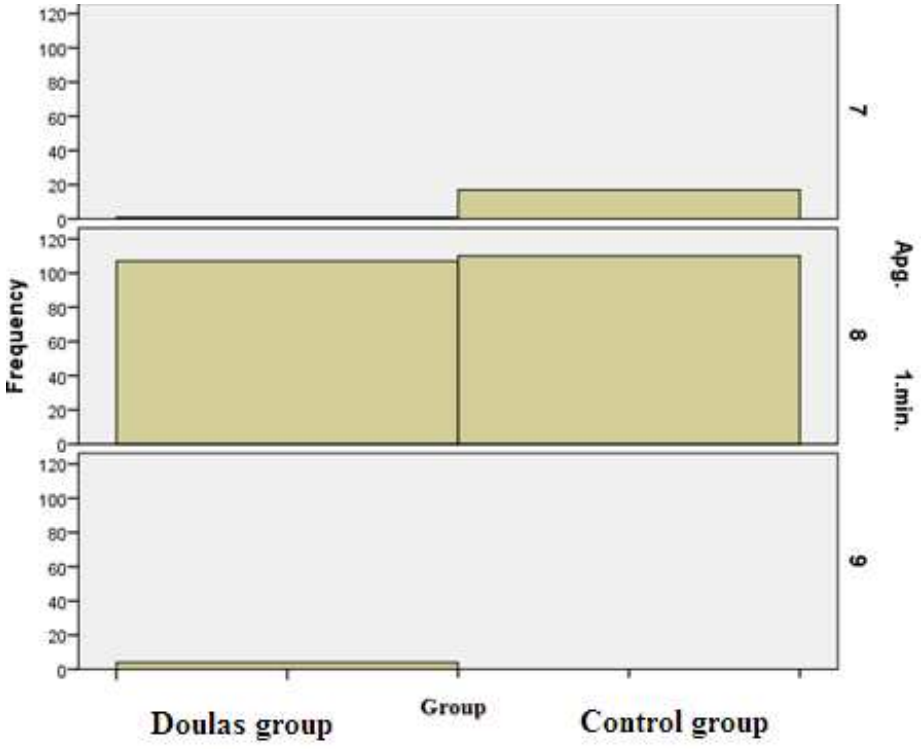

Figure 1. **Apgar scale in newborns in the first minute, comparing of the groups**

Also the use of epidural anesthesia (EA) was compared among women in both groups. And results shown that in research group from 112 women labors EA were used in 9 cases (8%), and in control group from 127 labors in 31 cases (24.4%). And it was significantly less in research group than in the control group ($p < 0.01$). Interesting results were in use of oxytocin for birth stimulation. This drug was used in all cases when women had dysfunction of the uterus. However, in research group from 112 labors the birth of 112 in 8 cases (7.1%) i/v oxytocin input was made without appropriate indications. And in control group from 127 labors in 25.2% or 32 cases. The study showed that oxytocin unreasonable application for stimulation purposes was lower in the research group and this is a statistically significant difference, where $p < 0.001$.

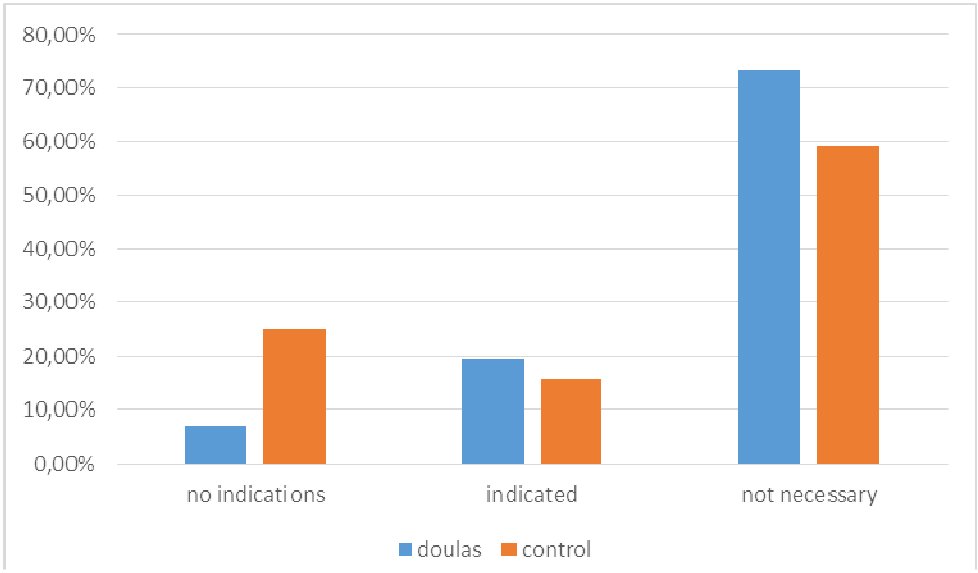

Figure 2. **The comparison of oxytocin use for stimulation purposes between the two groups**

Discussion

The study results revealed some new aspects, some of which are not viewed in previous studies. For example, such complications as labia rupture and fetus distress in women giving birth with doulas support occur statistically significantly less than women without doulas support. Probably, women who are giving birth with doulas feeling more relaxed and psychologically better prepared for the childbirth than women in control group. On the other side - the results also shown us that the women in research group statistically more often than women in control group had perineal ruptures. This study doesn't cover data on the performance of episiotomy in women in both groups, and it is unknown whether women research group refuse to do such procedures. It is clear that these results are inconsistent, and have difficulties for adequate interpretation.

Interesting results are also viewed in use of the oxytocin stimulation purposes. The literature had found data about side effects to use of this drug (Rezeberga *et al.* 2016). The World Health Organization (WHO) recommends to use oxytocin only in specific indications and protocol, which defines oxytocin doses and times (http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/augmentationlabour/en/). The study showed that oxytocin unreasonable application for stimulation purposes was lower in the research group than in control group.

This study also coincides with some results of other studies (Backes *et al.* 2013; Marshall *et al.* 2002; Nommsen-Rivers *et al.* 2009). It was found that the indices on the Apgar scale in newborns in the first minute are higher in the research group than in the control group. And that epidural anesthesia in the research group was performed significantly less than in the control group. However, as I was mention one of the most common complications for women in research group was perineal rupture. In the research group childbirth analgesia was used frequently less than for the

control group, on the one hand - it could be welcomed, because it could reduce related risks of this manipulation, but on the other hand – it may result as a longer period for women of suffering pain.

Conclusions

The results suggest that participation of doulas during labor have good potential benefits and potentially could improve maternity progress.

The foreign literature and publication on this topic are great, but these studies have no impartial META analysis and qualitative research design doesn't drawn up, so it is necessary to require number of objective studies with larger control groups to collect more data and to continue the research covering the situation throughout Latvia towards doula service.

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DELIRIUM ASSESSMENT IN THE INTENSIVE CARE UNIT

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Abstract
Key words: *Delirium, screening, ICDSC*
Introduction. Delirium defined as a disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period of time (hours to days) and fluctuates over time. It is independently associated with significant increases in the LOS (length of stay), inpatient mortality, long term mortality, cognitive decline, requirement for institutional care, functional impairment, healthcare costs, distress to the patient and family distress.
Aim. Find out if it is possible to apply description of patient to assessment scale and compare clinical diagnosis with scale result.
Materials and methods. Retrospective study of 130 medical histories with diagnosis delirium, 101 of them were included in further analysis. Intensive Care Delirium Screening Checklist (ICDSC) was used to assess state of patients.
Results. 101 clinical cases (79 males, 22 females) were included in further analysis. Median age was 50 (23-89) years. Median LOS was 8 (1-41) days. 89% of patients confirmed alcohol use and 72% were unemployed. Most common hospitalization causes were poisoning (39,6%; 95% CI= 30,7-49,5%), injury (23,8%; 95% CI=14,9-31,7%) and diseases of digestive system (15,8%; 95% CI=8,9-22,8%). According to ICDSC only 10,9% (95% CI=5,9-17,8%) had delirium, 76,2% (95% CI=67,3-84,2%) had subsyndromal delirium. 12,9% (95% CI=6,9-19,8%) were unable to assess by ICDSC with any of criteria.
Conclusion. Checklist provides more accurate diagnosis of delirium which affects further therapy tactics. It is possible to evaluate patient's state in progress by certain symptom. Checklist admits to assess patient in systemic way for better cooperation between medical professionals.

Kopsavilkums
Atslēgvārdi: *delīrijs, skrīnings, ICDSC*
Ievads. Delīriju definē kā apziņas aptumšošanās, kuru pavada izziņas vai uztveres traucējumi. Delīrija attīstās stundu-dienu laikā, un stāvoklis svārstās dinamikā. Delīriju neatkarīgi saista ar risku palielinātam stacionēšanas ilgumam, intrahospitālai mirstībai, ilgtermiņa mirstībai, kognitīvajiem traucējumiem, prasībai intahospitālai aprūpei, funkcionālajiem darbības traucējumiem, palielinātām veselības aprūpes izmaksām, stresu pacientam un viņa ģimenei.
Mērķis. Noskaidrot, vai ir iespējams novērtēt pacientus ar ICDSC skalu un salīdzināt klīnisko diagnozi ar scalas punktu skaitu.
Materiāli un metodes. Retrospektīvi tika analizētas 133 pacientu vēstures ar diagnozi delīrija, 101 no tām iekļāva tālākai analīzei. Pacientu novērtēja ar ICDSC novērtēšanas skalu.
Rezultāti. Tika atlasīti 101 pacients (79 vīrieši, 22 sievietes). Vidējais pacientu vecums sastādīja 50 (23-89) gadi. Vidējais stacionēšanas ilgums 8 (1-41) dienas. 89% pacientu lietoja alkoholu un 72% pacientu ir bezdarbnieki. Biežāki saindēšanas cēloni irsaindēšanas (39,6%; 95% CI= 30,7-49,5%), trauma (23,8%; 95% CI=14,9-31,7%) un gremošanas trakta saslimšanas (15,8%; 95% CI=8,9-22,8%). Pēc ICDSC skalas punktu skaita tikai 10,9% (95% CI=5,9-17,8%) pacientu ir delīrija, 76,2% (95% CI=67,3-84,2%) ir subsindromāla delīrija. 12,9% (95% CI=6,9-19,8%) pacientu vispār nebija iespējas novērtēt ar ICDSC skalu.
Secinājumi. ICDSC skala nodrošina precīzāku delīrija diagnostiku, kas var ietekmēt terapijas taktiku. Ar ICDSC skalu ir iespējams novērtēt pacienta stāvokļa izmaiņas dinamikā. ICDSC skala var palīdzēt novērtēt pacientu sistēmiskā veidā un uzlabot sadarbību starp medicīnas speciālistiem.

Introduction

Delirium defined as a disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period of time (hours to days) and fluctuates over time.

Early identification of delirium is important because it is associated with increases in the length of hospital stay, inpatient mortality, and requirement for institutional care, healthcare costs and distress.

Delirium may have a single cause or more than one cause. Sometimes no cause can be identified. The main causes mentioned in the literature are drugs, alcohol, dehydration and infection. The population of patients with delirium is multifarouse, so everyone with risk factors shoukd be assessed.

There is difference between expectations and reality of delirium management. The problem is that personnel in the ICU work in shifts and communication between medical staff is impaired because of lack of united assessment instrument. Sometimes decursusmorbi is not appropriately written and make difficulties in prospective evaluation. Often this negatively affects recovery process increasing complication risks and therapy length.

Materials and methods

We performed retrospective study of one hundred thirty medical histories with diagnosis delirium in 2014-2015 years; 101 of them were included in further analysis, 29 met exclusion criteria. Intensive Care Delirium Screening Checklist was used to assess state of patients. (Fig. 1) Each positive component is scored 1 point. A total score ≥4 is positive for delirium. 1-3 points termed subsyndromal delirium.

Intensive Care Delirium Screening Checklist
1. Anything other than normal wakefulness 2. Inattention 3. Disorientation 4. Hallucinations or delusions 5. Psychomotor agitation or retardation 6. Inappropriate speech or mood 7. Sleep/wake cycle disturbance 8. Symptom fluctuation

Figure 1. **Intensive Care Delirium Screening Checklist**

Inclusion criteria were age more than 18 years, more than one day admission in ICU and patients with diagnosis delirium.

Exclusion criteria were pediatric cases, additional psychiatric diagnosis or non-survivors.

The statistical analysis was performed to assess patient gender, age, admission diagnosis and length of hospital stay. Intensive Care Delirium Screening Checklist (ICDSC) was used to assess state of patients. Patients were evaluated on first day of diagnosis.

Data analysis was performed using SPSS and Microsoft Excel programs.

Results

101 clinical cases (79 males, 22 females) were included in further analysis.

Median age was 50 (23-89) years. Median LOS was 8 (1-41) days. 89% of patients confirmed alcohol use and 72% were unemployed.

Most common hospitalization causes were poisoning (39,6%; 95% CI= 30,7-49,5%), injury (23,8%; 95% CI=14,9-31,7%) and diseases of digestive system (15,8%; 95% CI=8,9-22,8%) (Figure 2).

		Frequency	Percent	Valid Percent	Cumulative Percent	Bootstrap for Percent[a]			
						Bias	Std. Error	95% Confidence Lower	95% Confidence Upper
Valid	Diseases of the digestive system	16	15,8	15,8	15,8	,1	3,5	8,9	22,8
	Poisoning	40	39,6	39,6	55,4	,2	4,9	30,7	49,5
	Injury	24	23,8	23,8	79,2	-,2	4,2	14,9	31,7
	Diseases of the circulatory system	7	6,9	6,9	86,1	,0	2,5	2,0	11,9
	Diseases of the respiratory system	7	6,9	6,9	93,1	-,1	2,5	3,0	11,9
	Endocrine, nutritional and metabolic diseases/ Diseases of the nervous system	7	6,9	6,9	100,0	,0	2,5	3,0	11,9
	Total	101	100,0	100,0		0,0	0,0	100,0	100,0

Figure 2. **Admission diagnoses**

According to ICDSC only 10,9% (95% CI=5,9-17,8%) had delirium, 76,2% (95% CI=67,3-84,2%) had subsyndromal delirium. 12,9% (95% CI=6,9-19,8%) were unable to assess by ICDSC with any of criteria (Figure 3).

		Frequency	Percent	Valid Percent	Cumulative Percent	Bootstrap for Percent[a]			
						Bias	Std. Error	95% Confidence Lower	95% Confidence Upper
Valid	Normal	13	12,9	12,9	12,9	,1	3,3	6,9	19,8
	SubsyndromalDelirium	77	76,2	76,2	89,1	-,2	4,2	67,3	84,2
	Delirium	11	10,9	10,9	100,0	,1	3,1	5,9	17,8
	Total	101	100,0	100,0		0,0	0,0	100,0	100,0

Figure 3. **Delirium diagnosis by ICDSC**

Discussion

In studied group of patients main diagnoses were poisoning, injury and diseases of digestive system. We cannot take them as causes of delirium in every concrete case, but it may correlate with most frequent etiological agents as told before.

According to ICDSC only eleven percent had delirium, majority of evaluated patients had subsyndromal delirium - the presence of one or more symptoms of delirium, not meeting criteria

for delirium and not progressing to delirium. It also can be explained by lack of information in a medical records. Thirteen percent were unable to assess by ICDSC with any of criteria. Two criteria of eight, which are sleep-awake cycle disturbance and symptom fluctuation, were not mentioned in clinical histories so that unable to value them in all patients. The reason of this may be that decursusmorbi is not appropriately written by medical staff.

Conclusion

Firstly, checklist provides more accurate diagnosis of delirium which affects further therapy tactics. Secondly, it is possible to evaluate patient's state in progress by certain symptom. At last, checklist admits to assess patient in systemic way for better cooperation between medical professionals but it requires education of ICU personnel.

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CORRELATION BETWEEN GLUCOSE LEVEL AND ICU LOS

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Abstract
Key words: *glucose, ICU, ICU LOS, hospital LOS*
Introduction. Failure in glucose homeostasis is an often complication in ICU patients. Both hyperglycemia and hypoglycemia are considered to be a negative factor.
Aim. Find out if it is the correlation between glucose level and length of hospital and intensive care unit stay.
Materials and methods. Retrospective study of 200 medical histories with diagnoses N_{00}-N_{99} and J_{00}-J_{99}, 122 of them were included in further analysis. Exclusion criteria were pediatric cases, non-survivors and refusal of treatment. Patients were separated by glucose level in the blood in five groups: <4.4 mmol/l, 4.4-6.1 mmol/l, >6.1-7.9 mmol/l, >8–10 mmol/l and >10.0 mmol/l. Gender, age, length of hospital and intensive care unit stay and glucose level were interpreted in admission, first, third and fifth day in ICU. Data analysis using SPSS and Microsoft Excel programs.
Results. 122 clinical cases (79 males, 43 females) with diagnoses N_{00}-N_{99} – 47% and J_{00}-J_{99} – 53% were included in further analysis. Median age was 64.5 (SD 16.7) years. Median length of hospital stay was 14 (SD 12) days. Median length of ICU stay was 4 (SD 6) days. Independent- Samples Kruskal - Wallis test showed the correlation between glucose level and ICU LOS (p=0.018) in first day (in group 1 and 3). No other correlation was found.
Conclusion. Glucose level can't be a predictor of LOS in patients admitted to an ICU in all days. Further analysis is required.

Kopsavilkums
Atslēgvārdi: *glikoze, ITN, stacionēšanas ilgums ITN, stacionēšanas ilgums slimnīcā*
Ievads. Traucējumi glikozes homeostāzē ir bieža komplikācija pacientiem ITN. Gan hipoglikēmija, gan hiperglikēmija tiek uzskatīti par negatīvu faktoru.
Mērķis. Noskaidrot, vai ir korelācija starp glikozes līmeni asinīs un dzimumu, vecumu, stacionēšanas ilgumu stacionārā un ITN.
Materiāli un metodes. No 200 pacientiem N00-N99 un J00-J99 tika atlasīti 122. Izslēgšanas kritēriji bija: pediatriskie gadījumi, letāls iznākums vai atteikums no ārstēšanas. Pacienti tika sagrupēti piecās grupās pēc glikozes līmeņa asinīs: 4.4 mmol/l, 4.4-6.1 mmol/l, 6.2-7.9 mmol/l, 8–10 mmol/l, >10.0 mmol/l. Tika analizēti pases dati, pamatdiagnoze, stacionēšanas ilgums slimnīcā un ITN, asins glikozes līmenis iestāšanās, pirmajā, trešajā un piektajā dienā ITN. Pētījuma datu apkopošanai un analīzei izmantotās: Microsoft Excel 2010 programma un datorprogramma IBM SPSS v.22
Rezultāti. Tika atlasīti 122 pacienti - 79 vīrieši un 43 sievietes ar diagnozēm: N00-N99 - 47% un J00-J99 - 53%. Vidējais pacientu vecums sastādīja 64.5 (16,69 SD) gadi. Vidējais stacionēšanas ilgums-14 (12 SD) dienas, bet vidējais stacionēšanas ilgums ITN bija 4 (6,09 SD) dienas. *Kruskal-Wallis* tests parādīja statistiski nozīmīgu glikozes līmeņa asinīs korelāciju ar stacionēšanas ilgumu ITN (p=0.018) pirmajā stacionēšanas dienā ITN (1. un 3. grupā). Citu statistiski nozīmīgu korelāciju nav.
Secinājumi. Glikozes līmenis asinīs nevar būt par prognostisku radītāju stacionēšanas ilgumam stacionārā un ITN visās dienās. Tālākie pētījumi ir nepieciešami.

Introduction

Hyperglycemia occurs frequently in hospitalized patients and affects patient outcomes, including mortality, inpatient complications, length of stay, and overall hospital costs. Similar to hyperglycemia, hypoglycemia is an independent risk factor for poor outcomes in the hospitalized patient.

Improved glycemic control throughout the hospital stay, preventing hyperglycemia and hypoglycemia, is associated with decreases in short- and long-term mortality, inpatient

complications, and hospital lengths of stay. Financial benefits of glycemic control are significant, not just in reducing direct hospital costs, but also in reducing length of stay and readmission rates.

The objective of this study was to find out if it is the correlation between glucose level and length of hospital and intensive care unit stay.

Materials and methods

We performed retrospective data analysis of 200 (Clinic of Toxicology and Sepsis, Riga East Clinical university hospital, Clinical Centre "Gailezers") medical histories with diagnoses diseases of genitourinary system (N_{00}-N_{99}) and diseases of respiratory system (J_{00}-J_{99}) by ICD-10 classification, 122 of them were included in further analysis.

Inclusion criteria were age more than 18 years, more than one day admission in Clinic of Toxicology and Sepsis and patients with diagnoses: diseases of genitourinary system (N_{00}-N_{99}) and diseases of respiratory system (J_{00}-J_{99}) by ICD-10 classification.

Exclusion criteria were pediatric cases, non-survivors or refusal of treatment.

The statistical analysis was performed to assess patient gender, age, length of hospital and intensive care unit stay. Also glucose level was interpreted in admission day, first, third and fifth day in the ICU.

Patients were separated by glucose level in the blood in five groups:

1. <4.4 mmol/l
2. 4.4 – 6.1 mmol/l
3. 6.2 – 7.9 mmol/l
4. 8 – 10 mmol/l
5. >10 mmol/l

Data analysis was performed using SPSS and Microsoft Excel programs.

Results

122 clinical cases – 79 (65%) males and 43 (35%) females with diagnoses: diseases of genitourinary system (N_{00}-N_{99}) – 57(47%) and diseases of respiratory system (J_{00}-J_{99}) – 65 (53%) by ICD-10 classification were included in further analysis.

Median patients age was 64.5 (16.7 SD) years. Median length of hospital stay was 14 (12 SD) days. Median length of ICU stay was 4 (6.1 SD) days.

Independent- Samples Kruskal- Wallis test showed the correlation between glucose level and length of intensive care unit stay (p=0.018) in first day (in groups 1 and 3). Median length of ICU stay in 1st group (glucose level in the blood <4/4 mmol/l) was 6 (12.2 SD) days, but in 3rd group (glucose level in the blood 6.2 – 7.9) - 3 (2.6SD) days.

Discussion

Independent- Samples Kruskal- Wallis test showed the correlation between glucose level and length of intensive care unit stay (p=0.018) in first day (in groups 1 and 3). Median length of ICU stay in 1st group (glucose level in the blood <4/4 mmol/l) was 6 (12.2 SD) days, but in 3rd group (glucose level in the blood 6.2 – 7.9) - 3 (2.6SD) days. Also in the study of more than 100,000 inpatient admissions in patients with diabetes, patients who experienced hypoglycemic episodes had longer hospital stays. But in our research the correlation was found only in first admission day in the ICU, so glucose level can't be a predictor of length of stay in patients admitted to the intensive care unit in all days. Further analysis is required.

Conclusion

Glucose level can't be a predictor of LOS in patients admitted to an ICU in all days. Further analysis is required.

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PREDICTION OF REGIONAL LYMPH NODE METASTASES OF COLORECTAL ADENOCARCINOMA USING MORPHOLOGIC CHARACTERISTICS

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Abstract

Prediction of regional lymph node metastases of colorectal adenocarcinoma using morphologic characteristics

Key words: *colorectal adenocarcinoma, regional metastases, surgery*

This study is devoted to evaluation of predictive values of pathological and clinical parameters in colorectal adenocarcinoma cases on lymph node status. Three hundred seventy-three patients with newly diagnosed colorectal adenocarcinoma were identified by archive search in a single clinical university hospital 2011-2014. The retrospective study design was selected. Were evaluated following parameters: age and gender, cancer spread by pTNMGR parameters, volume and localization of primary malignancy, number and status of evaluated lymph nodes, quantity of metastases in pericolonic fat. Histological cancer slides were evaluated by light microscopy to identify the grade of nuclear atypia, pattern of invasive border and mitotic rate in cancer tissues. SPSS software was applied for descriptive and analytical statistics. The results showed, that adenocarcinoma was the most frequent histological type comprising 86,9% ($p<0.001$). Predominantly affected site was rectum and sigmoid colon – 70.1%, followed by right side of colon. Direct relation was observed between presence and extent or regional lymph node metastases (pN) and tumour volume ($p<0.05$), between pN and type of the invasive border ($r=0.504$). Using the depth of invasion of primary tumour (pT) as predictive factor of pN has been established as moderate diagnostic test. There was a weak positive correlation between pN and nuclear atypia ($r=0.34$), and moderate positive correlation between pN and mitotic count ($r=0.43$). Although these parameters don`t have enough predictive value for using them alone for preoperative evaluation, so they could be used as additional investigations for preoperative predicting of lymphatic metastases to improve accuracy of standard preoperative evaluation.

Kopsavilkums

Kolorektālās adenokarcinomas morfoloģisku raksturlielumu izmantošana reģionālo limfmezglu metastāžu noteikšanā

Atslēgas vārdi: *kolorektālā adenokarcinoma, reģionālo limfmezglu metastāzes, ķirurģija*

Pētījuma mērķis ir noteikt klīnisko un patoloģisku parametru prediktīvu vērtību attiecībā uz metastāžu esamību reģionālajos limfmezglos kolorektālās adenokarcinomas gadījumā. Trīs simti septiņdesmit trīs pacienti ar pirmoreiz diagnosticētu kolorektālu adenokarcinomu periodā no 2011. līdz 2014. gadam bija atlasīti vienas klīniskās universitātes slimnīcas arhīvā. Retrospektīvs dizains tika izvēlēts par pētījuma dizainu. Tika izvērtēti sekojoši parametri: pacientu vecums, dzimums, audzēja izplatība pēc pTNMGR parametriem, primāra audzēja tilpums un lokalizācija, izvērtētu limfmezglu skaits un metastāžu esamība un skaits tajos, metastāžu klātbūtne un daudzums apzarņa taukaudos. Histoloģiskie audzēju preparāti izvērtēti ar gaismas mikroskopijas palīdzību, noteikta kodolu atipijas pakāpe, invāzijas robežas veids un mitožu daudzums audzēja audos. SPSS programmatūra tika izmantota datu apstrādei. Rezultātos var uzsvērt, ka adenokarcinoma ir atzīta par visbiežāko kolorektālā audzēja histoloģisku paveidu, sastādot 86.9% no visiem gadījumiem ($p<0.001$). Pārsvarā adenokarcinoma lokalizējas taisnajā zarnā un sigmā – 70.1% gadījumos, otrā pēc biežuma vieta – resnas zarnas labā puse. Tieša saistība ir identificēta starp metastāžu esamību reģionālajos limfmezglos (pN) un audzēja lielumu ($p<0.05$), starp pN un invāzijas robežas veidu ($r=0.504$). Audzēja invāzijas dziļuma (pT) izmantošana kā prediktīvu faktoru pN, tika atzīta par vidēji stipru diagnostisku testu. Vāja pozitīva korelācija tika atklāta starp pN un kodolu atipijas pakāpi ($r=0.34$), un vidēja stipruma pozitīva korelācija tika atklāta starp pN un mitožu skaitu ($r=0.43$). Taču šiem parametriem nav pietiekamas diagnostiskās vērtības, lai izmantotu tos kā patstāvīgus kritērijus pacientu izmeklēšanā pirms operācijas. Tie var tikt pielietoti kā papildus iespējami diagnostiskie testi limfātisku metastāžu atklāšanai un riska novērtēšanai, tādējādi uzlabojot standarta preoperatīvas izmeklēšanas precizitāti.

Introduction

Nowadays oncology is one of the most actual medical topics. Colorectal cancer (CRC) is one of the most frequent malignant tumours in Latvia and worldwide (Ferlay et al. 2015). Among patients with oncologic diseases colorectal cancer is also one of the leading causes of mortality (Ferlay et al. 2015; Puppa et al. 2010). The screening for CRC in Latvia and other countries

worldwide helps to diagnose CRC earlier in less advanced stages, reduce mortality and prolong survival rates (Kudo et al. 2017).

CRC spread is characterized using pTNMGR parameters (Puppa et al. 2010). T parameter represents entity and spread of primary tumour or the tumor depth of invasion. There are 4 stages: the higher stage means deeper invasion. N parameter characterizes the number of regional lymph node metastases. There are 3 stages: the higher stage means higher number of LN MTS. M parameter represents the presence of distant metastases. G parameter means the grade of histological differentiation of cancer tissues. R parameter represents the macroscopic or microscopic presence of cancer tissues on surgical resection line (Puppa et al. 2010; Marzouk and Schofield 2011).

Colorectal carcinomas arising from intestinal epithelium, and are divided in some histological types by World Health Organisation (WHO): adenocarcinoma, mucinous cancer, signet ring carcinoma, medullary carcinoma, micropapillary carcinoma, serrated adenocarcinoma, adenosquamous carcinoma, spindle cell carcinoma. Adenocarcinomas represents the majority of all colorectal carcinomas (Marzouk and Schofield 2011).

There is a very high significance of accurate tumour staging, because it affects plan of therapy, prognosis, type of operation and survival (Veit et al. 2006). Regional lymph node metastases have very high prognostic and predictive values regarding the outcome, options of therapy in colorectal cancer cases (Veit et al. 2006).

Usage of clinical, pathological, molecular characteristics and pre- and postoperative state values has been proposed as prognostic and predictive of survival, of outcome and also of regional lymph node metastases in colorectal adenocarcinomas (Marzouk and Schofield 2011).

Following pathological factors were studied in earlier researches: tumour stage, which is characterized by involvement of lymph nodes, cancer tissues in pericolonic fat, peritoneal carcinomatosis, distant metastases; characteristics of primary tumour as depth of tumour invasion in intestinal wall, histological subtype by WHO classification, histological grade and differentiation, tumour budding and its invasive front, tumour invasion in venous and lymphatic vessels, perineural invasion, lymphocytic infiltration; and also presence of cancer tissues on surgical resection margins (Marzouk and Schofield 2011; Ryu et al. 2014).

Some of these factors were found to be predictive for the greater risk of regional lymph node metastases - depth of primary tumour invasion, tumour differentiation grade, tumour volume and budding, venous, lymphatic and perineural invasion. (Ryu et al. 2014)

The presence and quantity of affected lymph nodes is very significant and has influence on prognosis. Therefore, the analysis of relations between lymph node status and other tumour

characteristics can give additional information concerning prognosis and help in diagnostics and preoperative evaluation of patients.

There are some other diagnostic investigations that preoperatively can help get information about regional lymph node status, evaluate the risk of presence of metastases in lymph nodes. One of these methods are pre-operative CT colonography, which promotes information about volume and location of tumour, also about potential metastases in lymph nodes and pericolonic fat, as well as distant metastases. Using CT can also differentiate benign polyps from malignant tumours. There are some special patterns of metastatic lymphadenopathy, which could be evaluated by CT – irregularity of borders, central necrotic masses, tendency to form groups and adhere to each other, calcifications, diameter greater than 1 cm, circular shape. Unfortunately, sometimes lymph nodes with metastases are small and looks unchanged on CT. The overall accuracy of the assessment of N stage on contrast enhanced CT colonography scans has been reported from 59% to 71%. (Kijima et al. 2014)

Pre-operative MRI investigation is another way to evaluate tumour before operation. Using this radiologic investigation involvement of regional lymph nodes could be predicted with sensitivity 80%-85% and specificity 97%-98%. As criteria for possible malignant tumour are used border irregularity and mixed signal intensity of lymph nodes. The presence of metastases in regional lymph nodes can be evaluated by uptake of ultra-small particles of iron oxide using MRI. (Kijima et al. 2014, Brown et al. 2003)

Pre-operative CT/PET also has been described as possibility for evaluation tumour characteristics, lymphogenic metastases and for staging before operation. However, CT/PET has low sensitivity of 42.9% and specificity of 87.9% for the detection of lymph node status. (Kijima et al. 2014; Veit et al. 2006)

Material and Methods

A retrospective study design was selected as appropriate. A representative patient group was identified by archive search in a Pauls Stradiņš clinical university hospital, 2011 – 2014, comprising 373 consecutive patients with histologically diagnosed adenocarcinoma after potentially radical colorectal surgery. The average age of patients was 69 ± 11 (range, 33-90) years; 193 females and 180 males.

Inclusion criteria was: histologically approved colorectal adenocarcinoma.

Exclusion criteria were following: patients with benign colorectal tumours, other histological types of colorectal cancers, incomplete data about patient, biopsy specimens, secondary tumours.

The following demographic, clinical and morphologic data were studied: patients' age and gender, spread characterised by pTNMGR parameters (Edge et al. 2010), number of retrieved lymph nodes, presence and quantity of metastases in lymph nodes and in pericolonic fat, volume

(calculated, using ellipsoid formula (V=4/3π*a*b*c (cm3))) and localisation of the tumour – caecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum and rectosigmoid area.

Light microscopy was used to analyse histological cancer slides and to evaluate the nuclear atypia in three-tiered scale, invasive border (rounded versus streaming dissection) and mitotic count in cancer cells within 10 high power (400x) fields of view (HPF).

The obtained study was registered and evaluated in a work-station using SPSS software and methods like 95% confidence interval for proportions and means, interquartile range, Pearson correlation, sensitivity and specificity, ROC curve, p-value were used for descriptive and analytical statistical analysis. Results were considered statistically significant if the p value was less than 0.05.

Results

The archive search comprised of 373 cases including 51.7% women [95% confidence interval: 46.5 – 56.9], and 48.3% men [43.1 – 53.5]. The median age of patients with histologically determined adenocarcinoma diagnosis was 71.0 year [Interquartile range (76-62): 14].

In our study, there was found no statistically significant correlation between age, sex and lymphogenic metastases ($p>0.05$).

Tumours predominantly affected sigmoid colon and rectum – 70.1% of cases [62.7 – 76.8], correspondingly. On the right side of colon - caecum and colon ascendens, tumour was localised in 29.9% of cases [23.2 – 37.3]. In our research was found no statistically significant correlation between localisation of tumour and pN ($p>0.05$).

Direct relation was observed between pN parameter and tumour volume ($p<0.05$). pN2 constituted 14.4% [9.9-19.9] of tumours <10cm3, 21.9% [15.1-30.0] of tumours with volume from 10 to 40 cm3 and 28.6% [14.6-46.3] of tumours >40cm3.

Between lymph node status (pN) and depth of tumour invasion (pT) was observed moderate positive correlation [$r=0.40$] ($p<0.05$). pT4 constituted 60.3% (n=41) of pN2 cases [47.7– 72.0], following by pT3, which constituted 39.7% (n=27) [28.0 -52.3] of pN2, thus, there are no pT1 and pT2 in pN2 group. Using pT as predictive factor for pN was determined as moderate diagnostic test, because of area under curve AUC = 0.71 ($p<0.05$).

There was a weak positive correlation between lymph node status (pN) and grade of differentiation of tumour (G) [$r=0.34$] ($p<0.05$). G3 comprised 41.2% (n=28) cases of pN2 [29.4 – 53.8], 13.1% (n=13) of pN1 [7.2 – 21.4] and 10.2% (n=21) of pN0 [6.4– 15.2]. Using G as predictive factor for pN was determined as moderate diagnostic test, because of area under curve AUC = 0.70 ($p<0.05$).

The pattern of invasive border was streaming dissection in 70.6% (n=48) [58.3-81.0] pN2 CRC cases. In contrast, the border pattern was rounded in at 88.3% (n=182) [83.2 – 92.4] pN0

cases. There was observed moderate positive relationship between invasive border type and pN [r=0,504] ($p<0.05$). Using a pattern of invasive front as predictive factor for lymph node status was determined as moderate diagnostic test, because of area under curve AUC = 0.74 ($p<0.05$). Sensitivity of using invasive border for predicting of metastases was 70.6%, specificity was 77.0% ($p<0.05$).

There was a moderate positive correlation between mitotic count and quantity and presence of lymphogenic metastases [r=0.43] ($p<0.05$). By ROC curve was detected AUC=0.75, so this test was defined as moderate test for predicting lymphogenic metastases ($p>0.05$).

A weak positive correlation was found between pN and nuclear atypia [r=0.34] ($p<0.05$), and by ROC curve was detected AUC=0,69, so this test was defined as low diagnostic test for predicting lymphogenic metastases ($p<0.05$).

Discussion

Possibility of using of morphologic characteristics to predict metastases in regional lymph nodes was described in earlier studies (Schneider and Langner 2014; Ryu et al. 2014; Marzouk and Schofield 2011; Bosch et al. 2013). Although, there were controversial results in those studies. Adenocarcinoma is the most frequent histologic type of colorectal cancer, it comprises more than 90% (Schneider and Langner 2014; Marzouk and Schofield 2011). Among all 429 colorectal cancer cases, we have studied, there were 86.9% (n=373) [95% confidence interval: 83.4-90.0] cases of colorectal adenocarcinoma, that we have included in our study.

Total number of newly diagnosed colorectal cancer patients in Latvia in 2015, according to Centre for Disease Prevention and Control of Latvia, was 1089 persons of which 48.1% (n=524) are men [95% confidence interval: 45.1 – 51.1], and 51.9% (n=565) women [95% confidence interval: 48.9 – 54.9] (Anonymous, 2015).

GLOBOCAN 2012 reported, that worldwide there were 1 360 602 patients with newly diagnosed colorectal cancer (Anonymous, 2012), including 54.9% (n=746 298) men and 45.1% (n=614 304) women.

Speaking about the incidence of colorectal cancer in Europa, total number of patients with newly diagnosed colorectal cancer in both sexes is 447 136 persons, of which, 54.1% (n= 241 813) men and 45.9% (n=205 323) women (Anonymous, 2012). Our study consisted of 373 cases including 51.7% women [95% confidence interval: 46.5 – 56.9], and 48.3% men [43.1 – 53.5]. Following on from the results, we can conclude, that in Latvia, there is slight predominance of women in colorectal cancer group, comparing with worldwide statistics. Although, both in Latvia and worldwide, both males and females are equally affected (Anonymous 2015; Anonymous 2012).

According to data from The Centre for Disease Prevention and Control of Latvia, the highest incidence of colorectal cancer is among those Latvian patients, who are seventy-five years old and

older (estimated incidence 246.7 per 100 000), followed by patients, who belong to age group from seventy till seventy-four years (estimated incidence 207.5 per 100 000) (Anonymous 2015). Regarding the age distribution in colorectal cancer patients worldwide, the highest incidence of colorectal cancer was found among patients, who are seventy-five years old and older (estimated incidence 196.2 per 100 000), and patients, who belong to age group from seventy till seventy-four years (estimated incidence 127.8 per 100 000) (Anonymous, 2012). In our study the median age of patients with newly diagnosed colorectal adenocarcinoma was 71.0 year [Interquartile range (76-62): 14], which correspond with Latvian and international tendency.

In our study, there was found no statistically significant correlation and associations between age, sex and lymphogenic metastases ($p>0.05$), so it can be concluded, that these factors have no significant influence on development of lymphogenic metastases in colorectal cancer cases.

The data about association between location of tumour and metastases in regional lymph nodes is controversial. Schneider and Langner (2014) have reported, that higher rate of metastases is associated with localisation of tumour in distal third of rectum. The location of tumour has not been confirmed as independent prognostic factor for colorectal adenocarcinoma and has no significant association with rate of lymphogenic metastases ($p=0.0647$) (Liu et al. 2017). Topographic, rectum and rectosigmoid junction are the first two locations of colorectal adenocarcinoma (Bădulescu et al. 2016). In our study, there were following trends – colorectal adenocarcinoma was predominantly located in sigmoid colon and rectum – 70.1% of cases [62.7 – 76.8], following by the right side of colon - caecum and ascending colon, where colorectal adenocarcinoma has been found in 29.9% of cases [23.2 – 37.3]. However, speaking about the influence of location of colorectal adenocarcinoma on lymphogenic metastases, in our study was found no statistically significant correlations between localisation of colorectal adenocarcinoma and status of lymphatic nodes ($p>0.05$).

Higher size of primary colorectal tumour is associated with higher rate of metastases in regional lymph nodes (Bosch and Nagtegaal 2014). Marzouk and Schofield (2011) reported, that tumour size has controversial prognostic value of lymphatic metastases in cases of colorectal cancer. In our research was observed the association between presence and quantity of metastases in regional lymph nodes (pN parameter) and volume of adenocarcinoma ($p<0.05$). pN2 constituted 14.4% [9.9-19.9] of adenocarcinomas with volume <10cm3, 21.9% [15.1-30.0] of adenocarcinomas with volume from 10 to 40 cm3 and 28.6% [14.6-46.3] of adenocarcinomas >40cm3. Using the volume of colorectal adenocarcinoma for predicting status of regional lymph nodes was found as test with low diagnostic value, because the AUC =0.61 ($p<0.05$). It can be concluded, that there could be the slight association between these parameters, but there is no significant predictive value.

The depth of invasion of primary tumour also was studied as potential predictive factor for lymphogenic metastases in colorectal adenocarcinoma cases. Tominaga et al. (2005) report, that deeper invasion of tumour in intestinal wall is associated with higher rate of metastases in regional lymph nodes, and that submucosal invasive front is a predictive factor of lymph node metastases in colorectal cancer ($p<0.05$), and also no metastases in regional lymph nodes were found in cancers with a depth of invasion smaller than 1,3mm. Results by Bosch and Nagtegaal (2014) showed, that the risk of metastases in regional lymph nodes increases with increasing of depth of invasion of cancer. Following on our results, between lymph node status and depth of tumour invasion was observed moderate positive correlation [$r=0.40$] ($p<0.05$). Using depth of tumour invasion (pT) as predictive factor for presence of lymphogenic metastases (pN) was determined as moderate diagnostic test (AUC=0.71 ($p<0.05$)). According to our and other studies T parameter could be used as additional predictive factor for lymph node status in colorectal cancer.

Grade of histological differentiation of colorectal cancer also was described as important factor in genesis of lymphatic metastases - focal dedifferentiation at the submucosal invasive front has significant influence on lymph node metastasis (Tominaga et al. 2005, Rasouli et al. 2017), tumour differentiation was significantly associated with lymph node metastasis ($p<0.01$) (Tateishi et al. 2010), and the absence of poor histological differentiation was associated with low risk of regional lymph node metastases (Bosch et al. 2013). In our research, there was a weak positive correlation between lymph node status and grade of differentiation of colorectal adenocarcinoma [$r=0.34$] ($p<0.05$). Using the grade of differentiation as predictive factor for lymphogenic metastases was determined as moderate diagnostic test, because of area under curve AUC=0.70 ($p<0.05$).

The pattern of invasive border and tumour budding is a prognostic factor of potential lymphogenic metastases in colorectal cancer, survival rates, depth of invasion and rate of distant metastases (Tateishi et al. 2010; Schneider and Langner 2014; Beaton et al. 2013). Results in our study were similar – the round pattern of invasive front was associated with no metastasis in lymph nodes, but streaming dissection pattern of invasive border was associated with higher rates or lymphogenic metastases. Using a pattern of invasive front as predictive factor for lymph node status was determined as moderate diagnostic test, because of area under curve AUC = 0.74 ($p<0.05$). Sensitivity of using invasive border for predicting of metastases was 70.6%, specificity was 77.0% ($p<0.05$).

There are few studies concerning influence of mitotic rate in cancer cells on rate of lymphogenic metastases. There are some studies about association between mitotic count and survival rates, and there has not been found relation between these parameters (Langlois et al. 1997). Some studies report, that a high mitotic rate is a hallmark of poorly differentiated

adenocarcinomas, and there is a correlation between higher mitotic rate and inferior survival (Compton et al. 2000). According to our results there was a moderate positive correlation between mitotic count and quantity and presence of lymphogenic metastases [r=0.43] ($p<0.05$).

Marked cellular atypia is a sign of high-grade tumours (Compton et al., 2000). A weak positive correlation was found between pN and nuclear atypia [r=0.34] ($p<0.05$), and by ROC curve was detected AUC=0,69, so this test was defined as low diagnostic test for predicting lymphogenic metastases ($p<0.05$).

Conclusions

The group of patients in our study is representative and correspond with results from other studies worldwide. Pathological and clinical characteristics of colorectal adenocarcinoma, we have studied (depth of invasion, volume of primary tumour, grade of differentiation, pattern of invasive border, mitotic count and nuclear atypia) are associated with presence and quantity of regional lymph node metastases, although, they have low and moderate predictive value. These parameters should be used only as additional possibilities in evaluation of patient before operation, in unclear cases.

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HNF1B AND *CYP19A1* GENES VARIATIONS GENOTYPE FREQUENCIES CORRELATION WITH ENDOMETRIAL CANCER INCIDENCE AMONG DIFFERENT POPULATIONS

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Abstract

***HNF1B* and *CYP19A1* genes variations genotype frequencies correlation with endometrial cancer incidence among different populations**

Key words: *HNF1B, CYP19A1, endometrial cancer*

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries, but EC incidence varies among different countries and populations. Genome-wide association studies have discovered several EC susceptibility loci e.g. *HNF1B* and *CYP19A1* genes loci.

The design of this study is – correlation study. Frequency of genetic variants' genotypes in different populations was obtained from The 1000 Genome project, HGDP and HapMap studies. The EC age standardized incidence was extracted from the WHO database and regional registries. Data of 17 populations was available for the analysis. Data analysis was performed using the SPSS 22.0 software. Spearmen's rank correlation (r_s) and linear regression were used.

Analyzing genotype frequencies, it was found that rs727479 dominant genotypes (CC+CA) strongly correlates with EC incidence (r_s=0.58, p=0.015). CC+CA genotypes frequency among general population may explain 31% of the EC incidence variability among different populations (R^2 = 0.31). *HNF1B* gene variants rs4430796, rs7501939 were not associated with EC incidence (p>0.05).

CYP19A1 gene variation rs727479 CC+CA genotypes are correlated with EC incidence among different populations and those genotype frequencies could clarify the variability of EC incidence among different populations. *HNF1B* gene variations rs4430796, rs7501939 were not associated with EC incidence among different populations.

Kopsavilkums

***HNF1B* un *CYP19A1* gēnu variāciju genotipu biežumu korelācija ar endometrija vēža incidence starp dažādām populācijām**

Atslēgvārdi*: HNF1B, CYP19A1, endometrija vēzis*

Endometrija vēzis ir biežākā ļaundabīgā ginekoloģiskā saslimšana attīstītās valstīs, bet endometrija vēža incidence ir atšķirīga dažādās valstīs un populācijās. Genoma plaši asociāciju pētījumi ir atklājuši vairākus endometrija vēža riska lokusus, piemēram, *HNF1B* un *CYP19A1* gēnos.

Pētījuma dizains ir korelācijas. Populāciju ģenētisko variāciju biežums tika iegūts no *The 1000 genome project, HGDP* un *HapMap* pētījumiem. Endometrija vēža vecuma standartizēta incidence tika iegūta no *WHO* datubāzes un vietējiem reģistriem. Analīzei bija pieejamas 17 populācijas. Statistiskā analizē tika veikta *SPSS 22.0* programmā. Tika izmantots Spīrmena rangu korelācijas tests (r_s) un lineāra regresija.

Analizējot genotipu biežumu, tika atklāts, ka rs727479 variācijas genotipi CC+CA cieši korelē ar endometrija vēža incidenci (r_s=0.58, p=0.015). CC+CA genotipu biežums vispārējā populācijā var izskaidrot 31% no incidences variabilitātes starp dažādām populācijām (R^2 = 0.31). *HNF1B* gēna variācijas rs4430796, rs7501939 nebija statistiski ticami saistītas ar endometrija vēža incidenci mūsu pētījumā (p>0.05).

CYP19A1 gēna variācijas rs727479 CC+CA genotipi statistiski ticami korelē ar endometrija vēža incidenci dažādās populācijas un šo genotipu biežumu atšķirības spēj daļēji izskaidrot endometrija vēža incidences atšķirības starp populācijām. *HNF1B* gēna variācijas rs4430796, rs7501939 nebija statistiski ticami saistītas ar endometrija vēža incidenci starp dažādām populācijām.

Introduction

Endometrial cancer (EC) is the second most common gynecological malignancy in developed countries, but EC incidence varies among different countries and populations (Ferlay et al. 2015).

EC arises from uterine epithelial lining (endometrium) and is classified into two subtypes which are based on clinical characteristics and histologic findings. Type I or endometrioid adenocarcinoma is the most common type of EC – approximately 80-90% of EC cases. Type II mainly consists of serous and clear cell carcinomas (10-20%) (De Vivo et al. 2014).

The prognosis for EC for the most common histological subtypes is considered as relatively good, the 5-year survival rate for women with stage IA is up to 98% (Matsuo et al. 2015).

According to international disease classification (ICD-10) EC is classified into disease group with code C54 – uterine corpus cancer. In previous made epidemiological studies of EC use cases with ICD-10 code - C54 assuming that majority of cases are actually EC and because EC and most of uterine corpus malignancies share risk factors (Matsuo et al. 2015; Wu et al. 2011).

Major risk factors for EC (ICD-10 code - C54) development include obesity, estrogen-only postmenopausal hormone therapy, early menarche, late age at menopause, nulliparity and infertility (Beral et al. 2005).

However, not much is known about the genetic etiology of EC. Genome-wide association studies (GWAS) have discovered several EC susceptibility loci. The strongest association was found with the HNF1B gene variants rs4430796, rs7501939 and CYP19A1 genes variant rs727479 (Cheng et al., 2016; Thompson et al., 2016). HNF1B gene encodes transcription factors, but its role in the development of EC is still unexplained. CYP19A1 encodes enzyme aromatase, which converts androgens to estrogens after menopause (Kolatsi-Joannou et al. 2001; Yang et al. 2002)

The aim of our study was to investigate whether the HNF1B gene variants rs4430796, rs7501939 and CYP19A1 gene variants rs727479 genotype frequencies in general population can explain the EC incidence difference among different populations.

Material and Methods

The design of this study is – correlation (ecological) study.

Genotype and allele frequencies of genetic allelic variants in different populations were obtained from freely accessible databases of The 1000 genome project (1000GP), Human genome diversity project (HGDP) and HapMap project (Altshuler et al. 2010; Auton et al. 2015; Rosenberg et al. 2005). Related individuals allelic variant genotypes were excluded from the population. Genotypes for 79 populations were available in the databases. The EC (ICD-10 code - C54) age standardized rate (ASR) for the World population was extracted from the World health organization (WHO) GLOBOCAN 2012 database (Ferlay et al. 2015) and regional registries (AIRTUM 2014; Badar et al. 2016; Ferlay et al. 2015; Qureshi et al. 2016). Included populations and sources of population genotype frequencies and EC ASR are shown at table 1.

Table 1. **Populations and sources of population genotype frequencies and EC ASR**

Nr.	Population	Population symbol	Super population*	Source of genotype**	Source of EC ASR (W)***
1	Han Chinese in China	CHB	EAS	1000GP; HGDP; HapMap	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
2	Utah residents with European ancestry	CEU	EUR	1000GP; HapMap	Utah cancer registry (Sweeney *et al.*, 2016)
3	Colombian in Medellin, Colombia	CLM	AMR	1000GP; HGDP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
4	Finnish in Finland	FIN	EUR	1000GP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
5	French in France	FRA	EUR	HGDP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
6	British in England and Scotland	GBR	EUR	1000GP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
7	Iberian populations in Spain	IBS	EUR	1000GP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
8	Central and North Italians	ITA	EUR	1000GP; HGDP; HapMap	ITACAN (AIRTUM, 2014)
9	Russians in Russian Federation	RUS	EUR	HGDP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
10	Sardinians in Sardinia, Italy	SARD	EUR	1000GP	ITACAN (AIRTUM, 2014)
11	Japanese in Tokyo, Japan	JPT	EAS	1000GP; HGDP; HapMap	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
12	Kinh in Ho Chi Minh City, Vietnam	KHV	EAS	1000GP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
13	Berbers in Algeria	ALG	AFR	HGDP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
14	Punjabi in Lahore, Pakistan	PJL	SAS	1000GP	Lahore cancer registry (Badar *et al.*, 2016)
15	Puerto Rican in Puerto Rico	PUR	AMR	1000GP	GLOBOCAN 2012 (Ferlay *et al.*, 2015)
16	Sindhi in Karachi, Pakistan	SIND	EAS	HGDP	Karachi cancer registry (Qureshi *et al.*, 2016)
17	Yoruba in Ibadan, Nigeria	YRI	AFR	1000GP; HGDP; HapMap	GLOBOCAN 2012 (Ferlay *et al.*, 2015)

*EAS = East Asian; EUR = European; AMR = American (native); SAS = South Asian; AFR = African
**1000GP = The 1000 genome project; HGDP = Human genome diversity project; HapMap = HapMap project
*** EC ASR (W) = Endometrial cancer Age standardized rate for World population per 100,000 population

In order to analyze populations that are more solid – multiethnic populations, where one ethnic group is less than 80% of total population were excluded from the study, data about ethnic group data were gained from United Nations Statistics Division open population database – UNdata (http://data.un.org). For the statistical analysis both allelic variant frequencies and endometrial cancer ASR data was available only for 17 populations. Included populations and source of the genotype and EC ASR are shown at table 1.

Pearson's Chi-Square test was performed using PLINK v1.07 software (Purcell *et al.* 2007) to assess genetic allelic variations' deviations from the Hardy-Weinberg equilibrium in the analyzed populations. Statistical analysis of the obtained data was performed using the SPSS 22.0 software. Correlation between variations genotypes and allele frequencies and EC incidence in different populations were calculated using Spearmen's rank correlation (r_s). To calculate the predictive

power of the genetic allelic variations genotypes and alleles frequencies on EC incidence linear regression was used. Variations association with endometrial cancer ASR (W) were analyzed in allelic, dominant and recessive types of inheritance. The significance level α=0.05 was used for the hypothesis testing and P value less than 0.05 was considered statistically significant.

Results

The EC age standardized incidence varied from 1.5 to 19.5 cases per 100,000 per year among populations included in our study. The minor allele frequency for *CYP19A1* gene variation rs727479 and *HNF1B* variations rs4430796 and rs7501939 also differed significantly between populations ($p<0.01$) (Table 2).

Table 2. **Population endometrial cancer age standardized rate and minor allele frequencies for variations rs727479, rs4430796 and rs7501939**

Nr.	Population symbol	EC ASR(W)	rs727479 MAF*(C), %	rs4430796 MAF*(G), %	rs7501939 MAF*(T), %
1	CHB	8.6	27.8	26.5	23.2
2	CEU	19.5	33.8	47.5	40.9
3	CLM	3.6	41.6	51	39.6
4	FIN	13.9	38.9	35.4	28.8
5	FRA	10.7	41.1	51.8	41.1
6	GBR	13.9	31.3	46.2	37.4
7	IBS	11.6	37.4	51.9	46.3
8	ITA	13.8	41	55.5	43.4
9	RUS	16.1	32	40	30
10	SARD	14.1	42.9	58.9	44.6
11	JPT	10.6	27.1	37.9	34.6
12	KHV	5.4	26.8	25.3	19.2
13	ALG	1.5	27.6	82.8	46.6
14	PJL	3.6	21.4	31.3	26
15	PUR	16.0	36.1	48.1	35.1
16	SIND	8.3	31.3	50	45.8
17	YRI	3.4	22.7	65.5	59.3

*MAF = minor allele frequency

Analyzing *CYP19A1* gene rs727479 variation it was found that minor allele (C) (Figure 1) and dominant genotype (CC+CA) (Figure 2) frequency among general population significantly correlates with EC incidence (r_s=0.518, p=0.033 and r_s=0.58, p=0.015 respectively) (Table 3). Performing linear regression analysis, it was found that C allele frequency may explain 25% and CC+CA genotype frequency – 31% of the EC incidence variability among different populations (R^2=0.25 and R^2=0.31 respectively).

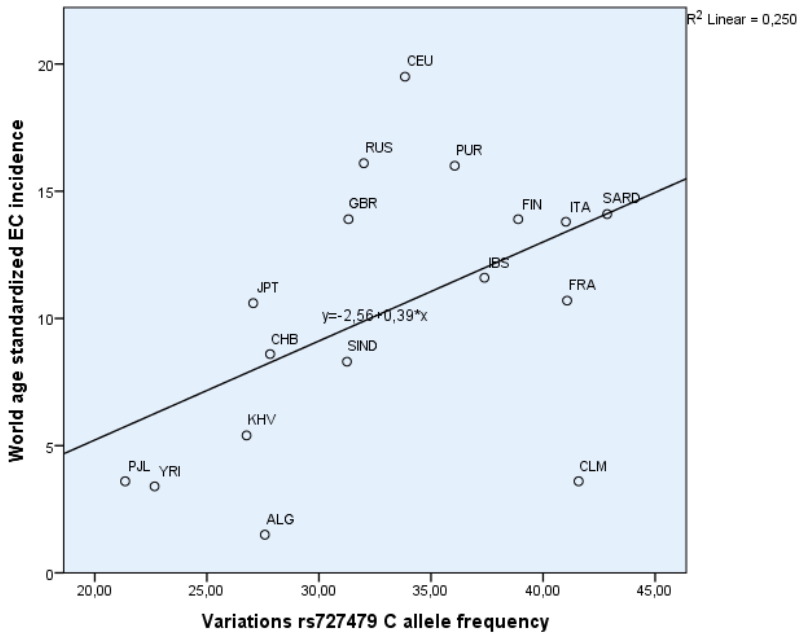

Figure 1. **Variation rs727479 C allele frequency correlation with EC incidence**

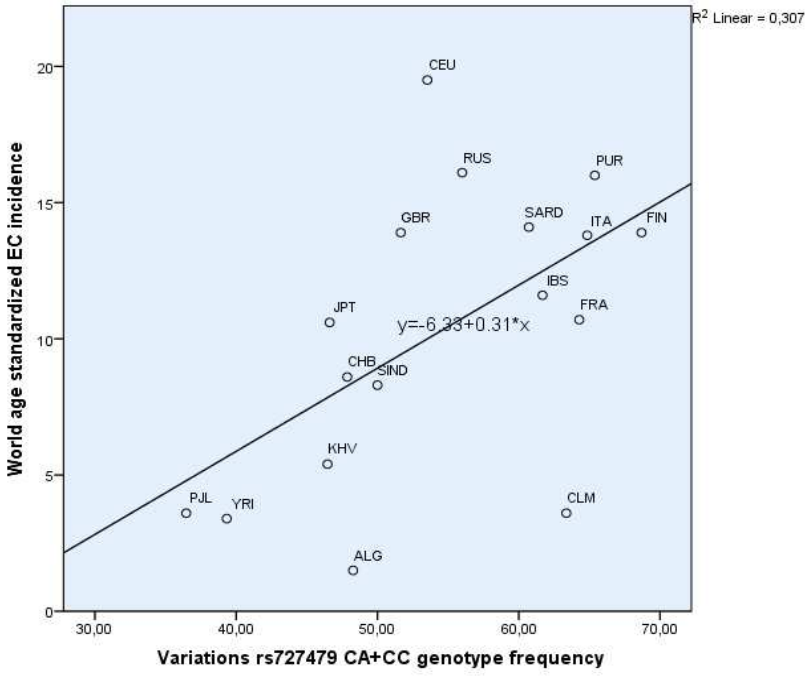

Figure 2. **Variation rs727479 CA+CC genotype frequency correlation with EC incidence**

There has been found weak negative correlation between EC incidence among different populations and *HNF1B* gene variations rs7501939 and rs4430796 allelic, dominant and recessive genotype frequencies in our study, although this correlations was not statistically significant ($p>0.05$) (Table 3).

Table 3. **Variations rs727479, rs7501939 and rs4430796 correlation with endometrial cancer age standardized rate among different populations**

Genetic allelic variation	Type of inheritance	Analyzed allele/genotype frequency	r_s	P value
rs727479. *CYP19A1*	Allelic	C	0.518	**0.033**
	Dominant	CC+CA	0.580	**0.015**
	Recessive	CC	0.389	0.123
rs7501939. *HNF1B*	Allelic	T	-0.162	0.535
	Dominant	TT+CT	-0.053	0.841
	Recessive	TT	-0.166	0.525
rs4430796. *HNF1B*	Allelic	G	-0.131	0.615
	Dominant	GG+AG	-0.038	0.885
	Recessive	GG	-0.161	0.538

Discussion

Endometrial cancer predominantly affects women in post-menopausal age – approximately 90% of EC cases are more than 50 years old (Allen *et al.* 2008).

Endometrial cancer is estrogen dependent and frequently is associated with endometrial hyperplasia. Endometrial hyperplasia is caused by increased levels of estrogens and/or decreased level of progesterone (Silverberg *et al.* 2003). Prolonged increased levels of estrogens, which is observed in patients with anovulation (for example in polycystic ovarian syndrome), obesity (adipose tissue is a source of estrogens), estrogen-only postmenopausal hormone use or late age at menopause significantly increase risk of endometrial cancer development (Beral *et al.* 2005), so candidate genes for EC could be also genes, which encoded proteins are involved in sex hormone metabolism.

The *CYP19A1* gene encodes an enzyme – aromatase, which converts a class of hormones called androgens into different types of estrogens (for example estradiol) and is responsible for the estrogen production after menopause. Several case-control studies have shown *CYP19A1* gene variations (including rs727479) association with risk of developing estrogen dependent cancers – endometrial, ovarian and breast cancers (Goodman *et al.* 2008; Low *et al.* 2010; Setiawan *et al.* 2009). *Thompson* with colleagues performing meta-analysis and replication study of *CYP19A1* variation association with risk of developing EC found that rs727479 variation is associated with EC on genome-wide significant level. The rs727479 variations A allele increased odds of developing EC by 1.15. Using Mendelian randomization approach *Thompson* with colleagues in their study proven that variations rs727479 A allele increases risk of EC by increasing estrogen level (Thompson *et al.*, 2016). Variation rs727479 in located in the second intron of *CYP19A1* and cause altered binding of transcription factors, possibly influencing the expression of the enzyme (ENCODE Project Consortium 2012). Our results are controversial with previous studies because variations rs727479 allele C, but not A allele is associated with increased incidence of EC among

included into the study populations. We hypothesize that this difference could occur because previous studies focused mostly on Caucasian populations (Cheng *et al.,* 2015). Our study included 17 different populations from 5 superpopulations (East Asian, European, American (native), South Asian, African). When we restricted analysis to European populations only, we have found that A allele weakly correlated with increased risk of EC, but this association was not statistically significant. Explanations for this discordance of the variations effect among populations could be various. One of the main reasons for possible difference we should consider is that our study is correlation, not case-control study. It is known that *CYP19A1* gene same variations discrete alleles could cause same effects on phenotype by combining with other variations into different haplotypes (Cai *et al.* 2008). And distinct effect of the rs727479 variations on different population could be explained by different genetic structure of each population and different haplotypes occurrence respectively. Also, the effects of *CYP19A1* gene could be influenced and modified by the environmental factors, for example obesity (Schmandt *et al.* 2011; Setiawan *et al.* 2009). Our study controlled only the effect of age on EC development, but because of the design of the study we cannot control other factors as obesity, estrogen use after menopause etc.

Other gene of interest is *HNF1B* gene, which encodes transcription factor – hepatocyte nuclear factor-1 β (HNF1B) that is involved in normal mesodermal and endodermal tissue development, including Mullerian duct and uterus (Kato *et al.* 2009). Previous genome-wide association studies (GWAS) have discovered that *HNF1B* gene variants rs4430796 and rs7501939 are associated with decreased risk to develop prostate cancer in men and endometrial cancer in women (Setiawan *et al.* 2012; Waters *et al.* 2009). The pathway of *HNF1B* gene and its variations in development of EC is not discovered yet (Mandato *et al.,* 2015). Our results show *HNF1B* gene variations correlation with decreased EC ASR which is consonant with previous studies (Mandato *et al.* 2015; Setiawan *et al.* 2012). Correlation with EC incidence was weak and not statistically significant, most likely due to small number of populations available as well as our study is correlation study, but previous studies were case-control.

Further EC case-control studies in different populations are necessary to confirm our finding.

Conclusions

1. *CYP19A1* gene variation rs727479 C allele and CC+CA genotype frequency are correlated with EC incidence among different populations.
2. Diverse occurrence of variation rs727479 C allele and CC+CA genotypes could clarify the variability of EC incidence among different populations.
3. *HNF1B* gene variations rs4430796, rs7501939 were not significantly associated with EC incidence among different populations.

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PATIENTS' LEVEL OF KNOWLEDGE OF STATE-FUNDED SCREENING PROGRAMS IN FAMILY PHYSICIAN'S PRACTICE

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Abstract

Patients' level of knowledge of state-funded screening programs in family physician's practice

Introduction. Screening tests have been shown to find cancer early and to reduce the risk of dying from cancer. In Latvia from 2000 - 2015 registered oncological patients had increased. At the end of year 2015 was registered 74540 patients with oncology.

Aim. To evaluate respondents' knowledge about screening and the reasons for non-use screening.

Materials and methods. A cross-sectional study using a survey of family physician's patients. Responded data was summarized and processed with IBM SPSS 23 descriptive and analytical statistics.

Results. In this study are used 102 patient survey data, at age group from 50 to 74 years. 67 % (n = 68) from of overall respondents were women, and 33 % (n = 34) of respondents were men. 35 % of respondents visited family doctor 5 to 10 times per year, 29 % - 2-5 times per year, 19 % - more than 10 times per year and 17 % - once per year. Knowledge about screening programs of all respondents: 21 % (n = 21) rated it as good, 26 % (n = 27) rated it as bad and 53 % (n=54) rated it as average. 49 % of respondents said that screening includes colorectal cancer test, 65 % that screening includes cervical cancer test, and 62 % noted that screening includes mammography. Respondents identified the following reasons why they cannot use screening: 22 % lack of informative material, 11 % fear that diagnosed oncology, 14 % do not feel that this is important, another 53 % of respondents always use screening. Correlation was found between the number of family doctor visit per year and respondent's knowledge about screening programs ($p = 0.015$, $r = 0.24$).

Conclusion. Despite the increased number of health improvement campaigns, lack of knowledge about screening programs still exists. The results show that half of respondents still do not use screening. Population health and knowledge can be improved by regular health check through family physician.

Kopsavilkums

Pacientu zināšanu līmenis par valsts organizētiem vēža skrīningiem ģimenes ārstu praksē

Ievads. Skrīninga testi palīdz atklāt agrīni audzēju un samazina risku nomirt ar audzēju. Latvijā no 2000. līdz 2015.gadam reģistrēto onkoloģisko pacientu skaits ir pieaudzis. 2015.gada nogalē bija reģistrēti 74 540 pacienti ar onkoloģiju.

Mērķis. Izvērtēt respondentu zināšanas par skrīningiem un iemeslus, kāpēc tos neizmanto.

Materiāli un metodes. Šķērsgriezuma pētījums, aptaujājot pacientus ģimenes ārstu praksēs. Iegūtie dati tika apkopoti un apstrādāti ar IBM SPSS 23 aprakstošu un analītisku statistiku.

Rezultāti. Pētījumā tika iekļauti 102 pacienti vecuma grupā no 50 – 74 gadiem. 67 % (n=68) no visiem respondentiem bija sievietes un 33 % (n=34) no respondentiem bija vīrieši. 35 % no visiem respondentiem apmeklē ģimenes ārstu 5 līdz 10 reizes gadā, 29 % apmeklē 2-5 reizes gadā, 19 % vairāk kā 10 reizes gadā un 17 % - vienu reizi gadā. Zināšanas par skrīningu programmām no visiem respondentiem: 21 % (n=21) novērtēja kā labas, 26 % (n=27) novērtēja kā sliktas un 53 % (n=54) novērtēja kā vidējas. 49 % no respondentiem apgalvo, ka skrīningos ietilpst kolorektālā vēža tests, 65 % - ka skrīningos ietilpst dzemdes kakla vēža tests, un 62 % atzīmēja, ka skrīnings ietver mammogrāfiju. Respondenti norādīja sekojošus iemeslus, kāpēc neveic skrīningu: 22 % - trūkst informatīvo materiālu, 11 % - bailes, ka atklās audzēju, 14 % - nešķiet svarīgs, un pārējie 53 % no viesiem respondentiem veic skrīningu. Tika atrasta korelācija starp vizīšu skaitu pie ģimenes ārsta un respondentu zināšanām par skrīninga programmām ($p=0.015$; $r=0.24$). **Secinājumi.** Neskatoties uz pieaugošo veselības uzlabošanas kampaņu skaitu, tomēr joprojām pastāv nepietiekamas zināšanas par skrīninga programmām. Rezultāti rāda, ka puse no respondentiem joprojām neizmanto skrīningu. Populācijas veselība un zināšanas varētu uzlabot ar regulārām veselības pārbaudēm pie ģimenes ārsta.

Introduction

Screening tests have been shown to find cancer early and to reduce the risk of dying from it. In the last years morbidity and mortality rates of cancer had been increased, especially of high ratio in late-stage cases in Latvia. From the year 2000 to 2015 the number of registered oncological

patients had increased in Latvia. At the end of the year 2015 there were 74540 patients registered with oncology (SPKC 2017).

Three state-funded screening programs have been created in Latvia since 2009. Screening programs includes: breast cancer screening, cervical cancer screening and colorectal cancer screening. Breast cancer screening includes mammography and it is offered once every two years for women who are 50 to 69 years old. Cervical cancer screening includes cervical cytology examination and it is offered once every three years for women who are 25 to 70 years old. Colorectal cancer screening includes fecal occult blood test and it is offered once every year for man and women who are 50 to 74 years old (VMNVD 2017).

In Latvia 2015, cervical cancer was in the 9th place, breast cancer was in the 1st place among all types of cancer in women and colorectal cancer was in the 3rd place among all types of cancer in both sexes. Since 2009 about 120 women in Latvia die from cervical cancer every year, from breast cancer approximately 435 women and 703 people died from colorectal cancer (SPKC 2017). Mortality rates show that early cancer detection and prevention capabilities are incompletely used in Latvia.

Cancer screening programs are secondary prevention, and their aim is to discover pathogenic states, lowering mortality of cancers and costs of treatment and rehabilitation and improving population health (Timmer *et al.* 2002, 19-21). In best cases, when people are using regularly screenings, the disease should be detected at early stage, then early treatment can stop or at least slow the progress of disease and possible impairment or disability (Timmer *et al.* 2002: 19-21).

Screening tests characterize sensitivity, specificity, positive predictive value, and negative predictive value and all of them measure test performance (DeVita *et al.* 2015: 370).

Timely diagnosis of cancer in most cases, patients can be completely cured of cancer. Screening is meant for health improvement to overall population.

Aim

First of all, to determine people's knowledge about screening programs. Secondly, to determine how often people visit their general practitioners and whether there is statistically significant correlation between visits and patients' knowledge about screening programs. In this study, we want to pay attention to reasons why people are not using state funded screenings as much as they should, thereby it would give ideas how to improve usage of screenings.

Material and Methods

This is a quantitative, cross-sectional, retrospective study. Data registration form was developed and survey method was used for data collection. The study included 102 patients' questionnaires from two family physician's practices. Nameless patient registration and numbering

were used. Patients were selected according to the Latvian organized cancer screening programs at age group from 50 to 74 years.

Research data was summarized and processed with IBM SPSS version 23 and Microsoft Excel 2013 software. Descriptive statistics, such as frequency and percentage, were applied. Pearson correlation test was used to detect possible correlation (p value <0.05 was accepted as statistically significant).

Results

The study included 102 patient's survey data, 67 % (n = 68) from overall respondents were women, and 33 % (n = 34) of respondents were men. The age of patients ranged from 50 to 74 years, average age – 60.95 ± 6.59.

35 % of respondents visited family doctor 5 to 10 times per year, 29 % 2-5 times per year, 19 % - more than 10 times per year and 17 % - once per year. Knowledge about screening programs of all respondents was as follow: 21 % (n = 21, 6 % were men and 15 % women) rated it as good, 26 % (n=27, 15 % were men and 11 % women) rated it as bad and 53 % (n=54, 13 % were men and 40 % women) rated it as average (Figure 1).

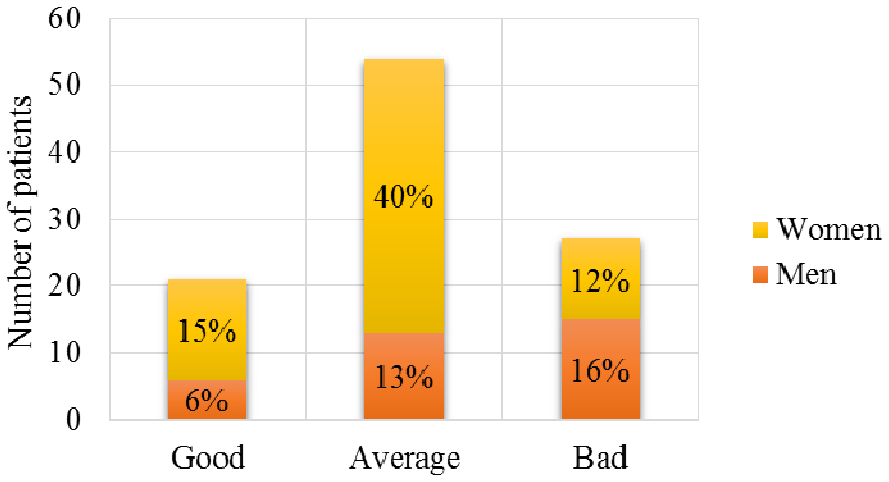

Figure 1. **Patients' level of knowledge of state-funded screening**

Only 49 % of respondents said that screening includes colorectal cancer test, 65 % that screening includes cervical cancer test and 62 % noted that screening includes mammography (Figure 2).

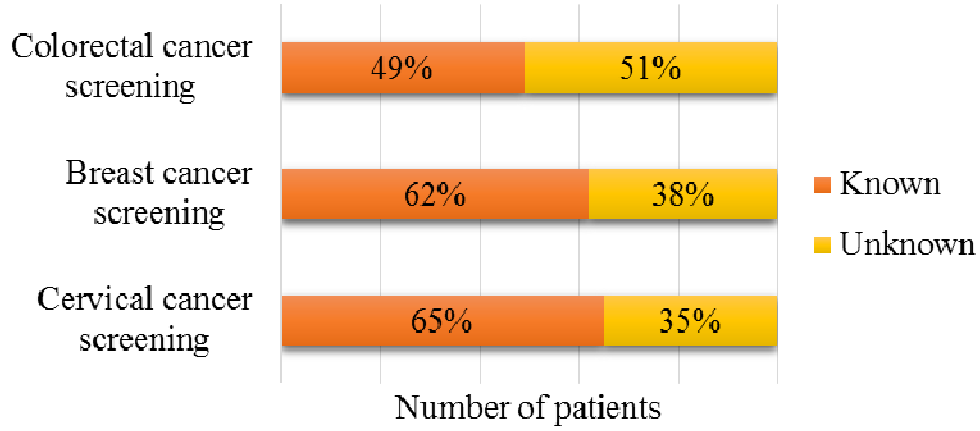

Figure 2. **Patients' knowledge about state-funded cancer screening programs in Latvia**

Respondents identified the following reasons why they cannot use screening: 22 % it is lack of informative material, for 11 % - fear from diagnosed oncology, 14 % - do not feel that it is important, another 53 % of respondents always use screening. The patients noted that a screening system is needed (98%) and patients' mood after the screening is completed was mostly positive (84%). Correlation was found between the number of visits to a family doctor per year and respondents' knowledge about screening programs (p = 0.015, r = 0.24).

Discussion

Currently, there are all of the necessary diagnostic and treatment facilities to be able to detect early precancerous conditions and cancer in Latvia. There are all of the elements for better outcomes in Latvia.

More than a half of European countries have developed guidelines and recommendations for each cancer screening program separately, unfortunately in Latvia, these guidelines still do not exist. Level of patients' awareness, of state-funded, fully compensated cancer screening tests influences the frequency of use of them. Target population involvement must be at least 75 % to provide well-organized and effective cancer screening. Cancer screening programs in Latvia have been working for 8 years and the results of population involvement for 2015 are as follows: cervical cancer screening was undergone only by 25 % of people, breast cancer screening only – 34,9 % and colorectal cancer screening – only 10,9 % (VMNVD 2017).

Study „Knowledge and attitudes of primary healthcare patients regarding population-based screening for colorectal cancer" of Ramos *et al*., (2011) – showed that patients not only care about their health, but also believe in advice received from doctors and nurses to take a screening test: of all respondents that answered, 72.1% were women and 69% were men (Ramos *et al*. 2011). This supports the findings, that for patients it is important, how primary health care providers communicate with them. Most mentioned reason for not doing fecal occult blood test is that patients

fear to have a cancer, where 42.5% women and 24.1% men mentioned that reason (Ramos *et al*. 2011). Comparison to our study, reason not doing screening 11% of all respondents, either men and woman, fear that diagnosed oncology.

Most common reasons for declining mammography amongst women in study in Georgia Region, were: „mammography hurt", „No one in my family has breast cancer", „ I`m too young/old to get breast cancer", „ Having too many mammograms can cause breast cancer", „I don`t have time to get mammogram", „My breasts are too small to get mammogram", „I am confused about how often I should get a mammogram" (NCBI 2005). Common reasons for not doing cervical cancer screening amongst women are embarrassment at exposing private parts, other reason is pain, because they experience painful test in the past and less common reasons are mistakenly believing that cervical cancer is not relevant to them and they do not realise importance of regular screening (HO 2015). Most of those reasons indicate about lack of information and therefore knowledge isn't good as should be. Our study revealed that 22% of all respondent's lack of informative material and 14% - do not feel that this is important.

General practitioners have an important role − women are more likely to attend for screening if they have discussed it with their general practitioner (Simon, C. *et al*. 2002). It is necessary to promote the fact that each patient once a year obligatory needs to visit his general practitioners. General practitioners should follow registered patients in their practices who do not use cancer screening programs. Health improvement campaigns activity need to be long-term. In our study there were found correlation between the number of family doctor visit per year and respondents knowledge about screening programs ($p = 0.015$; $r = 0.24$), respectively, the more visits patients make to their general practitioner, the bigger possibility is that there would be a conversation about screening including more information about it.

Conclusions

Despite the increased number of health improvement campaigns, lack of knowledge about screening programs still exists. The results show that half of respondents still do not use screening. On average, the main reasons why patients do not use cancer screening, is lack of informative material and fear of diagnosed oncology.

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ANALYSIS OF PATIENTS WITH PURE GONADAL DYSGENESIS

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Abstract

Analysis of patients with pure gonadal dysgenesis

Key words: *46,XY, female, primary amenorrhea, gonadoblastoma*

Pure gonadal dysgenesis or Swyer syndrome is a rare genetic disorder characterized by 46,XY karyotype and female phenotype. Patients with pure gonadal dysgenesis have increased risk for the development of malignant tumors.

The aim of the study was obtain and analyze data of patients with pure gonadal dysgenesis in 20 year period.

In a retrospective study data about 37 patients were selected from the registry of the Citogenetics laboratory and Children`s Clinical University Hospital between 1996 and 2016. Patients with mixed or partial gonadal dysgenesis (46,XY/45,X) were excluded. The clinical information of the investigation and treatment was available in 15 cases. Data was analyzed using MS Excel and SPSS Statistics program 22.0.

In all 37 cases was laboratory determined karyotype analysis. 97.3% (n=36) of women were confirmed with 46, XY karyotype, 2.7% (n=1) with karyotype 47, XY + 21.

The avarage age of the patients at the time of diagnosis was 15.4 ± 8.0 years. The study of 15 cases showed that 53.3% (n=8) were investigated for primary amenorrhea and incomplete development of secondary sexual characteristics, 33.3% (n=5) with abdominal pain and lower abdominal mass, 13.3% (n=2) were diagnosed at birth.

80% of patients (n=12) was performed gonadectomy. In two cases gonadectomy was made 7.3 and 5.3 years after diagnosis. In one case karyotype analysis was performed 11 years after ovarian tumor (dysgerminoma) treatment. Histological examination showed gonadoblastoma in four cases, dysgerminoma in three cases, gonadoblastoma with dysgerminoma in two cases, teratoma in one case.

Early diagnosis is necessary to decrease the risk of malignancy that can develop at an early age. The study showed the median time between diagnosis and gonadectomy was suboptimal. In most of cases, histology showed malignancy. Further studies of this rare genetic disorder should be performed.

Kopsavilkums

Pacientu analīze ar pilnu gonādu disģenēzi

Atslēgvārdi: *46,XY, sieviete, primāra amenoreja, gonadoblastoma*

Pilna gonādu disģenēze jeb Svaira sindroms ir reta ģenētiska slimība, kuru raksturo 46,XY kariotips un sievietes fenotips. Pacientēm ar pilnu gonādu disģenēzi ir paaugstināts ļaundabīdu audzēju attīstības risks.

Darba mērķis bija iegūt un analizēt datus par pacientiem ar pilnu gonādu disģenēzi 20 gadu periodā.

Retrospektīvā pētījumā dati par 37 pacientiem tika iegūti no Citoģenētikas laboratorijas reģistra un Bērnu klīniskās universitātes slimnīcas laika periodā no 1996. līdz 2016. gadam. Pacienti ar jauktu vai daļēju gonādu disģenēzi (46,XY/45,X) tika izslēgti no pētījuma. Klīniskā informācija par izmeklēšanu un ārstēšanu bija pieejama 15 gadījumos. Dati tika analizēti, izmantojot MS Excel un SPSS statistikasprogrammu 22.0.

Visos 37 gadījumos laboratoriski tika veikta kariotipa analīze. 97.3% (n=36) gadījumu sievietēm tika apstiprināts 46,XY kariotips, 2.7% (n=1) gadījumu ar kariotipu 47, XY + 21.

Vidējais pacientu vecums diagnozes noteikšanas brīdī bija 15.4 ± 8.0 gadi. No 15 gadījumiem, pētījums parādīja, ka 53.3% (n=8) gadījumu pacientes tika izmeklētas ar primāru amenoreju un sekundāro dzimumpazīmju trūkumu, 33.3% (n=5) ar sāpēm vēderā un veidojumu vēdera lejasdaļā, 13.3% (n=2) tika diagnosticēti uzreiz pēc dzimšanas.

80% no pacientēm (n=12) tika veikta gonādektomija. Divos gadījumos gonādektomija tika veikta 7.3 un 5.3 gadus pēc diagnozes uzstādīšanas. Vienā gadījumā kariotipa analīze tika veikta 11 gadus pēc olnīcu audzēja (disgerminomas) ārstēšanas. Histoloģiskā izmeklēšana uzrādīja gonadoblastomu četros gadījumos, disgerminomu trijos gadījumos, gonadoblastomu ar disgerminomu divos gadījumos, teratomu vienā gadījumā.

Agrīna diagnoze ir nepieciešama, lai mazinātu ļaundabīgo audzēju risku, kas var attīstīties agrīnā vecumā. Pētījums parādīja, ka vidējais laika periods starp diagnozi un gonādektomiju bija suboptimāls. Vairumā gadījumu histoloģiskā izmeklēšana uzrādīja malignitāti. Nākotnē ir jāveic papildus pētījumi par šo reto ģenētisko slimību.

Introduction

Gonadal dysgenesis is a unique subset of disorders of sexual development (DSD), a condition in which gonadal development is interrupted leading to gonadal dysfunction (McCann-Crosby et al. 2014). Since the first description of pure gonadal dysgenesis or Swyer syndrome in 1955, a number

of cases have been reported, but no large series exist in the literature. The exact incidence of the condition is unknown but can be estimated at 1:80 000 births (Michala et al. 2008).

Pure gonadal dysgenesis is characterized by a 46,XY karyotype, normal female external genitalia, completely undeveloped streak gonads and presence of normal Mullerian structures (uterus, fallopian tubes and vagina). These individuals are typically raised as females and have a female gender identity (Machado et al. 2014). The condition usually first becomes apparent in adolescence with delayed puberty and amenorrhea due to the fact that the gonads have no hormonal or reproductive potential (Michala et al. 2008).

This condition is thought to be caused by a mutation in the DNA-binding region of the SRY (sex determining region Y) gene in 10-20% of cases, but there are other genes involved in sex determination that have been identified in the past years. The risk of developing a gonadal tumor can be as high as 30%-40% and can occur during childhood or adolescence. Bilateral gonadectomy should be performed once the diagnosis is made, preferably by laparoscopy (Nunes et al. 2014). The most common tumor involved in this condition is gonadoblastoma, dysgerminoma and embryonal carcinoma (Azidah et al. 2013).

Affected individuals usually begin hormone replacement therapy during adolescence to induce menstruation and development of female secondary sex characteristics such as breast enlargement and body hair. This therapy also helps prevent reduced bone density (osteopenia). Women with this disorder do not produce eggs, but may be able to become pregnant with a donated egg or embryo (Machado et al. 2014).

The aim of the study was to obtain and analyze data of patients with pure gonadal dysgenesis in 20 year period, and show the importance of early diagnostics that decrease the chance of developing life threatening complications.

Material and methods

In a retrospective study data about 37 patients with a suspected disorder of sex development (46,XY) were selected from the registry of the Citogenetics laboratory and Children`s Clinical University Hospital between 1996 and 2016. Patients with mixed or partial gonadal dysgenesis (46,XY/45,X) were excluded. The clinical information of the investigation and treatment was available in 15 cases. Data was obtained from the registry of the Citogenetics laboratory, Children`s Clinical University Hospital Oncohematological department registry, electronic database, medical and ambulatory cards. All data were collected and analyzed with MS Excel 2010 and IBM SPSS Statistics program 22.0. The necessary calculations were made using descriptive statistical methods. Study have been approved by RSU Ethics Committee.

Results

In all 37 cases was laboratory determined karyotype analysis. 97.3% (n=36) of women were confirmed with 46, XY karyotype, 2.7% (n=1) with karyotype 47, XY + 21 (Down syndrome). The youngest patient was diagnosed a few days after birth, the older woman was 32 years old. The avarage age of the patients at the time of diagnosis was 15.4 ± 8.0 years (Figure 1).

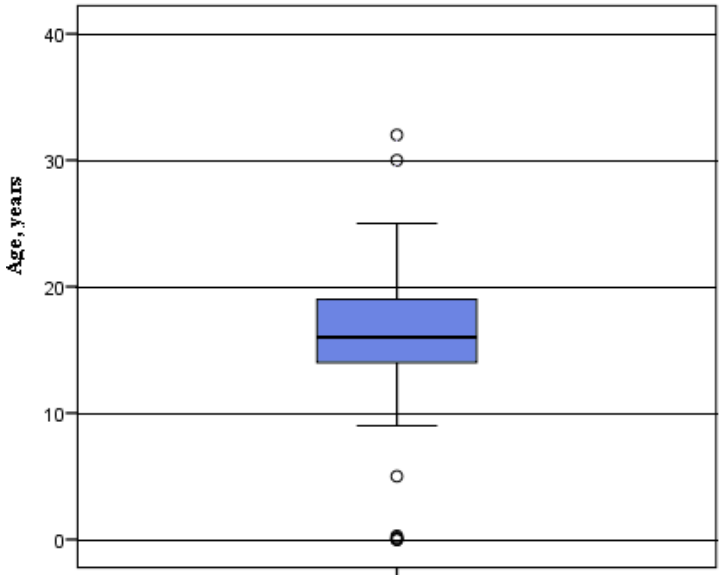

Figure 1. **Age distribution of patiens suspected with 46,XY disorder of sex development**

The study of 15 cases showed that 53.3% (n=8) were investigated for primary amenorrhea and incomplete development of secondary sexual characteristics, 33.3% (n=5) with abdominal pain and lower abdominal mass, 13.3% (n=2) were diagnosed at birth. The average age of patients was 12.7 years, range from birth to 24 years. 33.3% (n=5) were tested for SRY gene mutation (Yp11.3) with FISH method - the result was negative in all cases.

Bilateral gonadektomy was chosen for 80% of patients (n=12). Patient's surgical management will be performed in 13.3% (n=2) of cases. In 6.7 % (n=1) data were not available. The median time between diagnosis and gonadectomy was 0.4 ± 4.3 years.

As can be seen in figure 2, in two cases gonadectomy have been made 7.3 and 5.3 years after diagnosis respectively. In one case karyotype analysis was performed 11 years after ovarian tumor (dysgerminoma) treatment (showed as a negative time period).

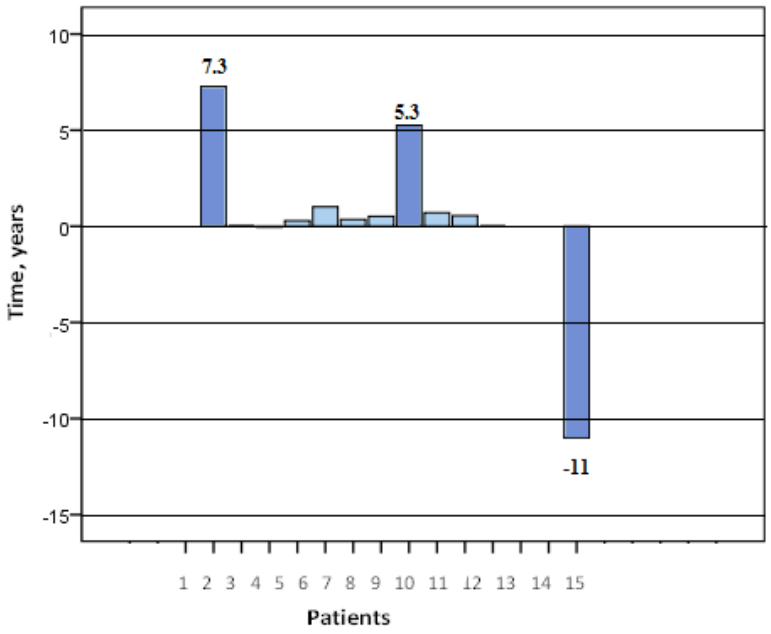

Figure 2. **Distribution of patiens acording to time between diagnosis and gonadectomy**

Histological examination showed gonadoblastoma in four cases, dysgerminoma in three cases, gonadoblastoma with dysgerminoma in two cases, teratoma in one case. In some cases laboratory data showed increased serum concentrations of alpha-fetoprotein (AFP), luteinizing hormone (LH), follicle-stimulating hormone (FSH). Hormone replacement therapy was used in 40% (n=6) of cases, adjuvant chemotherapy according to MAKEI protocol in 20% (n=3).

Discussion

In recent years, considerable progress has been made in our knowledge and management of disorders of sex development. As a consequence, it is expected that in the near future, this will lead to considerable changes in the management of patients with pure gonadal dysgenesis (Cools et al. 2009). Early diagnosis is important for a number of reasons: firstly, because of the risk of gonadal malignancy; secondly, early institution of hormonal therapy is vital for the induction of puberty; thirdly, HRT is required to prevent osteoporosis (Azidah et al. 2013). Survival rate is 90-100% in cases diagnosed in the early stages but decreases to 54% in those diagnosed in the advanced stages (Machado et al. 2014).

This study shows that most of the women were investigated for primary amenorrhea and incomplete development of secondary sexual characteristics and suspected of neoplastic transformations. In some cases delayed diagnosis and management was identified. The streak gonads should be removed shortly after diagnosis, regardless of age. The median time between diagnosis and gonadectomy was 0.4 ± 4.3 years. In most cases, was performed bilateral gonadectomy.

A study by Michala et al. also shows that many women experienced delay in reaching accurate diagnosis, as well as inefficient management. The diagnosis of Swyer syndrome was often reached several years after the presentation to their general practitioners (Michala et al. 2008). It is suggested that health professionals should update their scientific knowledge and be aware of sexual development disorders (Azidah et al. 2013)

Early diagnosis and treatment could help these patients have a normal sex life, reduce emotional trauma can provide the preservation of fertility and improve patient survival (Karimian et al. 2010; Da Silva Riosa et al. 2015).

Conclusions

1. Early diagnosis of pure gonadal dysgenesis (Swyer syndrome) is necessary in view of the risk of malignancy that can develop at an early age.
2. The study showed the median time between diagnosis and gonadectomy was suboptimal.
3. In most of cases, histology showed malignancy.
4. In some cases diagnosis of syndrome was made only after development of malignant process.
5. Further studies of this rare genetic disorder should be performed.

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PUERPERAL WOMEN'S OPINIONS OF NECESSITY TO TALK WITH GYNECOLOGIST ABOUT THEIR SEXUAL LIFE

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Abstract

Puerperal women's opinions of necessity to talk with gynecologist about their sexual life

Key words: *Pregnancy, childbirth, sexual life, gynecologist advice*

Introduction: Studies have confirmed that the most of the pregnant women feel the need for reliable information about sexual activity during pregnancy. Problem is that they rarely find the opportunity to discuss this issue with their physicians.

Aim: The aim of this study is to collect and analyze the information given by patients in postpartum units in the Maternity Department about their opinions of necessity to talk with gynecologist about sexual life in pregnancy and postpartum period.

Materials and methods: Cross-sectional study was carried out, involving 351 women in postpartum period in Riga Maternity Hospital. Data were collected from August 2016 until December 2016, using patient questionnaires. The data were analyzed by *Microsoft Office Excel* and *Statistical Package for the Social Sciences (SPSS).*

Results: Research included 351 women at a mean maternal age of 30 years (SD 5.1; range, 18–43 years). 92% (n=323) had coitus during pregnancy and 8% (n=28) did not have coitus during pregnancy. 49.6% (n=174) of the pregnant women got advice from gynecologist about their sexual life during pregnancy, but 50.4 % (n=177) did not get advice from gynecologist. 26.2% (n=92) of participants would want to talk generally about sexual life, but 73.5% (n=258) would not.

Conclusion: Most of the women are sexually active during pregnancy. Our study confirmed that the more important sexual life is to woman, the more is she willing to talk about it with her physician.

Kopsavilkums

Nedēļnieču viedokļi par nepieciešamību runāt ar ginekologu par seksuālo dzīvi

Atslēgvārdi: *Grūtniecība, dzemdības, seksuālā dzīve, ginekologa ieteikumi*

Ievads: Literatūras avoti liecina, ka sievietes izjūt nepieciešamību pēc uzticamas informācijas par seksuālo dzīvi grūtniecības laikā. Diemžēl sievietēm reti ir iespēja pārrunāt šo tematu ar ārstu.

Mērķis: Apkopot un analizēt nedēļnieču sniegtos viedokļus par nepieciešamību runāt ar ginekologu par seksuālo dzīvi grūtniecības laikā.

Materiāli un metodes: Veikts aprakstoša tipa šķērsgriezuma pētījums, izmantojot anketēšanas metodi. Pētījums veikts Rīgas Dzemdību namā Mātes un bērna aprūpes nodaļā, pētījums notika laika posmā no 2016. gada augusta līdz 2016. gada decembrim. Pētījums saskaņots Rīgas Stradiņa universitātes Ētikas komitejā. Datu statistiskajai analīzei tika izmantots *Microsoft Office Excel* un *Statistical Package for the Social Sciences (SPSS).*

Rezultāti: Pētījumā piedalījās 351 sieviete. Nedēļnieču vidējais vecums bija 30 gadi (SD 5,1; vecuma diapazons 18 – 43 gadi). 92% (n=323) sieviešu bija seksuāli aktīvas grūtniecības laikā, bet 8% (n=28) nebija seksuāli aktīvas. 49,6% (n=174) sieviešu saņēma ieteikumus par seksuālo dzīvi grūtniecības laikā no ginekologiem, bet 50,4 % (n=177) ieteikumus no ginekologiem nesaņēma. 26,2% (n=92) vēlētos apspriest jautājumus par seksuālo dzīvi ar savu ginekologu, bet 73,5% (n=258) sieviešu nevēlētos apspriest jautājumus par seksuālo dzīvi.

Secinājumi: Lielākā daļa sieviešu ir seksuāli aktīvas grūtniecības laikā. Ja sievietēm ir nozīmīga seksuālā dzīve, tad viņam ir lielāka vēlme runāt par to ar savu ginekologu, dzemdību speciālistu.

Introduction

Sexuality is an important component of health and well-being in a woman's life. Sexual behavior, which is influenced by biological, psychological, and social factors, modifies as pregnancy progresses. (Hsin-Li Liu et. al. 2013). Sexual health today is widely understood as a state of physical, emotional, mental and social wellbeing in relation to sexuality. It encompasses not

only certain aspects of reproductive health – such as being able to control one's fertility through access to contraception and abortion, and being free from sexually transmitted infections (STIs), sexual dysfunction and sequelae related to sexual violence or female genital mutilation – but also, the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. Indeed, it has become clear that human sexuality includes many different forms of behavior and expression, and that the recognition of the diversity of sexual behavior and expression contributes to people's overall sense of well-being and health. (WHO 2015). Complications associated with each mode of delivery are related to mothers' pain, physical functioning, and freshness. All of the mentioned factors, as well as the way of an individual's living, can be summarized as an individual's quality of life. Quality of life is an extensive and intricate concept, which has mingled with an individual's physical health, mental state, independence, social contacts, and personal beliefs. Childbirth affects mothers remarkably. After the postnatal period, the mother's quality of life is under the influence of medical, psychological, and social factors, associated with childbirth (such as mother's age, physical health during the prenatal period, beliefs, interests, and temperaments). Traditionally, the postnatal period is believed to last for six months; however, longitudinal studies, evaluating mothers' quality of life, have been indicative of physical and anxiety problems among 50% of women one year after delivery; even some of the symptoms persisted up to 18 months after c-section. (Majzoobi et. al. 2014).

Recent studies estimate that about a third of young and middle-aged women and about half of older women experience some sort of sexual problems such as low desire, difficulty lubricating, pain during intercourse, lack of pleasure, or inability to orgasm. (Sobecki et. al. 2012). Pregnancy is particularly important period when this topic becomes especially sensitive. Studies have confirmed that the most of the pregnant women feel the need for reliable information about sexual activity during pregnancy. Problem is that they rarely find the opportunity to discuss this issue with their physicians. More often they are looking for answers on the internet, in books or asking their friends. (Hsin-Li Liu et. al. 2013).

The aim of the study: To collect and analyze the information given by patients in postpartum units in the Maternity Department about their opinions of necessity to talk with a gynecologist about sexual life during pregnancy and postpartum period.

Materials and methods

Cross-sectional study was carried out, involving 351 women in postpartum period in Riga Maternity Hospital. Data were collected from August 2016 until December 2016, using patient questionnaires. The study was coordinated with the Ethics Committee of Riga Stradiņš University.

Inclusion criteria:

– Postpartum patients
– Agrees to participate in the study

Exclusion criteria:

- Refuse from participation in the study
- An incomplete questionnaire

A special research questionnaire consisting of 2 socio-demographic questions and 19 questions about pregnancy, delivery, partner's participation in delivery and gynecologist's role in discussing questions about sexual life was created.

The study included 351 correctly completed questionnaires. 24 patients refused to participate in the study, but 17 questionnaires were filled incorrectly.

The data were analyzed by *Microsoft Office Excel* and *Statistical Package for the Social Sciences (SPSS)*, using Chi-square test. The statistical significance was reached when $p < 0,05$.

Results

Research included 351 women at a mean maternal age of 30 years (SD 5.1; range, 18 – 43 years). The participants education level: 3.7% (n=13) elementary school; 14.8 (n=52) secondary school; 17.9% (n=63) professional school; 35.3% (n=124) bachelor's degree; 27.6% (n=97) master's degree; 0.6% (2) doctoral degree. 52.1 % (n=183) participants reported that they were primiparous, and 47.9% (n=168) reported that they were multiparous. 92% (n=323) had coitus during pregnancy and 8% (n=28) did not have coitus during pregnancy. Frequency of coitus during pregnancy: 28.5% (n=100) had coitus 1-3 times a week; 9.4% (n=33) had coitus more than 3 times a week; 35.9% (n=126) had coitus 1 to 3 times a week; 18.2% (n=64) had coitus less than 1 time a month; 8.0% (n=28) hadn't had sex during pregnancy. Importance of sexual life: 81.1% (n=285) was important; 0.9% (n=3) was not important; 17.9% (n=63) have not thought about that. Importance of sexual life during pregnancy: 43.3% (n=152) was important; 20.8% (n=73) was not important; 35.9% (n=126) have not thought about that. 49.6% (n=174) of the pregnant women got advice from gynecologist about their sexual life during pregnancy, but 50.4 % (n=177) did not get advice from gynecologist. 26.2% (n=92) of participants would want to talk generally about sexual life, but 73.5% (n=258) would not.

A correlation between importance of sexual life and the willingness to talk about it with gynecologist was observed in the study - the more important sexual life is to a woman, the more is she willing to talk about it with her gynecologist, obstetrician, comparing with women who have not thought about importance of sexual life; 29% versus 13%, p=0.029.

Discussion

Our study showed that for most women (81.1%) sexual life is important which means that woman are interested in the topic of sexual life. Sexuality is a key aspect of women's physical and psychological health. Numerous studies from all over the world has shown that both patients and physicians face barriers in communication about sexuality. (Sobecki et.al. 2012).

In our study, 49.6% of the pregnant women received recommendations from gynecologist about their sexual life during pregnancy. In many other studies carried out abroad most gynecologists have said that they discuss sexual problems during pregnancy and postpartum with their patients sufficiently. On the other hand, two thirds of females do not remember their gynecologists to have done so. Also in the studies carried out abroad most of pregnant females would recommend a discussion on sexuality during pregnancy as a topic in an antenatal clinic. Almost a half of pregnant women evaluate the information received from health care providers as insufficient. The literature data shows that about a half of pregnant women who discuss the issue of sexuality during pregnancy with their health care provider have to initiate the dialog, but approximately one-third of women do not feel comfortable discussing this topic (Brtnicka et.al. 2009) A study from Iran shows, that the majority of women want to discuss their sexual life with a professional but the problem is that they do not feel comfortable enough to initiate the conversation. (Babazadeh et. al. 2013).

Our study showed that in 50.6 % of cases women did not receive any recommendations from their gynecologists. Similar studies have shown that many antenatal care providers are uncertain in the issues of sexual consulting in pregnancy, especially in a high risk. It's quite common to prohibit sexual intercourse, mainly in the case of vaginal bleeding and the risk of a preterm labor. (Brtnicka et. al. 2009). In our study 8% of women admitted that they weren't sexually active during pregnancy, mentioning unwillingness as the most common reason not to have coitus during pregnancy.

Another problem is that there are no concrete recommendations about sexual life in pregnancy what gynecologists could give to their patients. Dubiousness and a lack of information are the common reasons for avoiding this topic. Dialogues on the sexual problems are usually not included in a routine antenatal care; and if so, partner is not a participant in this discussion. (Brtnicka et. al. 2009). During the visit in postpartum period gynecologists mostly talk about contraception and the right time to resume intercourse and rarely about possible changes or problems women might experience after delivery. (Barrett et. al. 2000). The medical professionals should provide information not only on the time of resuming sex after delivery, but also on dealing with problems such as vaginal dryness or pain during intercourse and on exercises improving the flexibility of vaginal muscles after childbirth. Another reason for this is the fact that postpartum sexual dysfunctions, including dyspareunia, are diagnosed in 41-83% of women 2-3 months after delivery. (Bien et. al. 2016). In the Taiwan study, 38.7% used the Internet to obtain information about coitus during pregnancy. Other information regarding this topic came from traditional sources, such as friends and books, rather than from newspapers or physicians. Other resources included nurses, healthcare providers, pregnancy manuals and discussions with postpartum women. The percentage of women who used these resources ranged from 35% to approximately 50% (Hsin-Li Liu et. al. 2013).

The transition into parenthood can be interconnected with feelings of stress, increased fatigue, reduced self-esteem and a significant decline in relationship quality. In a British study most couples were concerned about how their sexual life was going to affect the relationship once the baby was born. Both women and men requested more information and advice during the pregnancy about sexuality. Many parents felt isolated and abandoned due to having little or no information on the subject and this could lead to a feeling of discontent in the relationship and in some cases separation. Separation affects physical and mental health adversely both for parents and their children. (Hansson et. al. 2012).

Conclusions

Most of the women are sexually active during pregnancy 92%. For most of them questions about sexual life are topical and sexual life is important. Our study confirmed correlation between importance of sexual life and the willingness to talk about it with gynecologist - the more important sexual life is to woman, the more is she willing to talk about it with her physician.

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MEN'S KNOWLEDGE OF CONTRACEPTION DEPENDING ON THE THEIR LEVEL OF EDUCATION

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Abstract

Men's knowledge of contraception depending on the their level of education

Key words: *Men, contraception, knowledge, education level*

Introduction: Contraception has become a widely-discussed issue around the world. Men are used to mostly looking for information in media or asking their friends.

Aim: The aim is to find out if the men's and women's knowledge of contraception depends on the level of their education.

Materials and methods: The study group includes men's and control group- women's voluntary answers on 16 questions of originally created study protocol, collected from September 2015 to February 2017 in Latvia. Information about participant's level of education was collected. The level of knowledge was estimated as good if the amount of correct answers was ≥9.

Results: A total of 493 men and 297 women from Latvia participated in the study. Mean age of men was 29 and women - 25. 60% of men and 86.9% of women have showed good knowledge of contraception. 57.9% of men and 86.8% of women who's education level is secondary or lower, 50.0% of men and 83.7% of women who's education level is professional, 63.6% of men and 88.5% of women who's education level is bachelor's degree, 70.1% of men and 86.8% of women who's education level is master's degree or higher had good knowledge of contraception

Chi-Square test showed that men with higher level of education have better knowledge of contraception (p=0.034), for women test did not show statistical significance (p=0.7).

Conclusion: Men with higher level of education have better knowledge of contraception.

Kopsavilkums

Vīriešu zināšanas par kontrecepciju atkarībā no izglītības līmeņa

Atslēgvārdi: *Vīrieši, kontracepcija, zināšanas, izglītības līmenis*

Ievads: Kontracepcija ir plaši izplatīts sarunu temats visā pasaulē. Visbiežāk vīrieši informāciju par kontracepciju meklē plašsaziņas līdzekļos vai jautā draugiem.

Mērķis: Noskaidrot, vai vīriešu un sieviešu zināšanas par kontracepciju ir atkarīgas no izglītības līmeņa.

Materiāli un metodes: Pētījumā tika iekļauti vīrieši un sievietes, kuri brīvprātīgi atbildēja uz oriģinālu, pētījumam izveidotu anketu ar 16 jautājumiem. Pētījums norisinājās no 2015.gada septembra līdz 2017.gada februārim Latvijā. Tika iegūta informācija par dalībnieku izglītības līmeni. Pareizi atbildot uz ≥ 9 anketā uzdotajiem jautājumiem, zināšanu līmenis tika novērtēts kā labs.

Rezultāti: Kopumā pētījumā piedalījās 493 vīrieši un 297 sievietes no Latvijas. Vīriešu vidējais vecums- 29, sieviešu- 25 gadi. 60% vīriešu un 86.9% sieviešu uzrādīja labas zināšanas par kontracepciju. 57,9% vīriešu un 86.8% sieviešu ar izglītības līmeni ne augstāku par vidējo, 50,0% vīriešu un 83.7% sieviešu ar profesionālo izglītību, 63,6% vīriešu un 88.5% sieviešu ar bakalaura grādu, 70,1% vīriešu un 86.8% sieviešu ar maģistra grāda vai augstāku izglītbu uzrādīja labas zināšanas.

Chi-Square tests pierādīja, ka vīrieši ar augstāku izglītības līmeni labāk orientējas jautājumos par kontracepciju (p=0,034), bet sievietēm tests neuzrādīja statistiski ticamu sakarību (p=0.7).

Secinājumi: Vīrieši ar augstāku izglītības līmeni labāk orientējas jautājumos par kontracepciju.

Introduction

In the last 50 years, the number of contraception methods has dramatically increased. (Daniels et.al. 2013) Almost everyone in the developed world uses contraception at some time in his or her life. (Norman et.al. 2013) Nowadays contraception is available four everyone. The main challenge is to choose the right one four individual case. Couples who do not use any method of contraception

have an approximately 85% chance of experiencing a pregnancy over the course of a year. (Trussell 2011) Sexual intercourse is common among adolescents. In 2013, nearly one-half (48%) of those aged 17, 61% of 18-year-olds, and 71% of 19-year-olds reported ever having had sex. Yet, many teens are not using adequate and/or consistent protection against pregnancy and sexually transmitted infections (STIs). One in 4 four female teens report using no contraceptive method at last intercourse and only 20% report having used both a condom and a hormonal method, although dual method protection is considered the most effective way to prevent pregnancy and STIs. (Richards et. al. 2016). The most substantial benefits of contraceptive use for the health and survival of women and children stem from reductions in the number of pregnancies, especially those that are a greater-than-average risk to maternal, perinatal, and child survival. These risks are associated with pregnancies at very young (<18 years) and old (>34 years) maternal ages, at high parities, and with short interpregnancy intervals, and with pregnancies that would have ended in unsafe abortion. (Cleland et. al. 2012)

Contraceptives are used by the majority of married or in-union women in almost all regions of the world. In 2015, 64 per cent of married or in-union women of reproductive age worldwide were using some form of contraception. (United Nations 2015) Young adults in longer term relationships with greater conflict and lower intimacy and commitment were less likely than those in other long-term relationships to use hormonal and dual methods versus no method (relative risk ratios, 0.6-0.7). Hormonal method use, versus no method use or condom use, was more prevalent in short-term relationships with greater intimacy and commitment and lower conflict than in other short-term relationships (1.7 and 1.9, respectively). (Manlove et. al. 2014). As well, bouth of partners should know about emergency contraception- how and when to use. The ability to delay and space childbearing is crucial to women's social and economic advancement. Ability about contraception must be shared- not only on women shoulders but four men's too. Obtain and effectively use contraceptives has a positive impact on education and workforce participation, as well as on subsequent outcomes related to income, family stability, mental health and happiness, and children's well-being. (Frost et. al. 2014). Most men will have used only a condom – effective contraception and barrier methods and about other contraception methods they really know bad. Education is very important and particularly connected with bigger amount of information about different sciences and knowledges, but not everyone can afford studies and that's way it's so necessary to share the information about contraception with men`s independent of their level of education. (Schrager et. al. 2008).

Good reproductive health depends to a great extent on how well informed people are on contraception issues. (Tountas et. al. 2004). There is a lack of information about this issue in Latvia.

Because of that it is more interesting to get to know the results. Aim of our study was to find out if the men's and women's knowledge of contraception depends on the level of their education.

Materials and methods

A group of men and women from Latvia participated in the research. Data were collected starting from September 2015 until February 2017, using patient questionnaires. Two methods were used to collect answers - web questionnaires and paper-printed questionnaires. For web questionnaires we used Google Forms. Paper-printed questionnaires were given to students of Riga Stradiņš university. The research included 493 men. There were only two inclusion criteria – sex (male) and age at least 16 years. The control group included 297 women. Inclusion criteria – sex (female) and age at least 16 years. Exclusion criteria for both groups were the same - age less than 16 years and/or incomplete questionnaire.

Demographic data were also collected. We asked for age, level of education, number of children, frequency of coitus per week, number of current sexual partners. Level of education was divided in four groups - secondary education or lower, professional education, bachelor's degree, master's degree and doctoral degree. Questionnaire included 16 questions about contraception. The level of knowledge was estimated as good if the amount of correct answers was ≥9 and as bad if the amount was ≤8.

All data was analyzed using *Microsoft Office Excel* and *Statistical Package for the Social Sciences (SPSS)*. Descriptive statistics (frequency, percentage) and Chi-Square test were applied to get results. The statistical significance was reached when $p < 0,05$.

Results

A total of 493 men and 297 women from Latvia participated in the study. Age of study group ranged from 16 to 70 years (mean 29.05±22.32), but in control group from 16 to 48 years (mean 24.54 ± 4.64). In study group 60% (n=296) have showed good knowledge of contraception and in control group 86.9% (n=258) have showed good knowledge of contraception.

57.9% (n=106) of men and 86.8% (n=92) of women who's education level is secondary education or lower had good knowledge of contraception. 50.0% (n=47) of men and 83.7% (n=41) of women who's education level is professional education had good knowledge of contraception. 63.6% (n=83) of men and 88.5% (n=92) of women who's education level is bachelor's degree had good knowledge of contraception. 70.1% of men and 86.8% (n=33) of women who's education level is master's degree or higher had good knowledge of contraception

None of study's group gave correct answers to all 16 questions. 0.6% (n=3) of study group had 15 correct answers. 1.7% (n=5) of control's group answered correctly all 16 questions and 6.4% (n=19) on 15 questions.

Chi-Square test was used to detect if there was a statistically significant correlation between level of education and knowledge about contraception. Chi-Square test showed that in study group knowledge of contraception depends on the level of education, men with higher level of education have better knowledge of contraception (p=0.034), but for the control group Chi-Square test did not show statistical significance (p=0.7).

Conclusions

We have found that in men's group there is a statistically significant correlation between education level and contraception knowledge. Men with higher level of education have better knowledge of contraception. There is also a need to encourage more male participation in reproductive health activities. This correlation was not observed in the control group. Women more often receive information about contraception from health care professionals. Reason is that women visit gynecologist regardless of their level of education and get reliable information.

Discussion

Our study confirms that women have better knowledge of contraception comparing with men (86.9 % versus 60.0%). A study carried out in Greece has shown that only a small percentage of the respondents were able to answer correctly on 50% or more of the questions on knowledge of basic contraceptive issues (30.6% of women and 14.7% of men). (Tountas et.al. 2004). A research carried out in the US has shown that male partners have an important influence on contraceptive use in heterosexual relationships. (Marshall et.al. 2015). In addition a research in India has also shown that men play a crucial role in contraceptive decision-making. (Mishra et.al. 2014). Our study confirms that more than a half of all men (60.0%) have shown a good knowledge of contraception. We did not include a question about where men and women mostly look for information about contraception in our study questionnaire, but the study carried out in Greece shows that when asked about sources of information media and friends were reported as the primary sources for men of all ages and young women. Gynecologists become a significant source of information for women only after the age of 25. (Tountas et.al. 2004).

Our survey clearly shows that men's knowledge of contraception seems to be improving with their level of education. A research in Jordan also confirms that education has a significant effect on men's general knowledge about family planning. (Petro-Nustas, 1999). An international study by researchers from the US has shown that contraceptive knowledge is positively and significantly associated with men's level of education in 13 of 16 countries. (MacQuarrie et.al. 2015). An another research in North America shows that there are significant differences in contraceptive use based on demographics, even at the highest education levels. Personal choices of contraception for medical students may also influence their ability to accurately convey information about contraception to their patients. In addition, medical students may personally benefit from improved

knowledge of effective contraceptive practices. (Rowen et.al. 2011). Our study confirms that women have better knowledge of contraception regardless of their level of education. A woman can, of course, control her fertility without her husband's cooperation; yet when men and women are aware of and responsive to each other's health needs, they are more likely to obtain necessary services. Moreover, strengthening communication between partners about reproductive health and involving men in health promotion can lead to better health for the entire family. The first step towards increasing men's participation in reproductive health is to understand their knowledge, attitudes, and practices regarding a range of issues. (Petro-Nustas, 1999).

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AN OBSERVATIONAL STUDY ON ADRENAL INSUFFICIENCY

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Abstract

An observational study on adrenal insufficiency

Key words: *Adrenal insufficiency, Addison disease*

Background. Primary and secondary adrenal insufficiency is a rare clinical condition. It has been reported that the most common cause of primary adrenal insufficiency is autoimmune adrenalitis and comorbidity with other autoimmune disorders is high.

Aim. The aim of this study was to determinate the most common causes of primary and secondary adrenal insufficiency and to assess the prevalence of autoimmune comorbidity in patients with primary adrenal insufficiency.

Methods and material. In the study retrospectively were analyzed medical records of patients who had been hospitalized in the Riga East Clinical University hospital with the diagnosis of adrenal insufficiency during the time period from January 2010 till December 2016.

Results. 103 medical records of patients with adrenal insufficiency were reviewed. Mean patient age was 53 (SD=17) years. 61.8% of the patients had secondary adrenal insufficiency. The most common causes were iatrogenic adrenal insufficiency due to the use of glucocorticoids, and adenoma of hypophysis with complications related to the treatment of adenoma. Primary adrenal insufficiency was detected in 39.8% of cases. Most commonly the diagnosis was idiopathic primary adrenal insufficiency. 58.5% of these patients had an autoimmune comorbidity which is enclosed in the diagnosis of the autoimmune polyglandular syndrome.

Conclusions. Secondary adrenal insufficiency is more common than primary, with most frequent etiological agents being adenoma of the hypophysis, and iatrogenic adrenal insufficiency. In the case of primary adrenal insufficiency prevalence of associated autoimmune disorders is high and proper screening should be conducted.

Kopsavilkums

Novērojuma pētījums par virsnieru mazspēju

Atslēgvārdi: *Virsnieru mazspēja, Adisona slimība*

Ievads. Virsnieru mazspēja ir reta slimība. Primārās virsnieru mazspējas gadījumā visbiežākais slimības cēlonis ir autoimūns adrenalīts, un saslimstība ar citām autoimūnām blakusslimībām ir augsta.

Mērķis. Pētījuma mērķis bija noteikt biežākos virsnieru mazspējas cēloņus un izvērtēt autoimūnu blakusslimību prevalenci primāras virsnieru mazspējas pacientiem.

Metodes un materiāls. Pētījumā retsrospektīvi tika analizētas pacientu, kuri ārstējušies Rīgas Austrumu klīniskās universitātes slimnīcā laika posmā no 2010. gada 1. janvāra līdz 2016. gada 31. decembrim ar virsnieru mazspējas diagnozi, slimību vēstures.

Rezultāti. Pētījumā tika iekļautas 103 pacientu slimības vēstures. Vidējais pētījuma pacienta vecums bija 53 gadi (SD=17). 61.8% pacientu bija sekundāra visrnieru mazspēja. Biežākie šīs slimības cēloņi bija jatrogēna ar glikokortikoīdu lietošanu saistīta virsnieru mazspēja, hipofīzes adenoma, un ar tās ārstēšanu saistītas komplikācijas. Primāra virsnieru mazspēja tika konstatēta 39.8%. Biežākā diagnoze bija idiopātiska virsnieru mazspēja. 58.5% no primāras virsnieru mazspējas pacientiem bija kāda autoimūna slimība, kas ir iekļauta autoimūna poliglandulāra sindroma definīcijā.

Secinājumi. Sekundāra virsnieru mazspēja ir biežāk izplatīta salīdzinot ar primāru, un šīs slimības biežākie cēloņi ir jatrogēna virsnieru mazspēja glikokortikosteroīdu lietošanas rezultātā, un hipofīzes adenoma. Primāras virsnieru mazspējas gadījumā ir augsta komorbiditāte ar citām autoimūnām slimībām, un šai slimnieku grupai būtu jāpielieto atbilstošas sijājošās diagnostikas metodes.

Abbreviation
ACTH – Adrenocorticotropic hormone
TSH – Thyroid-Stimulating Hormone
Anti-TPO – Anti-thyroid peroxidase antibodies

Introduction

Adrenal insufficiency is a rare clinical condition when adrenal glands do not produce adequate amounts of glucocorticoids and/or mineralocorticoids. It can be caused by many etiological agents. Two types are being distinguished: primary and secondary adrenal insufficiency.

Primary adrenal insufficiency is a disorder characterized by disrupted synthesis of glucocorticoid and/or mineralocorticoid hormones in the adrenal cortex due to the damage of adrenal glands. It is characterized by low levels of cortisol, and high levels of serum ACTH (Bornstein 2016). Secondary adrenal insufficiency is caused by decreased synthesis of hormones in the adrenal cortex due to lack of stimulation from the pituitary gland due to damage or disorder of the pituitary gland. It is characterized by low levels of cortisol, and also low levels of serum ACTH (Steward 2011).

It has been reported that the most common cause of primary adrenal insufficiency is autoimmune adrenalitis, which in the Western societies occors in 90 % of all cases (Steward 2011). It can be an isolated disease or as a part of the autoimmune polyglandular syndrome type 1 or 2, or 3c also known as the autoimmune polyendocrine syndrome (Betterle 2012). In the case of primary adrenal insufficiency comorbidity with other autoimmune disorders is high, it has been reported to be approimately 50 % (Arlt 2003).

In this study, we aimed to determinate the most common causes of primary and secondary adrenal insufficiency, to analyze their biochemical and treatment properties, and to assess the prevalence of autoimmune comorbidity in patients with primary adrenal insufficiency who has been treated in the Riga East Clinical university hospital in past 5 years.

Methods and material

The study design was descriptive study. In this research retrospectively were analyzed medical records of patients who had been hospitalized in the Riga East Clinical University hospital with the diagnosis of adrenal insucficiency during the time period from January 1st, 2010 till December 31st, 2016.

Data about patients gender, age, diagnosis, comorbidities, duration of hospitalization, treatment-related data (supplementation medication used and it's dosage) and biochemical parameters (level of serum cortisol at 8 AM, level of 24 hour cortisol in urine, serum levels of ACTH, TSH, anti-TPO, and hemoglobin) were extracted from the patients medical records.

This study focused mainly on the descriptive statistics of different parameters of adrenal insufficiency patients. For independent group comparison, two-sample t-tests were performed in order to compare continuous data. Categorical data were analyzed for frequency distribution differences by using the $\chi 2$ test. Statistical analysis was performed using Microsoft Excel and IBM SPSS v22.

Results

In the study, 103 patient medical records were reviewed. Approximately one third (n=33; 32.0%) of them were male and 70 (68.0%) were female. Mean patient age was 53.0 (SD=17) years, and it ranged from 18 to 87 years (see Fig.1). Mean duration of the hospitalization was 7.2 (SD=5.3) days. No statistical difference in the two-sample t-test was found between the duration of hospitalization, and type of adrenal insufficiency (p=0.793).

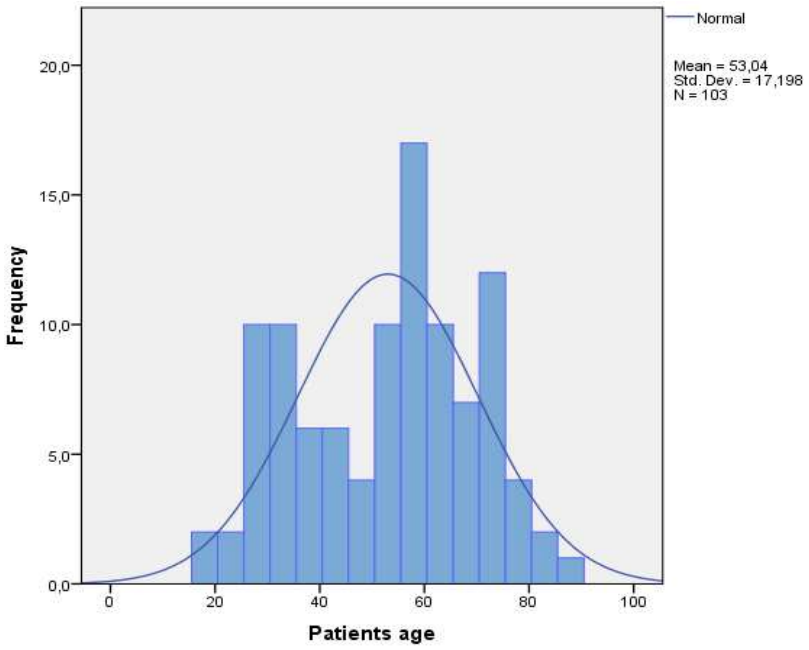

Figure 1. **Age distribution**

Types and causes of adrenal insufficiency

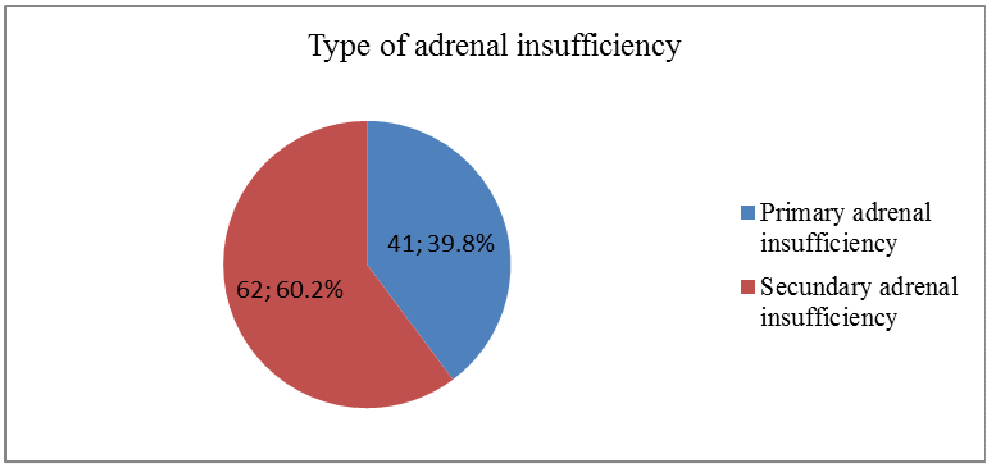

Figure 2. **Type of adrenal insufficiency**

The majority of patients (n=62 or 61.8%) included in this study had secondary adrenal insufficiency (see Fig. 2). The most common causes were iatrogenic adrenal insufficiency due to the use of glucocorticoids, and adenoma of the pituitary gland with complications related to the treatment of adenoma. One patient had Sheehan syndrome.

Primary adrenal insufficiency was detected in 41 (39.8%) patients (see Fig.2), and 10 (24.4%) of them were admitted to the hospital with adrenal crisis. Most common diagnosis in this group was idiopathic primary adrenal insufficiency. None of the patients had been examined for autoimmune adrenalitis by detecting 21-hydroxylase antibodies. For this reason, appropriate diagnosis of autoimmune adrenalitis cannot be made. However, according to statistics, this is the most likely cause. One case was due to bilateral adrenalectomy, and one case - due to tuberculosis of adrenal glands.

The majority of patients (87; 85.5%) with adrenal insufficiency, regardless of the type of disease, had one or more comorbidity.

Pearson's chi-square test showed a statistically significant association between type of adrenal insufficiency and gender ($\chi 2 = 7.006$; Df=1; $p<0.01$). Women were more likely to have primary adrenal insufficiency than men.

Autoimmune comorbidity in primary adrenal insufficiency

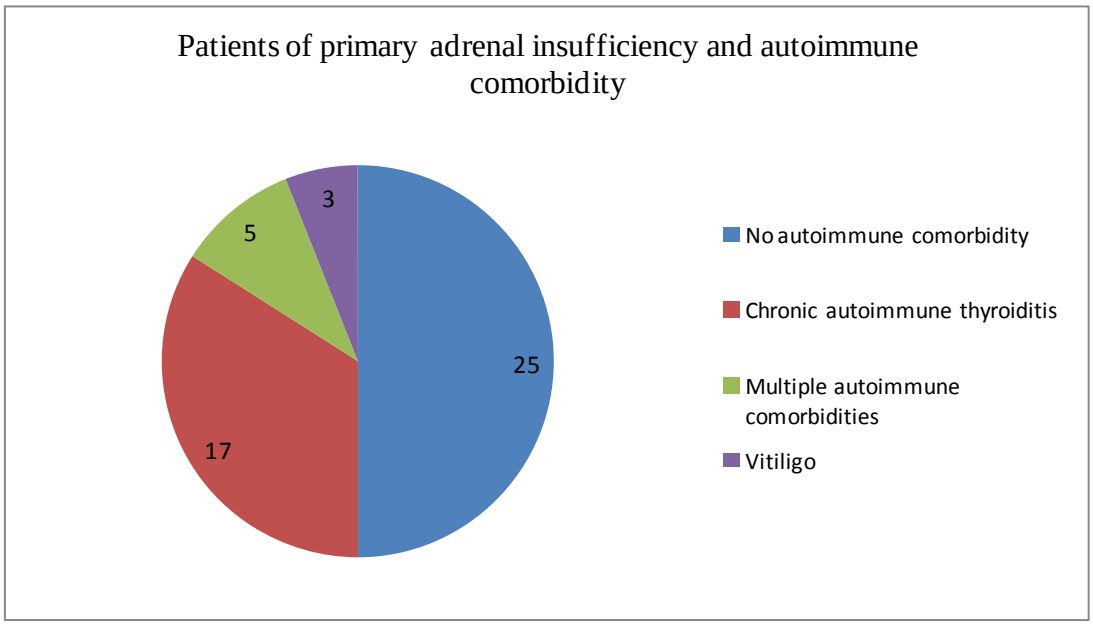

Figure 3. **Autoimmune comorbidity in the case of primary adrenal insufficiency**

More than a half (n=25; 58.5%) of the patients with primary adrenal insufficiency had an autoimmune comorbidity which is enclosed in the diagnosis of the autoimmune polyglandular syndrome. 17 patients had autoimmune thyroiditis, three patients had vitiligo, and five patients had both – vitiligo and autoimmune thyroiditis (see Fig. 3).

Two patients had an autoimmune disease not included in the autoimmune polyglandular syndrome. One patient had antiphosholipid syndrome, the other had rheumatoid arthritis.

The majority of 41 patients with primary adrenal insufficiency (n=37; 90.2%) were screened for possible hypothyroidism by detecting TSH in the patient's serum, and 27 (65.8%) also were tested specifically for possible autoimmune thyroiditis by detecting anti-TPO antibodies in the serum. Almost all patients were screened for anemia by detecting the level of hemoglobin in the serum, and 12 (29.3%) of them had anemia of unspecified etiology, which could also possibly be of autoimmune etiology.

Treatment-related and biochemical parameters of patients with adrenal insufficiency

Most patients received hydrocortisone as the hormone supplementation therapy (n=78). The most common algorithm for this therapy was 20 mg of hydrocortisone in the morning, 10 mg in the

afternoon, and 5 mg in the evening. The mean dose of hydrocortisone was 26.9 (SD=13.9) mg per day. The lowest daily dose was 5 mg of hydrocortisone per day and the highest – 70 mg of hydrocortisone per day. Few patients (n=13) used prednisolone as the supplementation therapy. Mean daily dose of prednisolone was 10.4 (SD=3.9) mg per day. The lowest daily dose was 5 mg of prednisolone per day, and the highest – 17.5 mg. For 12 patients there were no data available in the medical records about the hormonal therapy used for the treatment of adrenal insufficiency. Pearson's chi-square test showed a statistically significant association between type of adrenal insufficiency and the medication used in the supplementation therapy ($\chi 2$= 7.427; Df=1; $p<0.01$). Patients with secondary adrenal insufficiency were more likely to receive supplementation therapy with prednisolone than patients with primary adrenal insufficiency.

Approximately third (n=37; 35.9%) of patients also had mineral corticosteroid deficiency and needed additional supplementation with 50, 100 or 150 mcg of fludrocortisone per day. Mineralocorticoid deficiency was more common in the group of primary adrenal insufficiency (n=32; 78.0%), however, also five patients from the group of secondary adrenal insufficiency needed mineralocorticoid supplementation therapy.

Cortisol in urine was detected in 22 (21.6%) cases. The mean value was 66.4 (SD=85.7) µg/24 hours, and it ranged from 2 to 345.8 µg/24 hours. Morning cortisol at 8 A.M. was detected in 86 (83.5%) patients, and it ranged from 0 to 80.9 µg/dL, with the mean value being 5.78 (SD=10.7) µg/dL. ACTH was detected in 58 (56.3%) of cases. The mean value in the group of primary adrenal insufficiency was 575.8 (SD=688.3) pg/ml (reference interval 7.2 – 63.3 pg/ml), and in secondary adrenal insufficiency - 15.4 (SD=19.5) pg/ml.

Discussion

None of the patients with primary adrenal insufficiency was examined for the autoimmune adrenalitis by detecting 21-hydroxylase antibodies. It could be, firstly, because this test in not available in Latvia (although possibilities to run the test in laboratories located abroad exist), and secondly, results of the test does not change the treatment plan for the patients with primary adrenal insufficiency. For this reason, appropriate diagnosis of autoimmune adrenalitis cannot be made. However, according to statistics (Steward 2011), autoimmunity is the most likely cause of idiopathic primary adrenal insufficiency, and in the Western populations it occurs in 90% of cases. Another fact that suggests the autoimmune etiology of idiopathic adrenal insufficiency in this study, is that comorbidity with another autoimmune disease for was shown to be even higher than previously reported in the literature (Falorni 2004).

Mineralocorticoid deficiency was more common in the group of primary adrenal insufficiency (78%), which is consistent with the literature date (Bornstein 2016). In the case of secondary adrenal insufficiency it is usually not observed because synthesis of mineralocorticoids in regulated

by renin-angiotensin-aldosterone axis, and not influenced by hypothalamus-pituitary-adrenal axis, which is impaired in the case of secondary adrenal insufficiency. However, five patients with secondary adrenal insufficiency also had mineralocorticoid deficiency. This could be explained by coexistence of the both types of adrenal insufficiency (Akçay 1996), coexistence of defect in renin-angiotensin-aldosterone system (Root 2014), or simply by incorrect diagnosis or hormone supplementation plan.

The mean dose of hydrocortisone was 26.9 mg per day, which is consistent with the treatment recommendation about the average daily dose for the treatment of adrenal insufficiency (15-25 mg/m^2 per day) (Bornstein 2016).

Small patient sample due to the fact that this is rare disease could be considered as a limitation of this study. Prevalence of primary adrenal insufficiency has been estimated to be approximately 4/100 000 (Steward 2011), and in secondary – 15-28/100 000 (Arlt 2003).

It is not excluded that some patients may have received treatment with hydrocortisone or prednisolone prior the detection of hormone levels in the serum or urine, since not all of the patients were newly diagnosed. For this reason, data concerning cortisol and ACTH levels could be misinformative.

Conclusions

Primary adrenal insufficiency occurs in younger age than secondary adrenal insufficiency.

Secondary adrenal insufficiency is more common than primary, with most frequent etiological agents being adenoma of the hypophysis and iatrogenic adrenal insufficiency due to the use of glucocorticoids.

In the case of primary adrenal insufficiency prevalence of associated autoimmune disorders is high, and proper screening should be conducted.

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NEUROSARCOIDOSIS: MRI FINDINGS AND CORRELATION WITH DURATION OF THE DISEASE

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Abstract

Neurosarcoidosis: MRI findings and correlation with duration of the disease

Key words: *Sarcoidosis, Neurosarcoidosis, MRI, CNS, Granulomas*

Background: Sarcoidosis is chronic, systemic disease of unknown etiology, in which inflammatory cells form non-caseous granulomas in organs and tissues. In Neurosarcoidosis granulomatous inflammation can emerge in several sites of CNS therefore clinical symptoms are mostly non-specific. The goal of the study is to characterize clinical presentation and radiological findings of neurosarcoidosis and correlation with duration of the disease.

Methods: In retrospective study data of patients with diagnosis sarcoidosis (ICD-10 D86) between 01.01.2012 and 01.12.2015 was evaluated. 22 patients aged 22-65 met selected criteria. MRI findings were categorized by process location and correlated with duration of disease.

Results: Of 22 patients, pathological leptomeningeal enhancement was found in 19 (86,4%) cases. Dura mater involvement was found in 7 (32%) cases. 10 (45,4%) patients had lesions in white matter. 16 of 19 (84,2%) patients had cranial nerve involvement.

Dura mater involvement was observed more frequently (44% - 4 of 9 cases) in group where disease duration was over 5 years in comparison to group where disease duration was under 5 years (23% - 3 of 13 cases). Hypothalamus-hypophysis involvement was found more often (46% - 6 of 9 cases) in patients with disease duration under 5 years compared to group where disease duration was over 5 years (23% - 3 of 13 cases).

Conclusions:

1) In patients with proven neurosarcoidosis most frequently process is localized in leptomeninges with combination of cranial nerve involvement.
2) Dura mater involvement is usually associated with elderly patients with long disease duration.
3) Hypothalamus-hypophysis is involved more frequently in patients with shorter disease duration.

Kopsavilkums

Neirosarkoidoze: MR atrade un korelācija ar slimības ilgumu

Atslēgas vārdi: *Sarkoidoze, Neirosarkoidoze, MR, CNS, granulomas*

Ievads: Sarkoidoze ir hroniska, neskaidras etioloģijas imunoloģiskas ģenēzes sistēmiska slimība, kurai raksturīga nekazeozu granulomu veidošanās dažādos orgānos un audos. Neirosarkoidozes gadījumā granulomatozais iekaisums var parādīties jebkurā nervu sistēmas daļā, tādēļ klīniskā simptomātika pārsvarā ir nespecifiska. Darba mērķis ir raksturot neirosarkoidozes klīnisko un radioloģisko atradi, pētīt to korelācijā ar slimības ilgumu.

Materiāli un metodes: Retrospektīvi tika analizēti dati par pacientiem ar diagnozi sarkoidoze (ICD-10 D86) laika posmā no 01.01.2012. līdz 01.12.2015. Izvēlētajiem kritērijiem atbilda 22 pacienti vecumā 22-65 gadi. MRI atrades tika sakārtotas pēc procesa lokalizācijas un korelācijas ar slimības ilgumu.

Rezultāti: No 22 pacientiem 19 (86,4%) tika konstatēts patoloģisks granulomatozs iekaisums. Cietā smadzeņu apvalka iesaisti konstatēja 7 (32%) gadījumos. Galvas smadzeņu baltajā vielā perēkļus konstatēja 10 pacientiem (40,9%). No 19 pacientiem ar neirosarkoidozes leptomeningeālo formu, 16 gadījumos (84,2%) konstatēja procesa izplatību pa kraniālo nervu gaitu.

Cietā smadzeņu apvalka formu biežāk konstatēja pacientiem, kas ar sarkoidozi slimo vairāk kā 5 gadus – 44% (4 gadījumi no 9), savukārt, tiem, kas slimo mazāk kā 5 gadus tikai 23% gadījumu (3 gadījumi no 13). Hipotalama hipofīzes iesaisti biežāk konstatēja pacientiem, kas ar sarkoidozi slimo mazāk kā 5 gadus – 46% (6 gadījumi), savukārt, tiem, kas slimo ilgāk kā 5 gadus tikai 23% (3 gadījumi).

Secinājumi:

1) Biežākā patoloģiskā procesa lokalizācija pacientiem ar ticamu neirosarkoidozes diagnozi ir leptomeningeāla forma kombinācijā ar kraniālo nervu iesaisti.
2) Cietā smadzeņu apvalka iesaiste ir pārsvarā raksturīga gados vecākiem pacientiem ar ilgstošu sarkoidozes anamnēzi.
3) Hipotalama hipofīzes iesaiste biežāk vērojama pacientiem ar īsāku slimības anamnēzi.

Introduction

Sarcoidosis is chronic, systemic disease in which inflammatory cells form non-caseous granulomas in organs and tissues. Sarcoidosis is characterized by asymptomatic course and spontaneous regression, however, in numerous cases relapsing and progressive forms are observed, which leads to disability and risk of reduced life expectancy. Spontaneous remission is observed in approximately 60% cases. Mortality from all sarcoidosis forms is 1-5%. (James & Sharma 1967) (Hart et al. 2001) (Wiederholt 1965)

The cause of sarcoidosis is yet to be found. Study done in 2004 failed to find single environmental factor causing the disease, however study suggests that pesticides used in agriculture and bioaerosols inhaled at work and home could be contributing factors initiating sarcoidosis. (Newman & al. 2004)

Sarcoidosis affects both genders, all races and in all age groups. Most patients experience first symptoms by age 50, with peak at 20-39. Typical manifestation includes bilateral lymphadenopathy as well as lung, eye, skin and heart symptoms. Sarcoidosis granulomas can emerge in any organ system and in 5-15% cases CNS is involved, often in combination with lung sarcoidosis (88-94%), eye sarcoidosis (37-55%), skin sarcoidosis (30%). Isolated nervous system involvement is observed in 1% of cases. Neurosarcoidosis granulomatous inflammation can emerge in several sites of CNS therefore clinical symptoms are mostly non-specific. (Hoitsma et al. 2004) (Stern et al. 1985) (Delaney 1997) (Gullapalli & Phillips 2004) (Hart et al. 2001) (Kodrić-Trifunović et al. 2012)

Sarcoidosis, especially neurosarcoidosis, diagnosis should be considered only after exclusion of other diagnosis as symptoms are non-specific. Medical history, clinical signs, laboratory tests, radiological and histological examinations should be assessed. (Lower et al. 1997) (Hoitsma et al. 2004)

MRI is imaging method of choice in neurosarcoidosis diagnostics. It is used in workup and to verify results of selected therapy. Leptomeningeal enhancement is typical MRI sign in neurosarcoidosis found in 19-40% of cases. Dural enhancement is found in 34% of cases, cranial nerve involvement in 34-50%, enhancing parenchymal lesions are found in 19-22% and contrast non-enhancing lesions are found in 8-13% of cases. Hypothalamus – pituitary gland involvement is observed in 18% of cases. (Smith et al. 2004) (Shah et al. 2009) (Pawate et al. 2009) (Nowak & Widenka 2001)

The goal of the study is to characterize clinical presentation and radiological findings of neurosarcoidosis and correlation with duration of the disease.

Material and Methods

Study is retrospective. Patients stationed in Riga Eastern Clinical University Hospital (RECUH) Centre of Tuberculosis and Lung Disease (CTLD) between January of 2012 and

December of 2015 with sarcoidosis diagnosis (D86.0) have been included in the study. 22 patients aged 22-65 met selected criteria. Data has been acquired from RECUH patient data base. Patient records, laboratory tests and magnetic resonance imaging data have been reviewed. MRI data was assessed using radiology reports and by retrospectively analyzing MRI data from RECUH digital archive.

Zajicek et al. criteria (Zajicek & al. 1999) were used in patient selection process. Patients with diagnosis "probable neurosarcoidosis" was included in study. Patient demographic data, medical history, clinical symptoms and MRI data were analyzed.

Zajicek et al. criteria for probable neurosarcoidosis:

- Positive histology for sarcoidosis
- Clinical signs suggesting sarcoidosis with other diagnosis excluded
- MRI findings typical for neurosarcoidosis

MRI scans acquired using 1,5 Tesla MRI scanners using following sequences:

- T2 axial, coronal
- DWI
- SWI
- T1 IR 3D before and post contrast
- FLAIR axial Before and after contrast

MRI findings were categorized by process location and correlated with clinical signs and duration of the disease.

Results

Between January of 2012 and December of 2015 876 patients with diagnosis sarcoidosis (D86.0) have been stationed at RECUH CTLD. 22 patients – 16 females (72,7%) and 6 males (27,3%) met Zajicek et al. criteria.

Average age of patients when disease was first diagnosed was 36,6 years for sarcoidosis and 42 for neurosarcoidosis. Average time between sarcoidosis diagnosis and nervous system involvement was 67 months (84 months for female and 21 months for male).

All patients who met criteria had histologically diagnosed sarcoidosis.

Histology findings

Histological findings of 22 selected patients:

- Pulmonary sarcoidosis – 16 patients (72,7%)
- Pulmonary + cardiac sarcoidosis – 2 patients (9,1%)
- Skin sarcoidosis – 2 patients (9,1%)
- Pulmonary and skin sarcoidosis – 1 patient (4,5%)
- Pulmonary, skin and eye sarcoidosis – 1 patient (4,5%)

Clinical signs

All patients who met criteria had neurological symptoms. Leading neurological symptoms were headaches – 13 (59%), dizziness – 8 (36,4%) and vision problems – 6 (27,3%). Neurological signs are summarized in table 1.

Table 1.

Symptoms	Patients (%)
Headaches	13 (59%)
Dizziness	8 (36,4%)
Vision problems	6 (27, 3%)
Facial asymmetry / paresis	3 (13,6%)
Muscle atony	3 (13,6%)
Paresthesia	3 (13,6%)
Hearing loss	2 (9%)
Trigeminal neuralgia	2 (9%)
Dyslexia	1 (4,5%)

MRI findings

Pathological leptomeningeal enhancement was found in 19 patients (86,4%). In 15 (78,9%) cases pathological process was localized in infratentorial region, in 12 (63%) in supratentorial region, mostly in sellar region and chiasmatic cistern region. Hypothalamus – pituitary gland system involvement with thickened and contrast enhancing infundibulum was found in 9 cases (40%).

Dural enhancement was found in 7 (32%) cases in which 4 (57%) enhancement was found along cerebellar tentorium, mostly in tentorial incisure region.

In 9 (40,9%) cases contrast non-enhancing lesions were found in brain parenchyma, while in 1 (4,5%) case contrast enhancing lesion was observed.

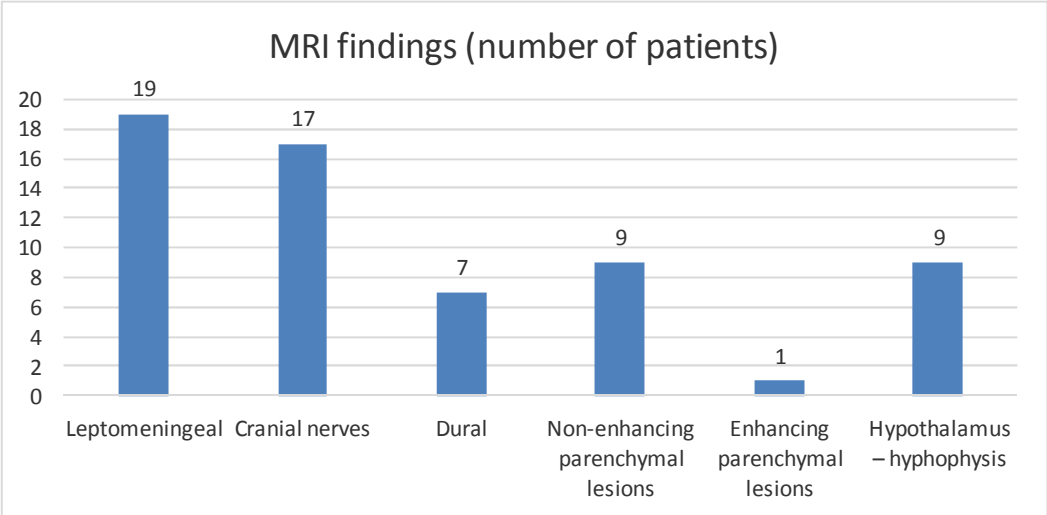

Figure 1.

Involvement of cranial nerves was found in 16 (84,2%) cases:

- optic nerve – 10 (62,5%), in 8 cases bilateral
- facial nerve – 4 (25%), in 1 case bilateral
- vestibulocochlear nerve – 2 (12,5%), in 1 case bilateral
- trigeminal nerve – 1 (6,25%), unilateral

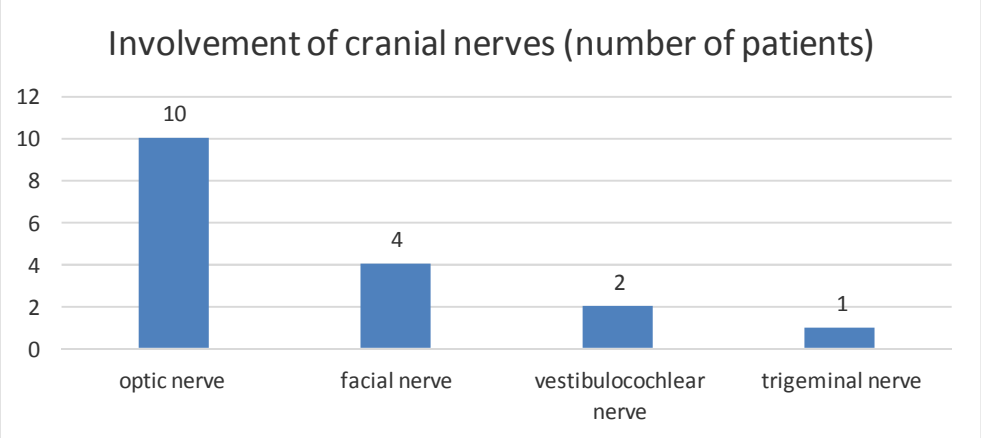

Figure 2.

Combined leptomeningeal and dural form was found in 5 cases;

Combined leptomeningeal and parenchymal form in 6 cases;

Combined leptomeningeal, dural and parenchymal form in 1 case.

MRI findings in correlation with duration of the disease

Patients were divided in two groups. First group consisted of patients with positive histology for sarcoidosis and disease duration is under 5 years (13 patients). Second group consisted of patients with disease duration more than 5 years (9 patients).

Comparing both groups significant difference in leptomeningeal and parenchymal involvement was not found. Dural involvement was found more frequently in group with disease duration over 5 years – 44% (4 of 9 patients), whereas in group with disease duration under 5 years – 23% (3 of 13 patients). Hypothalamus – pituitary gland involvement was observed more often in group with disease duration under 5 years – 46 (6 of 13 patients), while in group with disease duration over 5 years – 23 % (3 of 9 patients).

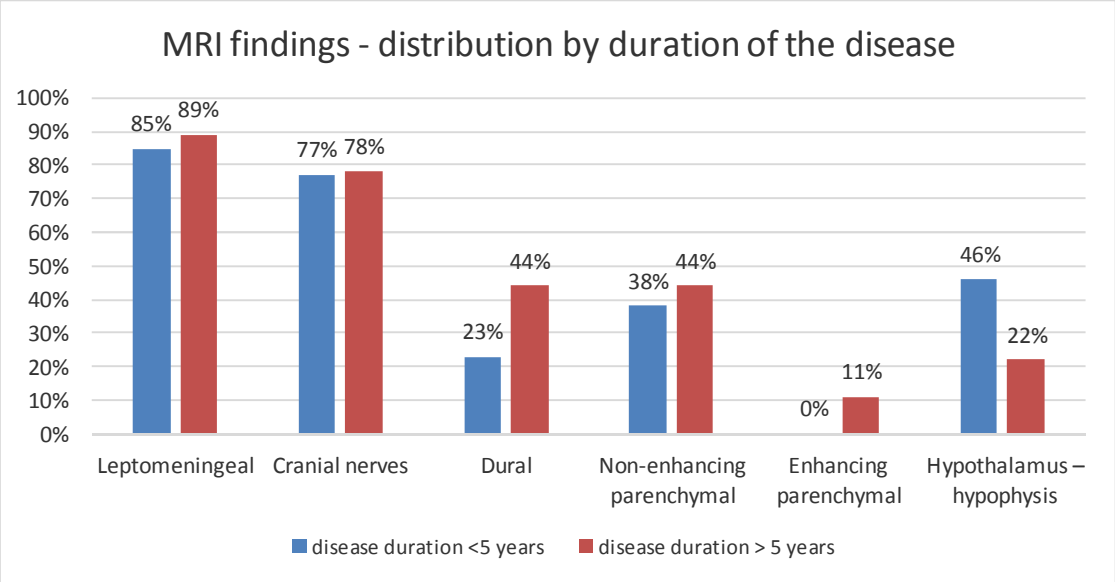

Figure 3.

Discussion

Neurosarcoidosis is rare sarcoidosis complication. Workup is complicated and other diagnosis with similar clinical signs and laboratory tests should be excluded before considering neurosarcoidosis diagnosis. MRI with contrast is modality of choice in neurosarcoidosis workup and evaluation of selected therapy. Although MRI is non-specific for neurosarcoidosis, in combination with other imaging studies, laboratory tests, histology and clinical signs it is beneficial and it allows to differentiate slight pathological alterations. It allows visualization of meninges, ventricles and cisterns, choroid plexus, cranial nerves and perivascular spaces. Additionally, it gives information about process location, size and extent of neurosarcoidosis inflammation in CNS.

In neurosarcoidosis neurological symptoms appear in 5-13% of patients. In prospective study 32 of 123 (26%) of patients had neurological symptoms, however in other retrospective study 33 of 74 (45%) neurological symptoms were caused by neurosarcoidosis. This indicates that only in roughly half of cases neurological symptoms were caused by sarcoidosis. Therefore, sarcoidosis should not be diagnosed based on clinical symptoms alone. (Ricker & Clark 1949) (Allen et al. 2003) (Stern et al. 1985)

According to literature neurosarcoidosis develops in 5-15% of sarcoidosis patients. (Delaney 1997) (Lower et al. 1997) (James & Sharma 1967) (Stern et al. 1985) This research concluded that only 22 of 876 (2,5%) RECUH CTLD patients were diagnosed with neurosarcoidosis.

Literature suggests peak age 20-39 for sarcoidosis and 33-41 for neurosarcoidosis (Rybicki et al. 1997) (Dragana et al. 2013) (Hart et al. 2001). This positively correlates with research data - average age of patients when disease was first diagnosed was 36,6 years for sarcoidosis and 42 for neurosarcoidosis.

Clinical signs for neurosarcoidosis is non-specific and variable. Often combinations of different forms are observed, which sometimes does not correlate with pathological location in CNS. Headaches (59%), dizziness (36,4%) and cranial nerve neuropathies (36,4%) were leading neurological signs in this study. In literature cranial neuropathy is leading neurological symptom found in 73% of patients, followed by headaches in 17-48% cases. (Gullapalli & Phillips 2004) (Allen et al. 2003) (Stern et al. 1985)

Depending on location different forms of neurosarcoidosis is recognized in MRI. Lesions can be localized in meninges, along cranial nerves, in parenchyma. However, most often it is combination of different forms.

According to literature:

- Leptomeningeal form is found in 19-40% cases, in our research – 86,4%; (Lower et al. 1997) (Hoitsma et al. 2004) (Kodrić-Trifunović et al. 2012)
- Dural involvement is found in 34% cases, in our research – 32%; (Hoitsma et al. 2004)
- Cranial nerve involvement is observed in 34-50% cases, in our research – 72,7%; (James & Sharma 1967) (Hoitsma et al. 2004)
- Enhancing parenchymal lesions are found in 19-22% cases, in our research – 4,5%; (Hoitsma et al. 2004) (Kodrić-Trifunović et al. 2012)
- Non-enhancing parenchymal lesions are observed in 8-13% cases, in our research – 40,9%; (Hoitsma et al. 2004) (Kodrić-Trifunović et al. 2012)
- Hypothalamus – pituitary gland involvement is observed in 18% cases, in our research – 40%. (Smith et al. 2004)

Comparing literature data and study results there are noticeable differences. It may be explained with selection criteria used in this study – patients were selected by certain criteria and with possible neurosarcoidosis diagnosis. Other research used different approach.

Conclusions

- In patients with probable neurosarcoidosis (Zajicek et al. criteria) most frequently process is located in leptomeninges with combination of cranial nerve involvement.
- Dura mater involvement is usually associated with elderly patients with long disease duration.
- Hypothalamus-hypophysis involvement is more frequently found in patients with shorter disease duration.
- Post contrast FLAIR in addition to post contrast T1 provides precise information about sarcoidosis inflammation size, location and extent in basal subarachnoid spaces and in subependymal zone. It may be beneficial to include FLAIR into standard imaging protocol.

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EVALUATION OF CEREBRAL INFARCTION RISK FACTORS AND ETIOLOGY IN MEN AND WOMEN UP TO 50 YEARS OF AGE

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Abstract

Evaluation of Cerebral Infarction Risk Factors and Etiology in men and women up to 50 years of age

Key words: *cerebral infarction, risk factors, etiology, young patients*

Introduction: Cerebral infarction in young patients imposes a significant burden on the society by losing the most productive years in people's lives and increasing healthcare expenses.

Material and methods: The entire medical documentation of patients in the age group of 18–50 available in the archives of Riga East University Hospital Gailezers for the period 2014–2015 was summarized and analysed. The obtained data were processed using Microsoft Excel and SPSS software.

Results: Medical documentation of 152 patients has been analysed. These patients included 49 women and 103 men. The most common risk factors include arterial hypertension (51.3 %), which was found in 38.8 % of women and 57.3 % of men, dyslypidemia (28.3 %) established in 36.7 % of women and 24.3 % of men, and smoking (17.1 %) – in 8.2 % of women and 21.4 % of men. Atherothrombotic cerebral infarction was diagnosed in 43.4 % of patients, i.e., 26.5 % of women and 51.5 % of men. Cardioembolic cerebral infarction was diagnosed in 14.5 % of patients, i.e., 26.5 % of women and 7.8 % of men.

Conclusions: The frequency of risk factors in women and men varies. Consequently, also the lifestyle modification in women and men is different. Cardioembolic cerebral infarction is most commonly found in women, but atherothrombotic cerebral infarction – in men.

Kopsavilkums

Cerebrāla infarkta riska faktoru un etioloģijas izvērtēšana vīriešiem un sievietēm līdz 50 gadu vecumam

Atslēgvārdi: *cerebrāls infarkts, riska faktori, etioloģija, jaunākie pacienti*

Ievads: Cerebrāls infarkts jauniem pacientiem rada lielo ekonomisko slogu sabiedrībai, zaudējot produktivākos cilvēku gadus un paaugstinot veselības izmaksas.

Materiāls un metodes: Tika apkopotas un analizētas visas RAKUS „Gaiļezers" arhīvā pieejamās pacientu medicīniskās dokumentācijas vecuma grupā no 18 līdz 50 gadiem, laika posmā no 2014. līdz 2015. gadam. Iegūtie dati tika apstrādāti ar Excel un SPSS programmas palīdzību.

Rezultāti: Tika izanalizēta medicīniskā dokumentācija 152 pacientiem. No tiem 49 sievietes un 103 vīrieši. Biežākakie riska faktori ir arteriāla hipertensija (51.3%), kas ir sastopama 38.8% sieviešu un 57.3% vīriešu vidū, dislipidēmija (28.3%), kas ir konstetēta 36.7% sieviešu un 24.3% vīriešu, un smēķēšana (17.1%), no tiem 8.2% sievietēm un 21.4% vīriešiem. Aterotrombotiskas ģenēzes cerebrāls infarkts tika diagnosticēts 43.4% pacientiem, no tiem 26.5% sievietēm un 51.5% vīriešiem. Kardioembolisks cerebrāls infarkts tika konstatēts 14.5% pacientiem, no tiem 26.5% sievietēm un 7.8% vīriešiem.

Secinājumi: Riska faktoru biežums atšķiras sieviešu un vīriešu vidū. Attiecīgi dzīvesveida modifikācija sievietēm un vīriešiem ir dažāda. Sievietēm biežāk konstatē kardioemboliskas ģenēzes cerebrālo infarktu, bet vīriešiem aterotrombotiskas ģenēzes cerebrālo infarktu.

Introduction

Cerebral infarction is a severe disease resulting in disability and causing a major economic burden on the society. This is particularly true of young patients because of the loss of the productive years. It is therefore important to identify stroke in due time in order to apply a specific treatment and to minimize the effects of stroke.

The most common cerebral infarction risk factors such as arterial hypertension, diabetes mellitus, extracranial and intracranial vascular atherosclerosis, and atrial fibrillation, which

significantly contribute to the development of stroke in the elderly people, occur far more seldom in young patients (Ferro et al. 2010). There is a number of other etiological factors causing cerebral infarction in young people, and it is important to identify them in order to choose the correct stroke prevention.

The occurrence of cerebral infarction in younger people is far more seldom. In Europe and the USA, it varies from 8.4 to 13.0 per 100,000 people and increases with age. There is a difference observed between different ethnic groups. Black people and Spaniards are exposed to higher risk (Smajlović 2015: 158).

Strokes of unidentified etiology are observed more often in young patients than in elderly ones. However, with the age the number of strokes of unidentified etiology decreases in percentage, and after the age of 35-40 the number of cerebral infarctions caused by large-artery atherosclerosis and small vessel disease increases (Ferro et al. 2010: 1085).

Risk factors and etiology of stroke for young patients significantly differ from those among elderly people. Traditional cerebral infarction risk factors such as hypertension, dyslipidemia and diabetes mellitus still can significantly affect younger patients, and their importance only increases with age (Katsnelson et.al. 2012: 348). Taking into account the fact that over the last few years there is a tendency of obesity in young people, the importance of these risk factors in young patients will grow more.

Smoking of cigarettes is an important risk factor of stroke for young patients. Studies have shown that smokers between the ages of 15 and 45 are exposed to cerebral infarction risk 1.6 times more than non-smokers. Besides, risk exposure is also affected by the number of cigarettes smoked per day (Katsnelson et.al. 2012: 348, Bhat et al. 2008).

Another risk factor in young patients is migraine. Studies have shown that cerebral infarction risk for people who suffer from migraine with aura is twice higher than for those who do not have migraine. Besides, the age under 45, smoking and the use of oral contraception reinforce this risk further (Ferro et al. 2010: 1086). Studies show that a combination of risk factors such as smoking, oral contraception and migraine with aura increases risk of stroke 10 times. (Laurell et.al.201 2: 256) Migrainous infarction affects women 2-3 times more than men, it is related to a higher prevalence of migraine among women ((Laurell et.al. 2012: 256).

Cerebral infarction etiology in young patients significantly differs from that of elderly patients. Etiological factors are as follows: arterial dissection (Ferro et. al. 2010: 1089, Katsnelson et.al. 2012: 349,), opened foramen ovale (Ferro et. al. 2010: 1090-1091, Katsnelson et.al. 2012: 350) , infections (HIV, syphilis, Varicella zoster virus, cysticercosis) (Ferro et. al. 2010: 1091-1092, Katsnelson et.al. 2012: 350) , systemic lupus erythematosus (Ferro et. al. 2010: 1092, Katsnelson

et.al. 2012: 349), thrombophilias (Ferro et. al. 2010: 1093, Kay et. al. 2011) genetic disorders (Ferro et. al. 2010: 1093, Katsnelson et.al. 2012: 350-351) .

The TOAST classification is the most common stroke classification, it classifies cerebral infarctions depending on their ethiopathogenetic mechanisms (Table 1) (Adams et al. 1993).

Table 1. **TOAST classification**

TOAST Classification
Large-artery atherosclerosis
Cardioembolism
Small-vessel occlusion
Stroke of other determined etiology
Stroke of undetermined etiology • Two or more causes identified • Negative evaluation • Incomplete evaluation

A number of countries have studied the breakdown of cerebral infarction risk and etiological factors for men and women, and in different countries they are different (Foerch et al. 2013, Xiao-ying Yao et al. 2012, Talebi et al. 2014).

The goal of our paper is to study the risk factors and ethiology of cerebral infarction depending on the gender of patients under the age of 50 years.

Materials and methods

All medical records of patients between the ages of 18 and 50 available at the RAKUS Gaiļezers archive were summarized and analysed during the period of time from 2014 to 2015. Patients diagnosed with acute cerebral infarction who underwent treatment at the hospital during the above referred period of time were selected. The patients were divided into two groups depending on gender. Risk factor prevalence and etiological breakdown by the TOAST classification were assessed in both groups. The following risk factors were assessed: arterial hypertension, atrial fibrillation, myocardial infarction, angina pectoris, chronic heart failure, valvular pathology, cerebrovascular episodes, smoking, dyslipidemia, alcohol addiction, obesity, diabetes mellitus, chronic infections, oncologic process, thyroid disease.

The data obtained were processed by means of SPSS and Microsoft Excel software.

Results

Medical records of 152 patients were examined of which 103 were males and 49 were females. The median age of men was 42.22 ± 6.93 years, the median age of women was 40.20 ± 7.38 years. The prevalence of cerebral infarction is shown in Figure 1. The prevalence of cerebral infarction for both males and females increases with age.

Looking at risk factor frequency we can see that 3 most common factors are as follows: arterial hypertension (51.3%), dyslipidemia (28.3%) and smoking (17.1%) (Figure 2). While

examining risk factors for males and females individually, arterial hypertension still is the most common risk factor both for males and females (57.3% and 38.8% respectively, $p<0.05$). The second most common risk factor is the same both for males and females. Dyslipidemia was reported in 24.3% of males ($p<0.05$) and 36.7% of females ($p<0.05$) respectively. The third most common risk factor for men is smoking (21.4%, $p<0.05$), while for women – thyroid disease (16.3%, $p<0.05$).

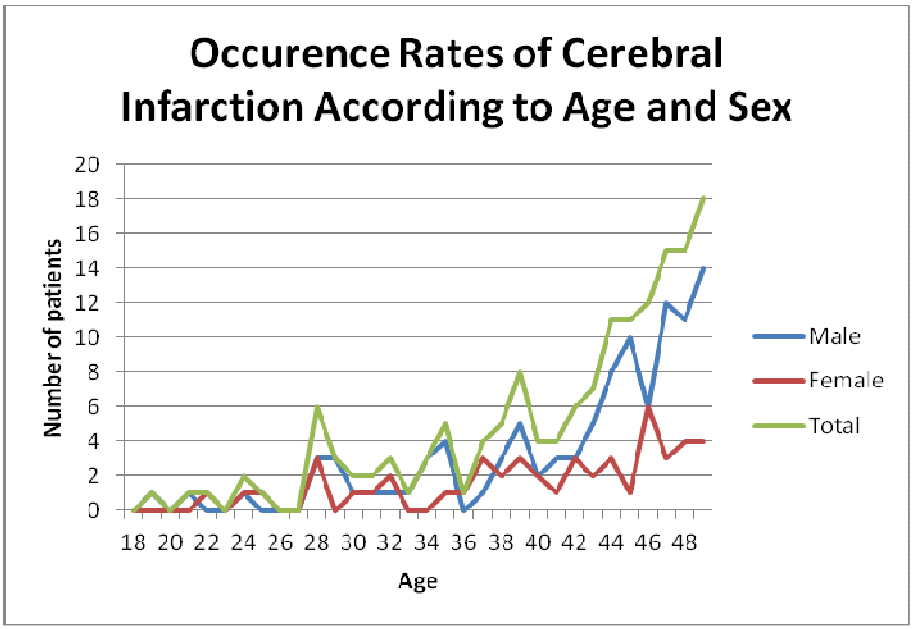

Figure 1.

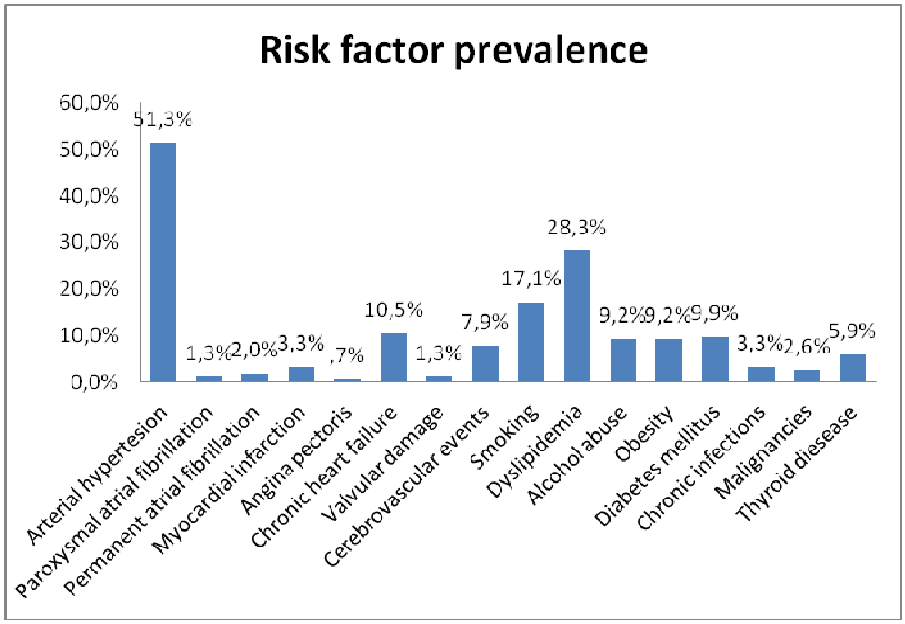

Figure 2.

Table 2. **Risk factor prevalence in males and females**

	Males		females	
	%	N	%	N
Arterial hypertension	57.3%	59	38.8%	19
Paroxysmal atrial fibrillation	1.0%	1	2.0%	1
Permanent atrial fibrillation	1.9%	2	2.0%	1
Myocardial infarction	3.9%	4	2.0%	1
Angina pectoris	1.0%	1	0.0%	0
Chronic heart failure	12.6%	13	6.1%	3
Valvular damage	1.0%	1	2.0%	1
Cerebrovascular events	8.7%	9	6.1%	3
Smoking	21.4%	22	8.2%	4
Dyslipidemia	24.3%	25	36.7%	18
Alcohol abuse	11.7%	12	4.1%	2
Obesity	7.8%	8	12.2%	6
Diabetes mellitus	11.7%	12	6.1%	3
Chronic infections	2.9%	3	4.1%	2
Malignancies	2.9%	3	2.0%	1
Thyroid disease	1.0%	1	16.3%	8
Chronic kidney disease	1.9%	2	0.0%	0

Examining etiological breakdown among males and females, the most common cause of cerebral infarction is large-artery atherosclerosis (51.5%, $p<0.05$). The second most common type of cerebral infarction for men is a stroke of undetermined etiology (26.2%, $p<0.05$). Cardioembolic cerebral infarction in men was found only in 8% ($p<0.05$) of cases (Table 3). Large artery atherosclerosis in women was found only in 26.5% ($p<0.05$) of cases, and cerebral infarction of cardioembolic genesis was in 28.6% ($p<0.05$) of cases (Table 3).

Table 3. **Aetiological distribution of cerebral infarction in males and females**

	Males		Females	
	Number	%	Number	%
Large-artery atherosclerosis	53	51.5%	13	26.5%
Cardioembolism	8	7.8%	14	28.6%
Small-vessel occlusion	4	3.9%	1	2.0%
Stroke of other determined etiology	11	10.7%	7	14.3%
Stroke of undetermined etiology	27	26.2%	14	28.6%
Total	103	100.0%	49	100.0%

Discussion

There is a number of studies carried out all over the world regarding the prevalence of cerebral infarction in men and women of different age groups (Foerch et al. 2013). Data vary from country to country due to different demographic and socio-economic situation of each country.

Other studies elsewhere in the world also have shown that the most common etiological factor for women is cardioembolism, while for men it is large-artery atherosclerosis (Caso et al. 2010, Petrea et al. 2009). The development of atherosclerosis in men is related to smoking. Our research also has shown that smoking is more often observed in male patients than in female patients.

Thyroid diseases contribute to the development of cerebrovascular events (Caso et al. 2010, Petrea et al. 2009, Yang et al. 2015). Our research shows that thyroid diseases were observed more often in women. It would be important to diagnose them in due time and to treat them effectively. Our research is the first research of the kind in Latvia. Its weak point is inequality of the male and female group making it difficult to compare etiology and risk factors within the groups. Thus, it is necessary to continue researching further.

Conclusions

The most common risk factors in patients under the age of 50 years are modifiable and they could be minimized in due time. The frequency of risk factors differs among females and males. Accordingly, female and male lifestyle modification is different. The most common risk factors for males are arterial hypertension, dyslipidemia and smoking. The most common risk factors for females are arterial hypertension, dyslipidemia and thyroid disease.

Females are more often diagnosed with cerebral infarction of cardioembolic genesis, while males are more often diagnosed with cerebral infarction of atherothrombotic genesis.

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KNOWLEDGE AND COMFORT LEVEL OF MIDWIVES AND OBSTETRICIANS DEALING WITH BEREAVEMENT AFTER STILLBIRTH

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Abstract

Key words: *stillbirth, knowledge, staff, education, bereavement*

Case of stillbirth is defined by fetal death after 22th week of gestation. A systematic review, published in 2016, showed that behaviors and actions of staff have a memorable impact on parents and parents are expecting support from staff. The aim of the research was to determine knowledge and comfort level of staff dealing with bereavement after stillbirth. Research was done by surveying midwives and obstetricians. Surveying was done at Riga Maternity Hospital and Perinatal Care Center of Pauls Stradiņš Clinical University Hospital in Riga. In total 106 respondents completed the survey: 103 women and 3 men; 66% were midwives and 34% obstetricians. 24.8% of the staff were in learning process and 75.2% certified specialists. 19.4% stated that their knowledge is not enough to deal with stillbirth cases; 21.4% have knowledge, but do not have experience; 47.6% have enough knowledge and experience, but still have to endure emotional difficulties. 53.4% never heard how to deal with it during their education. Total 81.2% mentioned insufficient education about stillbirth cases. Results showed that majority of staff do not feel confident dealing with cases of stillbirth. Healthcare professionals admit lack of knowledge and absent of trainings about stillbirth cases during education. Staff should receive special and adequate training to get personal ability and knowledge about how to act and feel confident in cases of stillbirth.

Kopsavilkums

Atslēgvārdi: *nedzīvi dzimis, zināšanas, personāls, izglītība, zaudējums*

Nedzīvi dzimis auglis ir nelabvēlīgs grūtniecības iznākums ar jaundzimušā nāvi pēc 22. gestācijas nedēļas. 2016. gadā publicēts sistemātisks apskats pierāda, ka slimnīcas personāla uzvedība un darbības šī gadījuma laikā atstāj spēcīgu iespaidu uz pacientiem un pacienti sagaida atbalstu no personāla. Pētījuma mērķis bija noteikt, kā medicīnas personāls vērtē savas zināšanas un komforta līmeni šajos gadījumos. Pētījums tika īstenots aptaujājot medicīnas personālu - vecmātes un ginekologus-dzemdību speciālistus. Aptauja tika veikta Rīgas Dzemdību namā un Perinatālās aprūpes centrā Paula Stradiņa Klīniskās universitātes slimnīcā Rīgā. 106 respondenti aizpildīja anketu: 103 sievietes un 3 vīrieši; 66% bija vecmātes un 34% - ginekologi. 24,8% no viņiem bija apmācības procesā un 75,2% - sertificēti speciālisti. 19,4% respondentu apgalvoja, ka viņu zināšanas nav pietiekamas. 21,4% apgalvoja, ka viņiem ir zināšanas, bet nav pietiekami pieredzes šajā jomā; 47,6% ir pietiekami daudz zināšanu un pieredzes, bet viņi joprojām saskaras ar emocionālām grūtībām. Kopā 81,2% atzīmēja, ka izglītības procesā iegūtā informācija par to, kā rīkoties šādos gadījumos, ir nepietiekama. Apkopojot rezultātus varēja secināt, ka lielākā daļa personāla nejūtas pārliecināti saskaroties ar nedzīvi dzimušo bērnu gadījumiem. Medicīnas personālam nepieciešams saņemt speciālu un adekvātu apmācību par to, kā rīkoties šajos gadījumos.

Introduction

In 2014 the World Health Organization released a statement on preventing disrespect during facility-based childbirth (World Health Organization 2014). Worldwide in 2015 about 2.7 million

babies were stillborn (Ellis et al. 2016); in Latvia there were 106 cases of stillbirth in 2015 (Slimību profilakses un kontroles centrs 2016).

The study is important because the death of any child is a tragedy for families, often with profound, long lasting psychosocial and economic effects. In addition to clinical care, quality maternity care incorporates interpersonal and emotional aspects of care. Because stillbirth is an indicator of quality of care, women's experiences of care associated with stillbirth can be deemed to be an indicator of quality of care processes. Just as actions can be taken to prevent stillbirth, actions can be taken to prevent adverse psychosocial outcomes after stillbirth and, in both instances, suboptimum interpersonal care can undermine even the best clinical care and lead to harm (Heazell et al. 2016: 387).

Pregnant women who previously experienced repetitive spontaneous abortions received increased attention but no specific medical therapy (“tender loving care”). These women (n = 16) were more likely (85%) to complete their pregnancy than women (n = 42) not offered such close attention (36%) (Joe Simpson and Eric Jauniaux 2016).

Caring for families during and after stillbirth places a substantial personal and professional burden on medical personnel. Negative effects on staff could be addressed by education, training, and provision of formal and informal support (Heazell et al. 2016: 387).

Aim is to determine how midwives and obstetricians measures their knowledge and comfort level dealing with bereavement after stillbirth in Riga Maternity Hospital and Perinatal Care Center of Pauls Stradiņš Clinical University Hospital in Riga.

In this study we want to give importance of educating staff, because that can enable them to cope better with stillbirth cases both - emotionally and professionally.

Material and Methods

The survey consisted of open- and close-ended questions about working with patients in case of stillbirth to evaluate knowledge and comfort level of staff dealing with bereavement after stillbirth. Midwives and obstetricians from Riga Maternity Hospital and Perinatal Care Center of Pauls Stradiņš Clinical University Hospital in Riga participated in the study.

Inclusion criterion was that the participant had to be a medical care specialist in gynecology and obstetrics department, currently working at related Maternity ward and had working experience with cases of stillbirth. Exclusion criteria were rejection to participate and incomplete questionnaire. Patients were interviewed in a 1 month period starting in January 2017 and finishing in February 2017.

The knowledge and comfort level of staff dealing with bereavement after stillbirth was assessed by Latvian version of survey - originally created study protocol in 15.01.2017. Survey included questions about education on working with cases of stillbirth (Was it mentioned in your

study process how to deal with patients in cases of stillbirth (how to talk, how to support them emotionally)? Answers: Yes; No.); about self-assessed knowledge and comfort level that provides the sense of confidence in cases of stillbirth. (Do you think that your education and experience on working with cases of stillbirth is sufficient to support patients? Answers: Yes; No; Knowledge is enough, but there is not enough experience; Enough knowledge and experience but still it is very emotionally difficult.) Respondents were also asked about their opinion about the quality of information about dealing with these cases in education process (Do you think that the information provided in education process about dealing with cases of stillbirth is sufficient? Answers: Yes; No.)

The survey also included questions about psychoemotional factors and emotions they encounter when working with cases of stillbirth and how it affects them in work and after work and knowledge about grief stages (Kubler-Ross, 1969) and do they think it was necessary to provide education on grief stages.

All the data were processed in IBM SPSS version 23.0. Descriptive statistics - frequency and percentage - were applied. Significance was detected using Pearson Chi-square, Fishers' Exact test with p values <0.05.

Results

In survey participated 106 respondents. Population consisted of 103 women (97.2%) and 3 men (2.8%), 66% of midwives and 34% of obstetricians, 24.8% of the staff were in learning process and 75.2% certified specialists. The majority - 72.6% - of participants were from Riga Maternity Hospital, - 27.4% - were from Perinatal Care Center of Pauls Stradiņš Clinical University hospital (PSKUS).

Respondents were asked about knowledge and confidence dealing with stillbirth and did they get appropriate information during education.19.4% stated that their knowledge is not enough to deal with stillbirth cases; 21.4% have knowledge, but do not have experience; 47.6% have enough knowledge and experience, but still have to endure emotional difficulties. The 54.5% of respondents, who have knowledge, but do not have enough experience, felt confused dealing with case of stillbirth. (p= 0.029)

In the next question 53.4% stated that it was never mentioned how to deal with stillbirth cases during their education and 12.7% of respondents, who did not heard about stillbirth cases during education - felt guilty dealing with cases of stillbirth. (p=0.014). And furthermore the 92.0% of surveyed, who did not heard about stillbirth cases during education - suppose, that knowledge of grief stages would be necessary. (p=0.036)

Total 81.2% mentioned insufficient education about stillbirth cases. And 57.3% of surveyed for whom the education was not enough, state that it affects their ability to take care of other patients and get work done. (p=0.043). But Other 66.0% of respondents, who heard about stillbirth during education, still mentioned that topic coverage was not enough. (p<0.00005)

Discussion

The understanding, how educated are midwives and obstetricians and how good they can cope with emotionally challenging situations such as stillbirth could improve the health care quality in Riga Maternity Hospital and Perinatal Care Center of Pauls Stradiņš Clinical University Hospital in Riga.

A lot of knowledge and skills are expected from clinicians moreover than medical help. For example, medical personnel should be sensitive to the emotional difficulties and needs of families' bereavement after stillbirth. Families should be offered the opportunity to see and hold their infant and be offered keepsake items such as photos, handprints or footprints, or special blankets or clothing. It is stated that all women should be offered bereavement services and psychological consulting and should receive close surveillance for development of depression. And it is also recommended to discuss all the results of the stillbirth evaluation and counselling regarding potential subsequent pregnancies (Resnik et al. 2014).

There are mentioned six "qualities" that summarized the findings — "support in chaos," "support in the meeting with and separation from the baby," "support in bereavement," "explanation of the stillbirth," "organization of the care," and "understanding the nature of grief." (Säflund K et al. 2004). Do Latvian medical professionals have sufficient knowledge?! Research results show that knowledge of how to support and the recommendations how to cope with bereavement are not provided during educational process. As a consequence, medical staff cannot be expected to demonstrate skills, which they were not taught. Some part of medical professionals was introduced to similar cases during education; still midwives and obstetricians measure their knowledge as insufficient.

Further research is important, especially to get clearer which skills are the most necessary to provide to midwives and obstetricians, making them to be able to improve situation with bereavement after stillbirth. The major challenge is to give possibilities for medical personnel to get knowledge, providing midwives and obstetricians more understanding and confidence.

For the moment the discussion about organization of educational process and about perspective to add psychosomatic or/and psychological, or/and emotional trainings as one specialized and differentiated subject is necessary. It is also necessary to discuss how this reorganization should be done to be effective. Furthermore, midwives and obstetricians stated that practical trainings are extremely important, because experience is especially valuable.

Conclusions

The most important and sensitive conclusion is that healthcare professionals admit their lack of knowledge by absence of training on stillbirth cases during medical education. Midwives and obstetricians do not feel confident dealing with cases of stillbirth.

Neither knowledge, nor experience is enough to deal with such cases. Absence of knowledge and experience leads to confusion, guilt and affects ability to take care of other patients and to get work done.

The majority of midwives and obstetricians did not get information how to deal with stillbirth cases during medical education. Moreover, medical specialists, who get information during medical education, measure it insufficient.

Midwives and obstetricians should receive special and adequate trainings to get personal ability and knowledge about how to act and feel confident in cases of stillbirth.

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THE PREVALENCE OF DEPRESSION AMONG THE ELDERLY PEOPLE AND THE INFLUENCING FACTORS

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Abstract

The prevalence of depression among the elderly people and the influencing factors

Key words: *Primary care, elderly person, depression*

Introduction: It is estimated that in 2030 22% of the Latvian population will be between 60 to 79 years old and 6% of the population will be above the age of 80. Depression is a common mental disorder. Globally, an estimated 350 million people of all ages suffer from depression.

Aim: By using the means of questionnaires, analyze whether the depression as a mental disorder is common among the elderly as well as understand which factors influence the development of depression.

Materials and methods: A questionnaire was used to gather data. Respondents answered 20 questions about their general state of health and completed a short depression test designed to evaluate the level of depression. Data was compiled in Excel tables and processed with SPSS 16.0 data processing method.

Results: From the 100 respondents with an average age 75 years the depression test showed average depression level 4,3 points, which means these people do not have depression. Study showed that people who have tendency to depression visit their family doctor twice as often as those who do not have such a tendency. It could also could be seen that for people who have a hobby the average level of depression ranges 2 - 3 points, but those who do not have any hobbies average depression level is 3-7 points. At the same time it did not demonstrate a clear correlation between age and depression. People with signs of depression have indications of cognitive dysfunction. From those people who live in a nursing home 20,6% show signs of depression, whereas from those people who live at home 45 % have sings of depression.

Conclusion: After compiling the results it is clear that the age does not affect level of depression, but many other factors are significant.

Kopsavilkums

Depresijas izplatīta vecu cilvēku vidū un to ietekmējošie faktori

Atslēgas vārdi: *ģimenes medicīna, depresija, pensijas vecuma cilvēki*

Ievads: Ir aprēķināts, ka ap 2030. gadu 22% no visas Latvijas populācijas būs 60 līdz 79 gadus veci un 6% cilvēku būs vecāki par 80 gadiem. Depresija ir viena no visbiežāk satopamām mentālām saslimšanām. Visā pasaulē ir apmērsm 350 milj. cilvēku, kuri cieš no derpesijas.

Mērķis: Novērtēt pensijas vecuma cilvēku mentālo stāvokli un salīdzināt to ar depresijas līmeni.

Materiāli un metodes: Pētījumā tika izmantotas trīs dažādas anketas: Mentālā stāvokļa īsais novērtējums (Mini mental state examination), depresijas pašnovērtējuma tests (PHQ-9) un aptauja par pacientu vispārējo veselības stāvokli. Dati tika apkopoti ar Microsoft Excel un SPSS 16.0 statistikas apstrādes programmām.

Rezultāti: Pētījumā piedalījās 100 respondentu ar vidējo vecumu 75 gadi. Vidējais iegūtais punktu skaits depresijas testā bija 4,3, kas norāda, ka respondentiem nav depresija. Pētījuma rezultāti parādīja, ka cilvēki, kuriem ir nosliece uz depresiju, savu ģimenes ārstu apmeklē divas reizes biežāk. Kā arī tika pierādīta korelācija starp hobiju esamību un zemāku depresijas līmeni – cilvēki, kuriem bija hobiji vidēji testā uzrādīja rezultātu 2 – 3 punkti, taču tie, kuriem hobiju nebija vidēji ieguva 4 – 7 punktus. Tika pierādīts, ka cilvēkiem ar depresiju ir kognitīvo funkciju traucējumi. No tiem cilvēkiem, kuri dzīvoja sociālās aprūpes iestādē 20,6 % uzrādīja depresijas pazīmes, savukārt, no tiem, kuri dzīvoja mājās, 45 % bija depresijas iezīmes.

Secinājumi: Apkopojot pētījuma rezultātus, ir skaidrs, ka vecums neietekmē depresiju, bet daudzi citi faktori gan.

Introduction

According to WHO data, the ageing of the population is happening at a much faster rate than previously considered. The number of people ageing 60+ is expected to double between 2000 and 2050. It estimated that by 2030, 22% of the Latvian population will be in ages between 60 and 79 years old. Furthermore, 6% - above the age of 80 years. Along with the development of medical

possibilities and human age spectrum changes the health priorities are changing. Depression is the leading cause of ill health and disability worldwide. According to the latest estimates from WHO, more than 300 million people are now living with depression, an increase of more than 18% between 2005 and 2015. Lack of support for people with mental disorders, coupled with a fear of stigma, prevent many from accessing the treatment they need to live healthy, productive lives (WHO 2017).

Depression is a common mental illness characterized by persistent sadness and a loss of interest in activities that people normally enjoy, accompanied by an inability to carry out daily activities, for 14 days or longer. In addition, people with depression normally have several of the following: a loss of energy; a change in appetite; sleeping more or less; anxiety; reduced concentration; indecisiveness; restlessness; feelings of worthlessness, guilt, or hopelessness; and thoughts of self-harm or suicide (WHO 2017).

Centers for Disease Control and Prevention (CDC) study showed that the age group of 50 years 7.7% of respondents notes that are currently suffering from depression, and 15, 7% lifetime has been diagnosed with depression. It is a curable disease, therefore earlier diagnosis improves patient's future health and quality of life (CDC, January 31, 2017).

General practitioners are usually the first health care professionals who are involved if the patient or a family member is suspected of a disease development. It has been shown that patients with depression visit the GP more often, use more drugs and staying in the hospital longer. Although studies have shown that with increasing age the prevalence of depression, it is not age-related illness.

Materials and Methods

The study was conducted in a GP practice, during the period from January to February 2017. Study design - cross sectional study. The study involved 100 respondents. Inclusion criterion: age over 62 years. Exclusion criteria: age under 62 years of age, the patient's unwillingness to participate in the study.

The study used 3 questionnaires: pacient health questionnare (PHQ-9), a short mental status examination (Mini Mental state examination) and questionnaire of the general state of health and quality of life. To evaluate the health status, patients were asked 20 questions about chronic illnesses, complaints lately, exercise, hobbies, living conditions, medication habits, cooperation with the family doctor, as well as the quality of sleep.

Statistical calculations were performed using *Microsoft Excel* and *SPSS Statistics 18*

Results

Of all respondents 67% are women, while 33% - men. The average age of respondents is 75 years (SD 8.8 years). Most study participants living at home - 72%, and 28% - in social care institution. But 8% of respondents still working. With his family living 72%, while 28% said that

they live alone and rarely come into contact with their relatives. Of all the study participants most have secondary education (55%). Second place in terms of the level of education is secondary professional education (35%), 8% of respondents have a master's degree, but 2% of bachelor's degree.

Complaints about sleep noted 36%, of which 17% stated that in the morning feeling tired and it is difficult to start the day. Regular physical activity have 69% of the respondents (at least 2 times a week), 31% are not physically active, and has a different reasons - and inability (movement disorder) and unwillingness to leave the house.

None of the respondents stated that they are currently taking any medications that are linked to depression treatment, and no one has had a history of depression diagnosis. However, among the respondents are patients who are diagnosed with cognitive impairment and dementia.

As the most common health concerns were mentioned dizziness (24%), and heart rhythm disorders (14%). However, 53% of respondents admitted that lately have not experienced any of the symptoms listed in the questionnaire. The most common chronic diseases related to the cardiovascular system (76% of respondents) and musculoskeletal system (20%). Daily medication are useing the majority of respondents - 86% and the most common are hypertension corrective medication. In contrast, dietary supplements and vitamins used in only 34%.

Loss of concentration themselves noticed in 24% of study participants. But everyday fatigue feels 55% of respondents. Once a month, a family physician visits 26% of the respondents, 35% do so every three months, and the most common purpose of visit is to get a prescriptions. Most of the study participants (39%) goes to the family doctor only acute case of necessity, and it is usually not more than once a year.

During the research, the results show that the respondents average depression level is 4 points (SD 3.3), indicating that those respondents who had such a number of points, there is no clinically significant depression (figure 1).

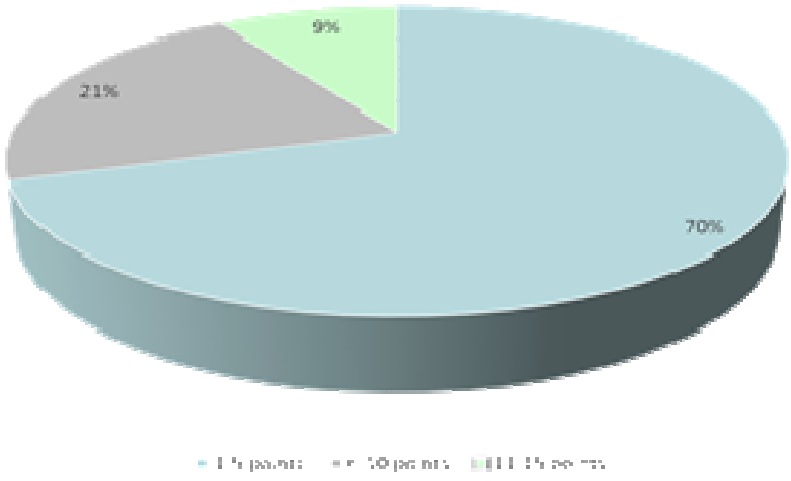

Figure 1. **Results of depression test**

However, as of 5 points, it recommends that patients take the test again after some time. Thus excluding the possibility of the development of a deep depression. It should be noted that during the trial two patients were found to suffer from severe depression and thoughts of suicide. For it was immediately reported to the family doctor, who offered further treatment (figure 2).

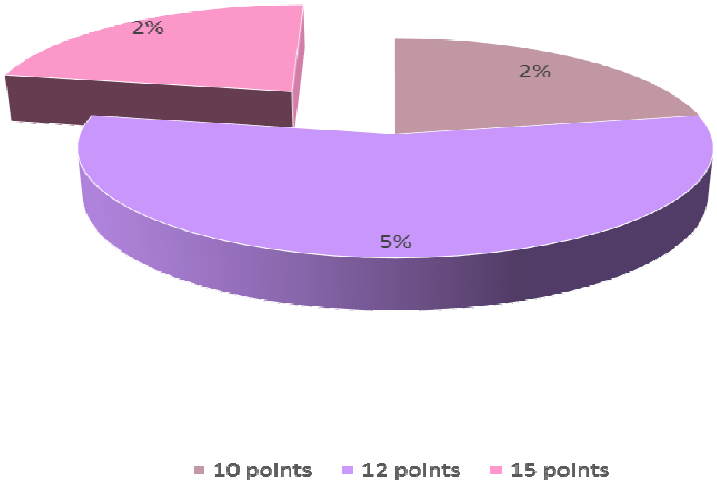

Figure 2. **Clinically significant depression**

Analyzing the data by the Mann-Whitney U test, it can be concluded that in the general population depression is more common among women ($p < 0.05$) (Figure 3).

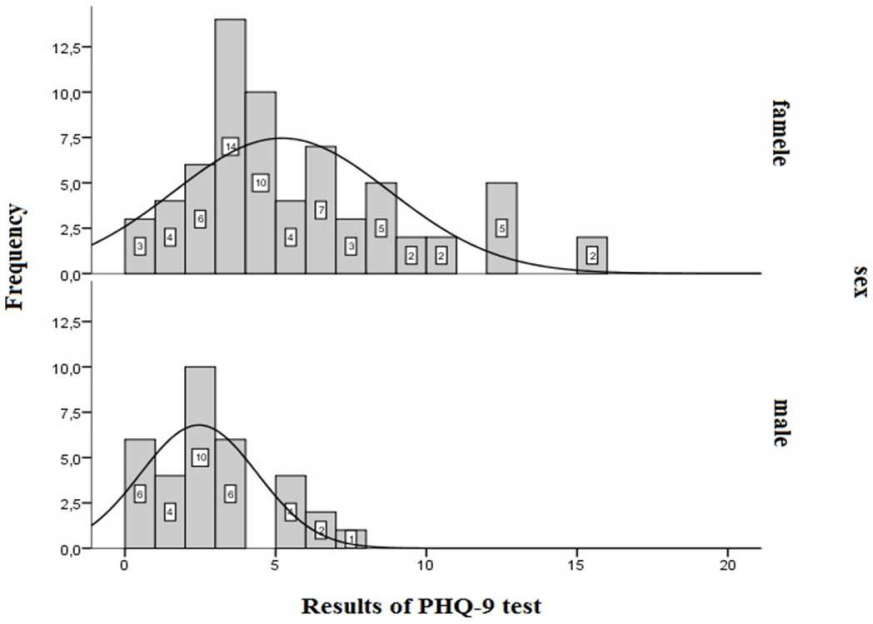

Figure 3. **Depression comparison between men and women**

By contrast, observing hobby association with the development of depression, there is a relationship that people who have any hobby every day (not relevant or linked to physical activity)

shows an average of 2 points lower result depression test (Figure 4). Also, physical activity has a positive effect on the development of depression - those who do not engage in physical activity, depression test scores are an average of 7% worse.

Evaluating the family situation, the data shows that people who live in nursing homes or who meets loved ones rarely, more likely to suffer from depression. As well as the presence of chronic disease increases the level of depression.

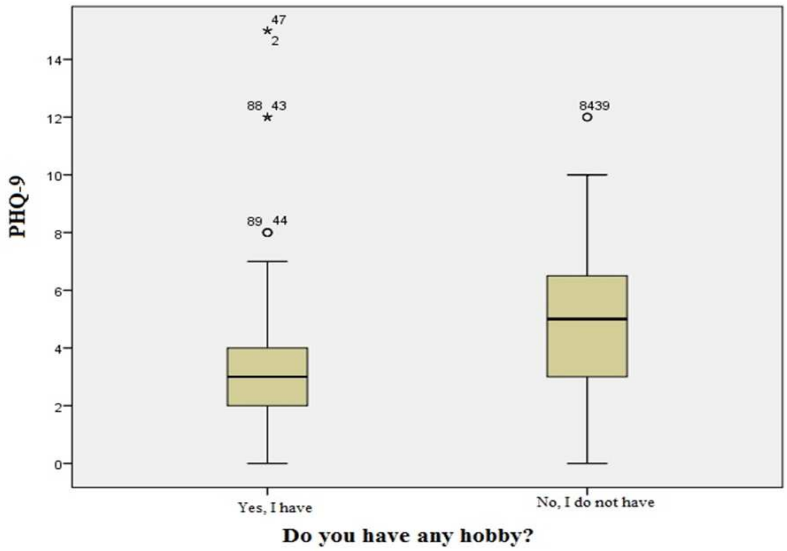

Figure 4. **Hobby impact on the level of depression**

As with mental status examination, the depression rate is higher in those patients who are more likely to visit a family doctor or do not do it at all (except for emergencies).

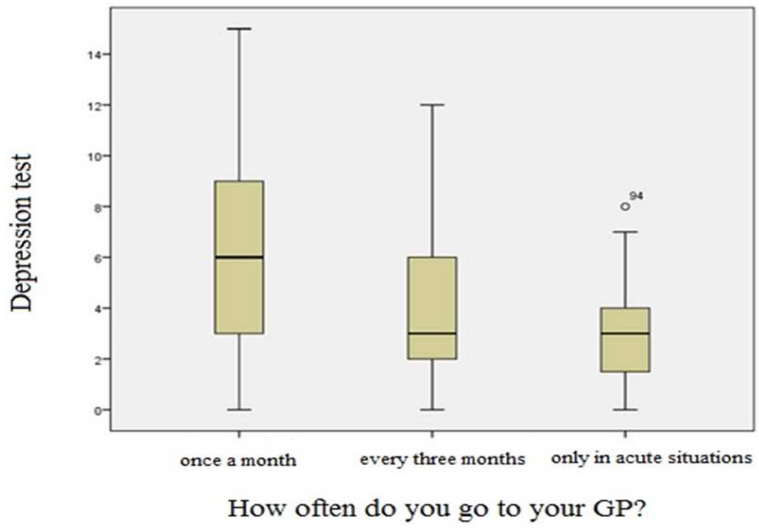

Figure 5. **Depression comparison with the frequency of general practitioner visits**

Discussion

Mitchell T Heflin in his study of geriatric patients indicate that older people have relatively more chronic diseases - 80% of patients have at least one disease and 50% at least two chronic diseases. Chronic conditions often associated with geriatric syndromes such as cognitive function decrease, frequent injuries resulting from falls, incontinence, etc., that affect the quality of life. In turn, the quality of life directly affects patients emotional state, so that the development of depression. Also in this study it appeared in the correlation between chronic disease and mental function loss, and depression levels. It can be concluded that the optimal chronic disease management improves the patient's general condition (Mitchell T Heflin et all., 2017).

Studies recommends to take depression test all patients, regardless of symptomatology. US study on depression, found that, after 85 years of age on average 20% -80% of people suffering from depression. The suicide rate is twice as high among the elderly compared to the general population. However, data on the gender is different. After *Mithchel T Heflin* research data in the US from depression in senior years suffering most Caucasian men. In carrying out this study analysis, statistically significantly more likely from depression are suffering women. Perhaps these results is because Latvian women's life expectancy is 10 years longer than men, which is why depression rates are higher (Heflin et al 2017).

Statistically significant correlations also showed better results in the tests and vitamin use habits. But after other studies not confirmed the relationship between better mental or physical health and vitamin daily use. However, a scientifically are proven that old people have critical of vitamin D and calcium, so these substances need to be used an additional (Beck et al 1997).

Meta-analysis of the relationship of depression with cognitive function loss found that those people who suffered from depression after the age of 60 is much higher risk of developing all types of dementias. However, the study also points out that, perhaps, depression is the first symptom of dementia. This study found a statistically significant correlation between depression and dementia. However, the controversial question of whether depression is an independent disease, or one of the other disease symptoms. To answer this question requires further research (CDC, Depression in Older Adults: Selected Evidence-Based Programs 2009).

Conclusions

1. Summarizing the literature data it can be concluded that aging is an individual process, and each person takes place otherwise. Age is not the main factor that affects the mental condition.
2. The survey results show that on average, respondents cognitive function are unchanged and depression levels are low. However, 9% of the respondents are shown no clinically significant depression, as well as 5% - severe cognitive function deficits.

3. At the same time the study showed that those people who are in nursing homes suffer from depression less often, however it should be noted that the study did not indicate whether these people use any kind of medication to treat symptoms of depression (anti-depressants).

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IMPACT OF CPB TIME DURING VSD CORRECTIVE SURGERY ON EARLY POSTOPERATIVE PERIOD IN CHILDREN

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Abstract

Impact of CPB time during VSD corrective surgery on early postoperative period in children

Key words: *ventricular septal defect (VSD), cardiopulmonary bypass (CPB), extubation, inotropic therapy, postoperative period*

VSD is the most common congenital heart defect that can be treated either conservatively for small defect or surgically by closed or open heart surgery for larger septal defects. CBP use during operation inflicts an additional challenge for the already abnormal circulation.

The aim of the study was to determine whether CPB time is affected by patient's preoperative condition and has significant effect on postoperative period.

In retrospective study data of 85 patients who had undergone VSD corrective open heart surgery until 2 years of age during years 2011.-2016. were obtained and analyzed. The data was collected from electronic database *Andromeda*, ICU database *ICIP,* medical histories and cardio surgery operation registry. The analysis of gathered data was carried out using *IBM SPSS* 22.0.

Analysis showed statistically significant correlation between CPB time and preoperative parameters as defect localization ($p = 0.007$), defect size ($p<0.0005$), cardio-thoracic index CTI value ($p<0.0005$) and pro-BNP value ($p<0.0005$). Results showed correlation between longer CPB time and postoperative parameters as the need for inotropic therapy ($p = 0.02$), use of combined inotropic therapy ($p = 0.007$), the time of inotropic drug use ($p=0.001$), intubation time ($p = 0.001$), time of removal of the pleural drain ($p = 0.011$), total days spent in ICU ($p=0.001$). Correlation between CPB time and rhythm disturbances after CPB discontinuation ($p = 0.015$) was also found. It was found that lower weight is associated with longer period of time spent in ICU ($p<0.0005$).

Conclusions: CPB time depends on defect localization and size. Longer CPB time is associated with the need for inotropic therapy and the possibility that combined inotropic therapy will be used. Longer CPB time is associated with higher chance of arrhythmias in postoperative period. Longer CPB time is associated with more challenging early postoperative period. Children with lower weight are expected to spend longer period of time in ICU.

Kopsavilkums

Mākslīgās asinsrites laika ietekme uz agrīno pēcoperācijas periodu bērniem pēc ķirurģiskas kambaru starpsienas defekta korekcijas

Atslēgas vārdi: *kambaru starpsienas defects (VSD), mākslīgā asinsrite (MA) , ekstubācija, inotropo medikamentu terapija, pēcoperācijas periods*

VSD ir visbiežāk sastopamā iedzimtā sirdskaite bērniem, ko var ārstēt gan konservatīvi, maza defekta gadījumuā, gan ķirurgiski ar vāļēja vai slēgta tipa sirds operācijām, lielāka defekta gadījumā. Mākslīgās asinsrites izmantošana vaļējās sirds operācijās rada papildus slodzi jau tā patoloģiskajai cirkulācijai.

Pētījuma mērķis bija noskaidrot vai MA laiks ietekmē agrīno pēcoperācijas periodu un vai MA laiku ietekmē bērna pirmsoperācijas stāvoklis.

Tika veikts retrospektīvs pētījums, kur tika ievākta un analizēta informācija par 85 bērniem janunākiem par 2 gadiem, kam tikusi veikta VSD slēgšanas operācija izmantojot MA no 2011-2016. gadam. Dati tika ievākti no Bērnu klīniskās universitātes slimnīcas elektroniskās datubāzes Andromeda, intensīvās terapijas nodaļas datubāzes ICIP, medicīnas kartēm un operāciju žurnāliem. Datu apstrāde un analīze tika veikta izmantojot IBM SPSS 22.0.

Datu analīze uzrādīja statistiski nozīmīgu korelāciju starp MA laiku un tādiem preoperatīvajiem parametriem kā defekta lokalizācija ($p = 0.007$), defekta izmērs ($p<0.0005$), kardio – torakālo indeksu KTI ($p<0.0005$) un pro-BNP vērtībām ($p<0.0005$). Rezultāti uzrādīja korelāciju starp lielāku MA laiku un nepieciešamību pēc inotropās terapijas ($p = 0.02$), kombinētas inotropās terapijas pielietošanu ($p = 0.007$), inotropo medikamentu lietošanas laiku ($p=0.001$), ekstubācijas laiku ($p = 0.001$) un pleirālās drenas ekstrakcijas laiku ($p = 0.011$), kā arī laiku, kas pavadīts intensīvās terapijas nodaļā ($p=0.001$). Analīze uzrādīja korelāciju starp MA ilgumu un ritma traucējumiem pēc tās atvienošanas ($p = 0.015$). Kā arī tika noskaidrots, ka zemāks svars pirms operācijas korelē ar ilgāku laiku intensīvās terapijas nodaļā ($p<0.0005$)..

Secinājumi: Mākslīgās asinsrites laiks ir atkarīgs no defekta lokalizācijas un izmēra. Ilgāks MA laiks tiek asociēts ar nepieciešamību pēc inotropās terapijas un vairāku inotropo medikamentu pielietošanu. Ilgāks MA laiks paaugstina risku ritma traucējumiem pēc MA atvienošanas. Ilgāks MA var tikt asociēts ar smagāku agrīno pēcoperācijas periodu. Ir sagaidāms, ka bērni ar mazāku svaru pirms operācijas pavadīs ilgāku laiku intensīvās terapijas nodaļā.

Introduction

Ventricular septal defect (VSD) is the most common cardiac malformation in newborns, accounting for up to 25% of all congenital heart diseases. (Nelson 2011) VSD differs in size, location and the effect on the overall condition of the child. Small VSD's only abnormal finding prior to closing is a loud, harsh holosystolic murmur best heard over the lower left sternal border, and it is frequently accompanied by a thrill. Large VSDs with strong left-to-right shunt and excessive pulmonary blood flow and pulmonary hypertension are responsible for dyspnea, feeding difficulties, poor growth, recurrent pulmonary infections, and cardiac failure in early infancy. Cyanosis is usually absent, but duskiness is sometimes noted during infections or crying. The prominence of the left precordium is common, as are a palpable parasternal lift, a laterally displaced apical impulse and apical thrust, and a systolic thrill. The holosystolic murmur of a large VSD is generally less harsh than that of a small VSD and more blowing in nature because of the absence of a significant pressure gradient across the defect. Defects may occur in any portion of the ventricular septum. (Nelson 2011) Most are perimembranous type, but there is also conoventricular, inlet and muscular VSD. In most cases, it is hard to define one exact type, because the defect may be too large.

In large VSDs, the chest x-ray shows gross cardiomegaly with a prominence of ventricles, the left atrium, and the pulmonary artery. It is described with cardiothoracic index – CTI. CTI < 0,6 is considered to be normal in children until 1 year of age, and CTI < 0,5 in children until 2 years of age and older. Pulmonary vascular markings are increased, and frank pulmonary edema, including pleural effusions, may be present. The electrocardiogram shows biventricular hypertrophy; P waves may be notched or peaked. (Nelson 2011) Rhythm disturbances may be present.

VSD can be treated either conservatively for small defect or surgically by closed or open heart surgery for larger septal defects. A significant number (30-50%) of small defects close spontaneously, most frequently during the 1st 2 yr of life. Some long-term studies of adults with unoperated small VSDs show an increased incidence of arrhythmia, subaortic stenosis, and exercise intolerance. Guidelines from the Council on Cardiovascular Disease in the Young of the American Heart Association state that an isolated, small, hemodynamically insignificant VSD is not an indication for surgery. In infants with a large VSD, management has 2 aims: to get the symptoms of heart failure under control and prevent the development of a pulmonary vascular disease. Transcatheter occlusion closure is most successful in treating muscular VSDs, the rest are managed with open heart surgery with cardiopulmonary bypass during which patch of fabric or pericardium (the normal lining around the outside of the heart) is sewn over the VSD which later is covered by the normal heart lining tissue and becomes a permanent part of the heart. (Nelson 2011)

Cardiopulmonary bypass (CPB) is a procedure to circulate and oxygenate the blood outside the body. CPB is commonly used in heart surgery because of the difficulty of operating on the beating heart. It uses a heart–lung machine to maintain perfusion to other body organs and tissues while the surgeon works in a bloodless surgical field. To provide a dry, motionless, operative area, a cross-clamp is placed across the ascending aorta above the coronary ostia and proximal to the aortic cannula, thus isolating the coronary circulation and preventing blood entering the chambers of the heart. Therefore, techniques of myocardial protection are used to preserve myocardial function and prevent cell death. Cardioplegic techniques for myocardial protection involve the delivery of cardioplegic solution to the myocardium to provide diastolic electromechanical arrest. (Chang 1998) Cardiopulmonary bypass use during operation inflicts an additional challenge for the already abnormal circulation. CPB time is a predictor of immediate postoperative morbidity and mortality.

The results of primary surgical repair are excellent, and complications leading to long-term problems (residual ventricular shunts requiring reoperation or heart block requiring a pacemaker) are rare. After surgical obliteration of the left-to-right shunt, the hyperdynamic heart becomes quiet, cardiac size decreases toward normal, thrills and murmurs are abolished, and pulmonary artery hypertension regresses. The patient's clinical status improves markedly. Most infants begin to thrive, and cardiac medications are no longer required. Catch-up growth occurs in most patients within the next 1-2 yr. The long-term prognosis after surgery is excellent. Patients with a small VSD and those who have undergone surgical closure without residual are considered to be at standard risk for health and life insurance. (Nelson 2011)

Material and Methods

In retrospective study data of 85 patients who had undergone VSD corrective open heart surgery using cardiopulmonary bypass until 2 years of age during years 2011.-2016. were obtained and analyzed. The exclusion criteria were the age and other congenital heart diseases, mainly cyanotic type. We also included children whose VSD was combined with atrial septal defect and patent ductus arteriosus, whereas it does not have a significant impact on cardiopulmonary bypass time. The data was collected from Riga Children Clinical university hospitals electronic database *Andromeda,* ICU database *ICIP*, medical histories and cardio surgery operation registry. The analysis of gathered data was carried out using *IBM SPSS* 22.0.

Results

Carrying out descriptive data analysis we found that 54% (46) of the children were male and 46% (39) female with mean age of 10±4 months with the most frequent age being 7 months. The average size of VSD was 8.7 ± 2.1mm with variations from 4 mm to up to 15 mm. 50.6% of the defect was with perimembranous, 31.8% mixed, 12.9% conoventricular, 4.7% with muscular localization. Isolated VSD was found in 78.8% of the patients; 14.1% had VSD + ASD, 4.7%

VSD + PDA and 2.4% VSD + ASD + PDA. Preoperatively 52% had increased CTI of 0.62 ± 0.05 with reference values being CTI < 0.6 until 1 year of age and CTI< 0.5 till 2 years of age and older. 82,3% had increased pro-BNP of 1283 ± 1425pg/mL with reference interval pro-BNP < 125 pg/mL. 74.7% of the patients had a lower weight in average by -1.7 SD. At least 1 chronicle illness was found in 38,8% of patients, with most common being trisomy of 21. chromosome (5.9%). Rhythm disturbances were found in 48% of the patients preoperatively.

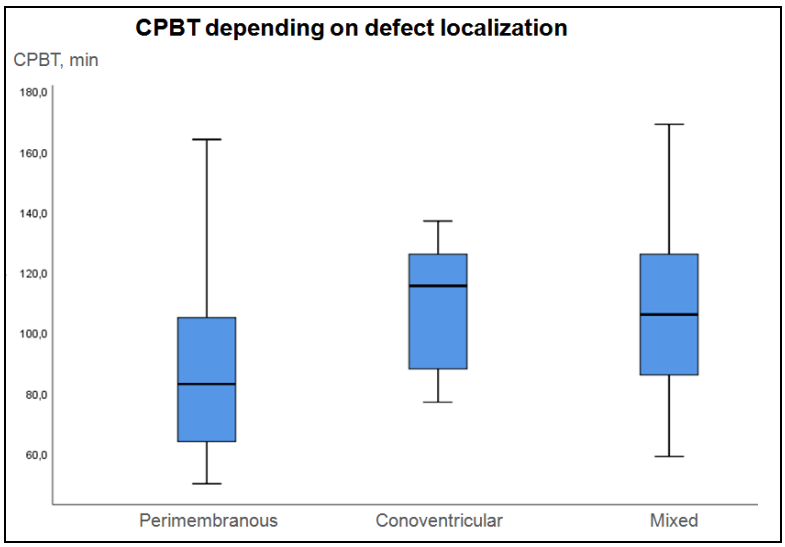
Average CPB time was 98 ± 30 min. All of the patient's myocardial protection was carried out using Martindale cardioplegic solution. 18.8% of the patients developed rhythm disturbances after discontinuation of the CPB and only 1 patient developed bleeding. Rhythm disturbances were with a tendency to a slower rhythm – bradycardia, atrioventricular blockage in different stages and sinus node weakness. As a result of the operation, 24.7% of patients hearts developed trivial tricuspid valve insufficiency, which remained in the postoperative period in 17.6% of the patients. During the intraoperative transesophageal echocardiogram, a hemodynamically insignificant residual body was found in 16% of the patients and hemodynamically significant in only 1 patient who underwent instant revision surgery.

In average 4.5 ± 2.2 days were spent in ICU. Postoperative supportive inotropic therapy was used in 86,4% of patients – 70.3% received Milrinone lactate and 16.1% - Milrinone lactate with Adrenaline. The average time of Milrinone use was 2.6 ± 1.5days. Mean duration of intubation was 28.0 ± 24.7 hours. 65% of the patients were extubated in the first 24h after surgery. The mean time of pleural drainage was 3.8 ± 1.6 days post operation.

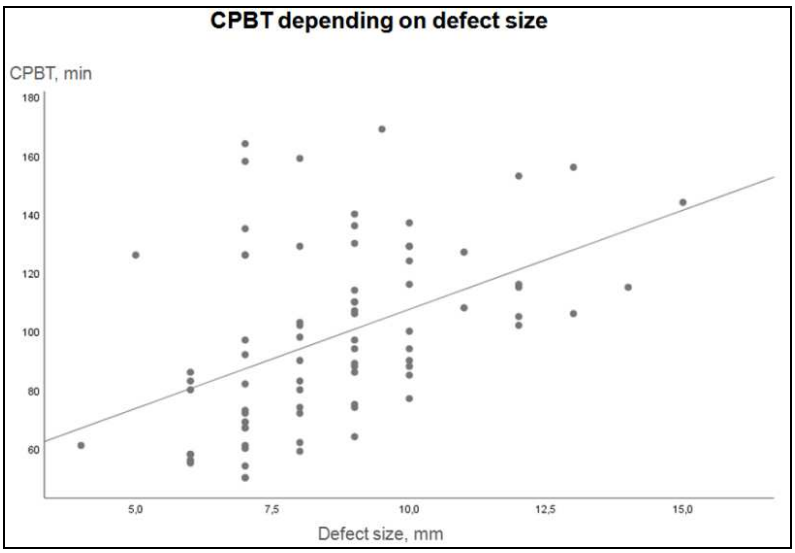
55.3% (47) of patients developed postoperative complications - rhythm disorders occurred in 44.6% of patients, tricuspid valve insufficiency in 32%, infection and atelectasis in 12.7%, neurological complications in 4.7% and acute kidney failure in 3.5% of patients. During postoperative control echocardiogram, hemodynamically insignificant residual defect was found in 29.4% of the patients.

Analysis showed statistically significant correlation between CPB time and preoperative parameters as defect localization ($p = 0.007$) *Picture 1*, defect size ($p<0.0005$) *Picture 2*, CTI value ($p<0.0005$) and pro-BNP value ($p<0.0005$).

Results showed correlation between longer CPB time and postoperative parameters as the need for inotropic therapy ($p=0.02$) *Picture 3*, use of combined inotropic therapy ($p=0.007$) *Picture 4*, the time of inotropic drug use ($p=0.001$) *Picture 5*, intubation time ($p = 0.001$) *Picture 6*, time of removal of the pleural drain ($p=0.011$) *Picture 7*, total days spent in ICU ($p=0.001$) *Picture 8.*



Picture 1.



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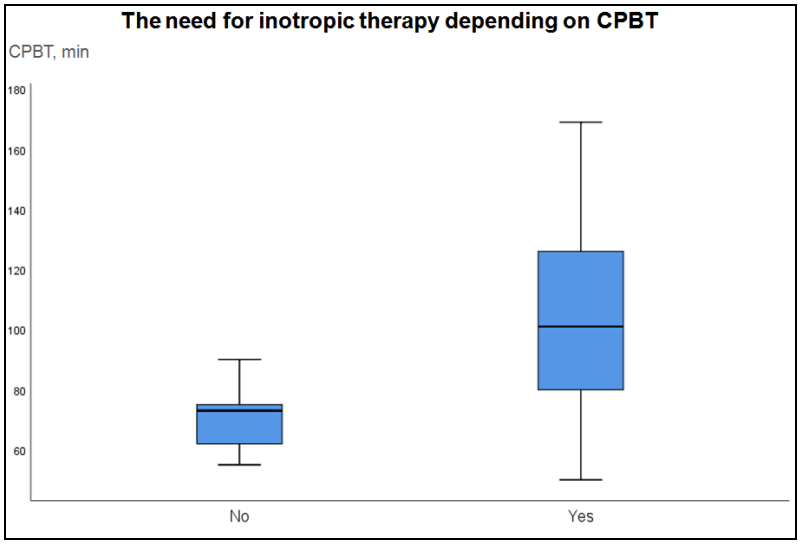

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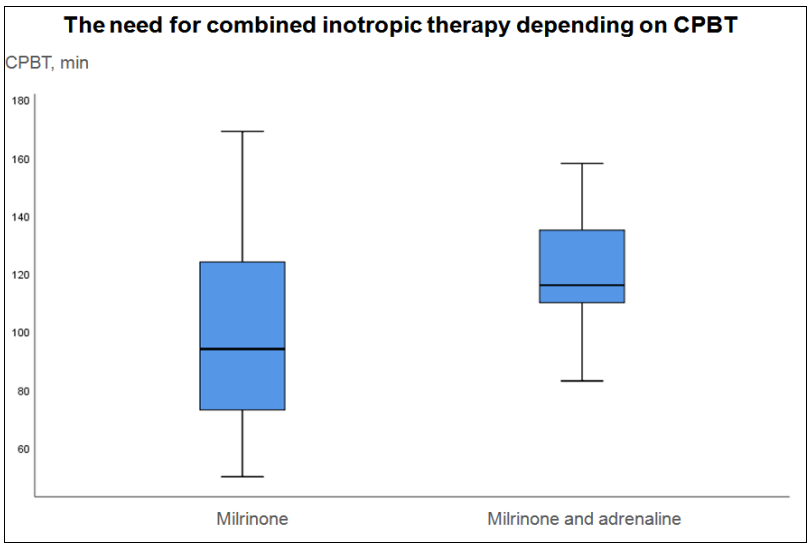

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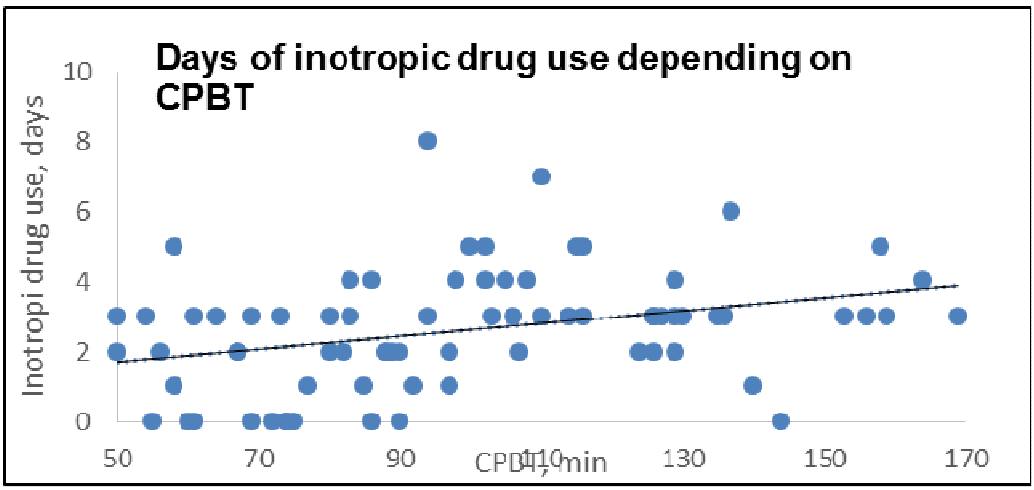

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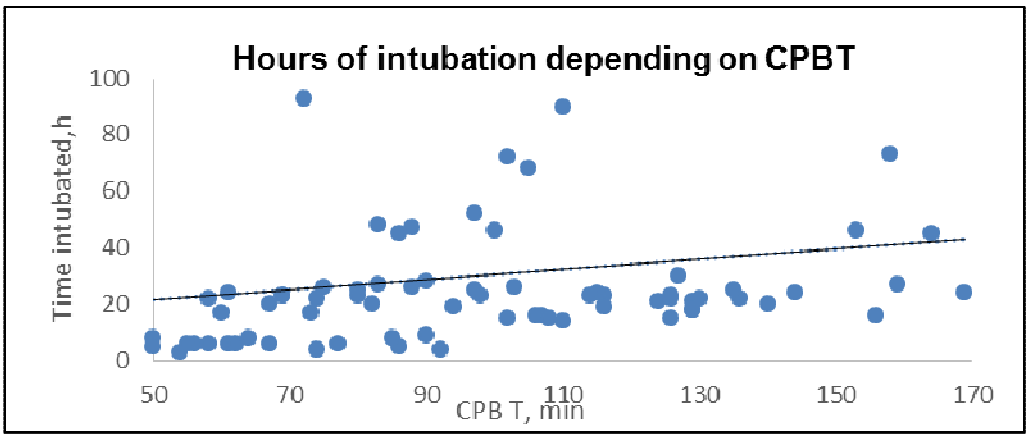

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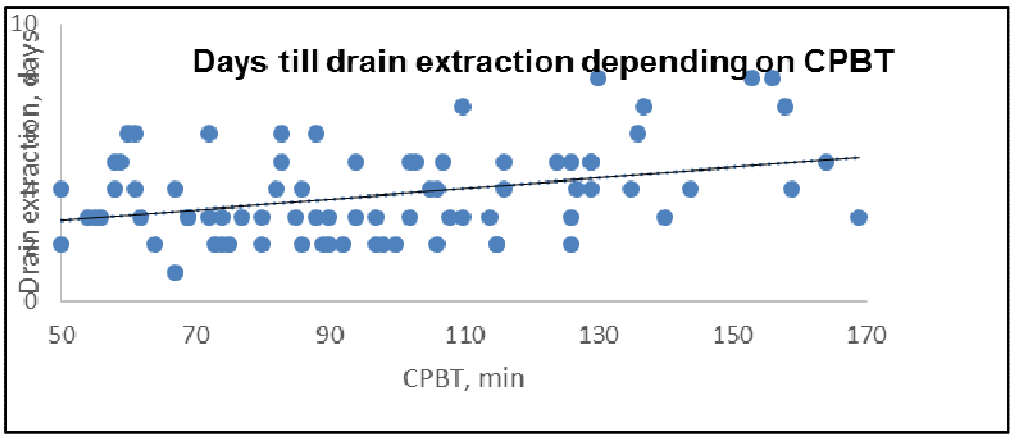
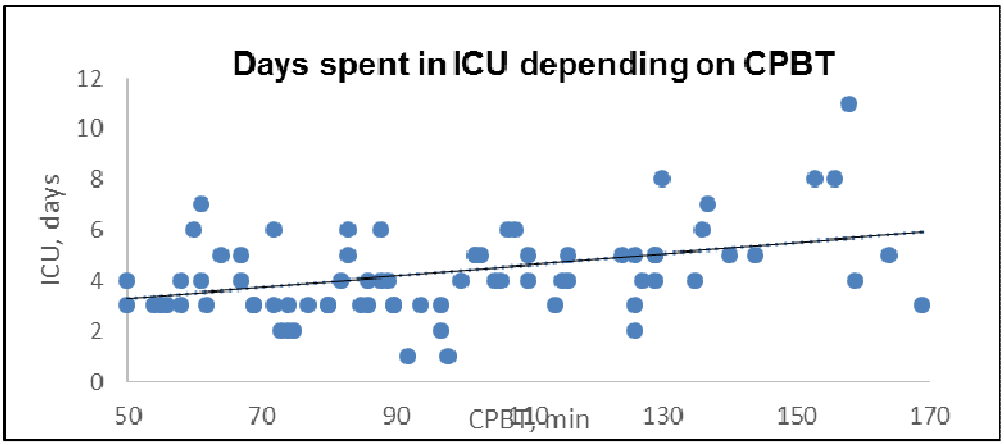
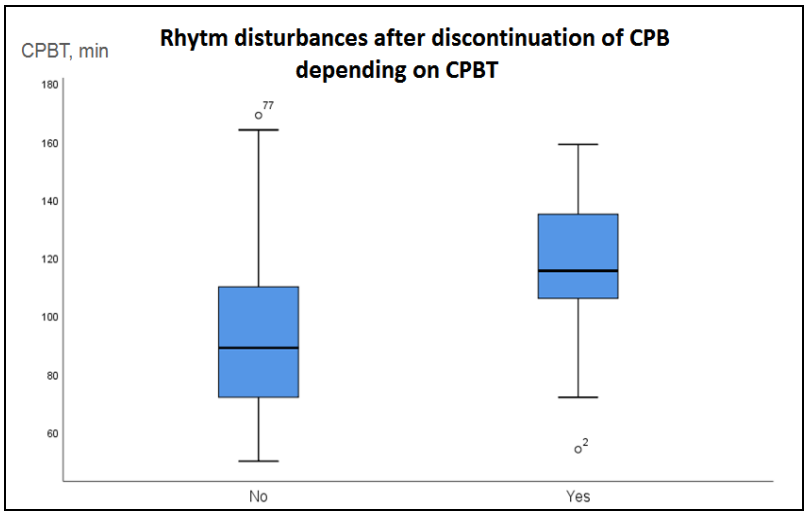


Picture 7.



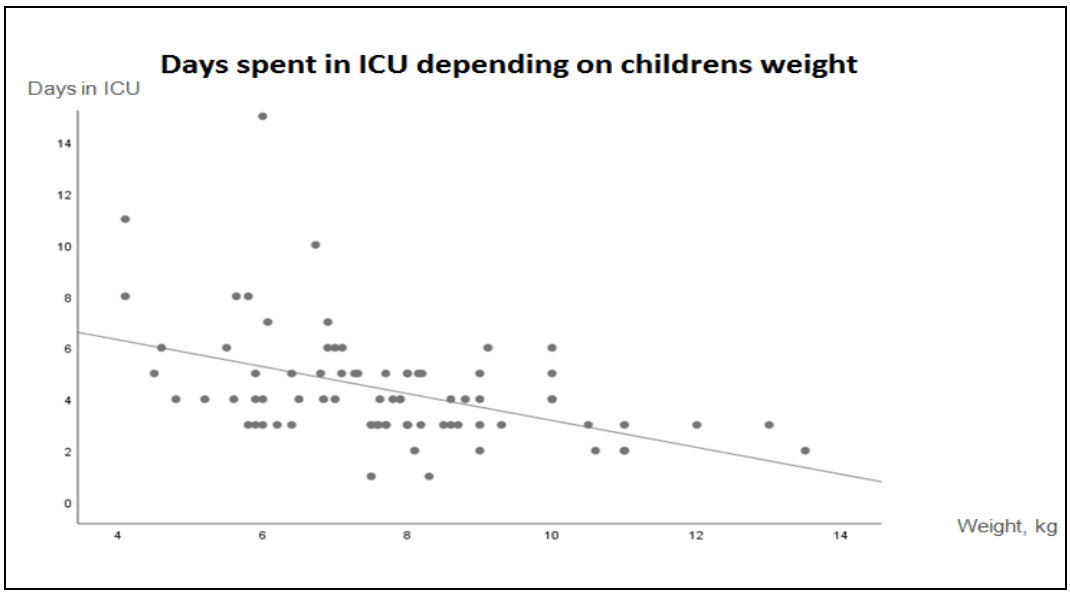
Picture 8.

Correlation between CPB time and rhythm disturbances after CPB discontinuation (p = 0.015) was also found *Picture 9*.



Picture 9.

It was found that lower weight is associated with a longer period of time spent in ICU ($p<0.0005$) *Picture 10*.



Picture 10.

Discussion

Given the fact that our research focused on specific parameters there are no researches on our topic and we cannot compare our results to others. Referring to our results we can say that they are plausible and possible.

Defect localization *Picture 1* and size *Picture 2* can be the reason for longer cardiopulmonary bypass time given that bigger defects take a longer time to be sewn closed and that defects with difficult access will take a longer time to be repaired. Relating to the correlation between CPB time and CTI and pro-BNP we can say that it was also found that bigger CTI and higher pro-BNP correlates with lower weight and bigger defect size. So we can't unequivocally say that those two parameters are the reason for longer bypass time.

Referring to the correlations between longer CPB time and need for inotropic therapy *Picture 3*, use of combined inotropic therapy *Picture 4*, the time of inotropic drug use *Picture 5,* these results can be considered plausible as well, given that there have been many researches on CPB time influence on metabolic processes in myocardium and the whole organism. Given that cross-clamping causes ischemia in myocardium, it is consequential that longer cross-clamping during bypass will result in weaker myocardial function, lesser ejection fraction and pulmonary complications therefore coherence with intubation time *Picture 6*, time of removal of the pleural drain *Picture 7* and total days spent in ICU *Picture 8* also can be explained by physiological processes arising from myocardial ischemia.Correlation between CPB time and rhythm disturbances after CPB discontinuation *Picture 9* also can be seen as consequence of myocardial ischemia, but defect localization and size also can be seen as a cause, because of the possible conduction system damage during repair.

The fact that it was found that lower weight is associated with a longer period of time spent in ICU *Picture 10* can be related to the fact that being lower weight children organism is already in a lack of nutrients, which are crucial for regenerative and healing processes in the organism. Referring to other researches it is known that lower weight prior to cardiac surgery is associated with higher morbidity and mortality.

55.3% (47) of patients developed postoperative complications - rhythm disorders occurred in 44.6% of patients, tricuspid valve insufficiency in 32%, infection and atelectasis in 12.7%, neurological complications in 4.7% and acute kidney failure in 3.5% of patients. There have been many researches corresponding to postoperative complications after cardiopulmonary bypass. Taking in consideration the results of these researches and overall principle in postoperative intensive care our results can be considered believable.

Conclusions

1. CPB time depends on defect localization and size.
2. Longer CPB time is associated with the need for inotropic therapy and the possibility that combined inotropic therapy will be used.
3. Longer CPB time is associated with higher chance of arrhythmias in the postoperative period.
4. Longer CPB time is associated with the more challenging early postoperative period.
5. Children with lower weight are expected to spend a longer period of time in ICU.
6. There is a strong correlation between child’s weight, the size of the defect, CTI and pro-BNP and these parameters should be viewed as a unit while evaluating their effect on CPB time.

Acknowledgement

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HOW STAFF MEMBERS DEAL WITH CASES OF STILLBIRTH REGARDING THEIR AGE AND EXPERIENCE

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Abstract
Key words: *stillbirth, staff, experience*
Stillbirth is an adverse pregnancy outcome, defined by fetal death prenatally. Both families and staff go through many challenges dealing with stillbirth. Young staff members sometimes have to work with these cases without any experience or insufficient experience, which could be emotionally challenging. Experience helps staff to provide support and information for parents. The aim of the research was to find out how staff members deal with stillbirth cases regarding their age or experience. Research method was surveying midwives and obstetricians in maternity wards. Surveying was done at *Riga Maternity Hospital* and *Pauls Stradins Clinical University Hospital Perinatal Care Center* in January 2017. Survey consisted of questions about experiences working with stillbirth cases. In total 106 respondents completed the survey. 66% (N=70) were midwives and 34% (N=36) obstetricians. Regarding age there were 26.4% (N=28) respondents below the age of 30, there were 35.8% (N=38) respondents with work experience less than 10 years and 24.5% (N=26) staff members were only in learning process. Results showed, that there are differences in the way staff members deal with cases of stillbirth regarding their age and experience. Younger and less experienced staff tends to have more confusion, middle aged and those with experience 10-30 y. have their working abilities affected, but those older than 50 y. feel that these cases are very time and energy consuming.

Kopsavilkums
Atslēgvārdi: *nedzīvi dzimis, personāls, vecums*
Nedzīvi dzimis auglis ir nelabvēlīgs grūtniecības iznākums, kas tiek definēts ar augļa nāvi pēc 22.gestācijas nedēļas un šī augļa dzemdībām. Šajos gadījumos gan ģimenei, gan personālam ir jāsaskaras ar daudzām grūtībām. Gados jauniem personāla locekļiem var nākties strādāt ar šādām pacientēm bez pieredzes, kas var būt liels emocionāls izaicinājums. Pieredze palīdz personālam nodrošināt atbalstu un sniegt atbilstošu informāciju vecākiem. Pētījuma mērķis bija noskaidrot, kā personāls tiek galā ar šādiem gadījumiem darbā, atkarībā no personāla vecuma un stāža. Kā instruments tika izmantota oriģināli veidota aptauja. Intervēšana notika Rīgas Dzemdību nama un Paula Stradiņa Klīniskās universitātes Perinatālās aprūpes centra ārstiem-dzemdību speciālistiem un vecmātēm. Aptauja sastāvēja no dažādiem jautājumiem par pieredzi, strādājot ar pacientēm antenatāli/intranatāli bojā gājuša augļa gadījumos. 106 respondenti aizpildīja anketas. 66% (n=70) bija vecmātes un 34% (36) ārsti-dzemdību speciālisti. Vecuma grupā zem 30 g.v. bija 26,4% (n=28) respondenti, 35,8% (n=38) respondentiem darba stāžs bija mazāk par 10 gadiem un 24,5% (n=26) respondenti bija tikai mācību procesā (ārsti-rezidenti vai vecmātes studiju procesā). Apkopojot rezultātus varēja secināt, ka ir atšķirība starp to, kā personāls tiek galā ar pacienšu aprūpi šādos gadījumos atkarībā no personāla vecuma un darba stāža. Jaunākam un mazāk pieredzējušam personālam biežāk jāsastopas ar apjukumu, vidējā vecuma un pieredzes grupā (30-50 g.v un 10-30g. pieredze) biežāk atzīmēja ietekmētas darbaspējas un vecumā virs 50 g. biežāk atzīmēja, ka šie gadījuma prasa ļoti daudz laika un enerģijas.

Introduction

Stillbirth is an adverse pregnancy outcome, defined by fetal death antepartum or intrapartum. (Da Silva et al. 2016; WHO 2006) It is associated with great sadness and distress not only for parents, but also for the health professionals, especially midwives. In case of stillbirth it is essential to have bereavement care. Health care professionals should respect the individuality and diversity of parents' grief. Grieving parents want staff to show sensitivity and empathy, validate the emotions of parents, provide clear information. Supportive bereavement care can help parents deal with their loss. (Homer et al. 2016; Peters et al. 2015)

Staff members have reported emotional, knowledge and system-based barriers to provide effective care, they distance themselves from parents and focus on guidelines or tasks as coping strategies. (Ellis et al. 2016) Healthcare professionals who felt that they have received adequate training reported less guilt and fear of litigation. The negative effects of stillbirth on professionals should be addressed by education, trainings provision of formal and informal support during and after stillbirth. (Heazell et al. 2016) Bereavement training should be included in midwifery education. But the problem is that students are often protected from caring for parents' who have had stillbirth because of inexperience. Students are unable to give bereavement care because they have little preparation for stillbirth. (Homer et al. 2016) Experience and knowledge may help in bereavement care, but also can increase the emotional burden. Experienced staff feel they have more to offer parents and can find caring for bereaved parents rewarding, also they may feel guilt and depression following a diagnosis of stillbirth. (Ellis et al. 2016)

Aim of study was to find out how staff members deal with stillbirth cases regarding their age or experience.

Materials and methods

Study design was a descriptive cross-sectional study. Study population consisted of 106 midwives and obstetricians in Maternity wards. Surveying was done at *Riga Maternity Hospital* and *Pauls Stradins Clinical University Hospital Perinatal Care Center* in January 2017. Inclusion criteria were following - participant should be obstetrician or midwife and currently working at related Maternity ward and had experience working with cases of stillbirth. Exclusion criteria also were two- refusal to participate and incomplete questionnaire.

Survey was done by originally created study protocol, based on previous studies. The protocol consisted of demographic data (age, gender, profession, sertified specialist/in learning process, working experience in healthcare in years). The protocol included questions about experiences working with stillbirth cases. All of the questions were aimed to collect subjective, self-assessed experience while working with stillbirth cases. The questions were stated: "How would you describe working with patients in cases of stillbirth?" (we offered choices: does not differ from other cases; confusion and bewilderment; a huge challenge emotionally and professionally; requires more time and energy, and the chance to write their own opinion and the ability to choose multiple choices); "Do you encounter any of these emotional factors when working with these patients?" (we offered our choices: stress; confusion, tiredness, feelings of inferiority and the chance to write their own opinion and to choose multiple choices); "Does working with these patients affect your ability to work with other patients and executing other work duties?"; "Does working with these patients affect you after work?" It also included questions about self-assessed knowledge and comfort levels when working with these patients and knowledge about grief that were not the aim of this study.

All the data was analyzed using Statistical IBM SPSS version 22. Descriptive statistics methods used were frequency, percentage. Cross tabulations were used to detect significances in variables between different age or experience groups. Statistically significant differences between age or experience groups were found using Adjusted residual (bigger than 1.9 and smaller than -1.9). Significance was detected using Chi-square, Fishers' Exact test and linear correlation test with values <0.05.

Results

Of all respondents women accounted for 97.2% (n=103). Staff members from Riga Maternity Hospital were 72.6% (n=77) and 27.4% (n=29) were from Pauls Stradins Clinical University Hospital Perinatal Care Center. 33% (n=34) were doctors and 67% (n=72) were midwives. Regarding age, 26.7% were younger than 30 years, 39% were in age group 30-50 years and 34.3% were older than 50 years. Regarding their work experience in years, 38% had less than 10-year experience, 36% had 10-30 y. experience and 26% had over 30 y. experience working in healthcare. 24.5% (n=26) were still in studying process (interns or students).

Respondents were asked about various psychoemotional factors they encounter when working with patients in cases of stillbirth. 52.4%(n=54) mentioned stress, 31.1%(n=32) mentioned confusion, 25.4%(n=26) mentioned other factors (empathy, pain, depression, fear, powerlessness, feeling of unfairness, wanting to ease the pain, to help). 16.5%(n=17) answered that they do not encounter any of these factors but 9.7%(n=10) agreed that they feel inferiority. 60% (15 of 25) of members younger than 30 years expressed confusion when working with these patients, it was statistically significant more than in other age groups (p=0.002). Results were similar regarding work experience in years, 51.4% (18 of 35) of those with experience less than 10 years expressed confusion more than their more experienced colleagues (p=0.002); and regarding certification: 60.9% (14 of 23) staff members who were still learning (interns, midwifery students) expressed confusion more than those, who were certified: only 22.8% (18 of 79) of them expressed confusion (p=0.001).

They were asked, how they would describe their experience with patients in cases of stillbirth: 70.6%(n=72) mentioned that these cases requires more time and energy, 47.1%(n=48) mentioned that it is huge challenge professionally and emotionally. 15.7%(n=16) agreed that they feel bewildered and confused, and 2.9%(n=3) said these cases do not differ from other cases. There were no statistically significant differences between age or experience groups when describing the experience.

When asked about their ability to work with other patients and executing other work duties, 68.3% (28 of 41) of members 30-50 y.o. said their ability to work is affected but 66.7% (24 of 36) members older than 50 y. said their ability to work is not affected when working with these patients

(p=0.006). Addressing the same question regarding work experience, 69.4% (25 of 36) members with work experience 10-30 y. expressed affected working abilities, whereas 73.1% (19 of 26) staff members with more than 30 y. experienced said their working abilities are not affected (p=0.003); regarding certification 73.1% (19 of 26) of members who were still learning expressed affected working abilities when dealing with patients in cases of stillbirth.

There was a linear by linear association between age of staff members and amount of members who agreed, that working with these cases takes more time and energy. The association was positive – older members more frequently feel that these cases take more time and energy. (p=0.04). 56% of members aged <30 y.o. agreed to before mentioned statement, but in the age group >50 y.o. there were 80.6% of members who agreed to this statement.

Discussion

The major statistical findings indicate that there are differences in the way younger-older or less-more experienced staff members deal with cases of stillbirth. The most prevalent finding in younger and less experienced staff members was confusion. Confusion about what to say, relating to the education and preparation students had for these experiences and emotional responses as 'Crying like a fool,' describing their feelings and the support they did or did not receive have been described by Begley, 2003. Young specialists should be able to receive support, based on their confusion when working with these patients. Receiving support is a major problem, there is evidence about very low quality support: none of the students sourced professional support readily available to them through their university. (McKenna 2011)

Specialists who are more experienced are more likely to provide effective bereavement care, but are more likely to be emotionally affected. (Curtis 2000; Farrow et al. 2013; McKenna et al. 2011) Specialists with great experience are more likely to be comfortable to provide care for stillbirth patients and other patients as well. Developing significant work experience, specialists report such situations as rewarding and feeling they had something substantial to offer. (McKenna 2011) Midwives refer to experience as a valuable commodity and a resource that should be used to ease a woman's distress when she gives birth to a stillborn baby. (Curtis 2003) Our findings state that professionals with work experience 10-30 years are more likely to have affected working abilities, which is a similar finding to the responding literature, but majority of specialists with work experience above 30 years expressed that their working abilities are not affected. This could be because specialists with great experience feel comfortable providing care and can manage cases of stillbirth more easily.

However, our results showed that older staff members express more time and energy consumption. Age and experience correlates in our study (p<0.0005) so we could say although

experienced and older members do not feel as confused or affected as their younger colleagues, they do have challenges that are related with time and energy consumption.

Experience helps staff to provide intermittent care and to care for other patients equally, but only when substantial amount of experience has been acquired. Specialists with under 30 years of experience still feel their working abilities with other patients are affected. This indicates emotional difficulties still reach professionals who have had a decent amount of experience. Older and experienced staff members also feel that these cases are very energy consuming. Young and inexperienced staff members have to deal with confusion and should be supported by their colleagues or support providers, such as psychologists or psychotherapists to help them overcome difficulties when working with these patients. Education process should involve lessons about how to deal with stillbirth cases.

Conclusions

Healthcare specialists who work with patients in cases of stillbirth have some differences in the way they deal with these patients regarding age, work experience and certification. Overall there are many challenges for all staff members, but some factors are more characteristic for subgroups. Staff members who are younger and less experienced (<10 y.exp. and <30 y.o.) have to deal with confusion more than others. Middle aged and experienced (10-30 y.exp. and 30-50 y.o.) specialists feel that their working abilities are affected. Specialists with greater experience and older staff members (>30 y.exp. and >50 y.o.) are more likely to not have their working abilities with other patients affected, but still working with these cases can be time and energy consuming for these staff members.

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FEMALE SEXUAL DYSFUNCTION IN ASSOCIATION WITH DIABETES MELLITUS

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Abstract

Female sexual dysfunction in association with diabetes mellitus

Key words: *female sexual dysfunction, diabetes mellitus, female sexual function index, sexual desire, sexual satisfaction*

Introduction: Sexual dysfunction (SD) in up to 60% is one of the most significant complications in women with diabetes mellitus (DM). According to latest studies, female sexual dysfunction (FSD) with DM is associated with many complications.

Aim: To explore the prevalence and associated complications of FSD in women with DM.

Materials and methods: The study was conducted among women with DM, who completed a questionnaire *Female Sexual Function Index (FSFI).*

Results: The study included 100 women with mean age of 53, 82 (±14, 33) years. 75 % of all patients had type 2 DM, 19 % - type 1 and 6 % had other type of DM. According to the FSFI scores, 71 % of the women had SD. The highest rated were arousal (2, 97 p), pain(2,84 p) and satisfaction(2,82 p). The lowest score was evaluated for sexual desire (1, 61 p). Lubrication and ability to reach orgasm scored 2, 75 points.

Conclusion: DM is an important cause of FSD. Result of this study of 71% female DM patients having SD is high comparing to other available data. Although women have SD, the satisfaction with their sexlife and sexual arousal is also rated as one of the highest criteria. The lowest rated section was sexual desire. This conclusion raises a discussion about psychological aspects of DM that are involved in the development of FSD.

Kopsavilkums

Sieviešu seksuālās disfunkcijas saistība ar cukura diabētu

Atslēgvārdi: *sieviešu seksuālā disfunkcija, cukura diabēts, sieviešu seksuālās funkcijas indekss, seksuālā vēlme, seksuālais apmierinājums*

Ievads: Sieviešu seksuālā disfunkcija (SSD) ir viena no nozīmīgākajām cukura diabēta (CD) komplikācijām, kas sastopama līdz pat 60 % sieviešu. Saskaņā ar jaunākajiem pētījumiem, SSD asociējas ar daudzām komplikācijām.

Mērķis: Noteikt SSD prevalenci un tās saistītās komplikācijas sievietēm ar CD.

Materiāli un metodes: Pētījums tika veikts starp sievietēm ar CD, aizpildot *Female Sexual Function Index (FSFI)* aptaujas anketu.

Rezultāti: Pētījums iekļāva 100 sievietes ar vidējo vecumu 53, 82 (±14,33) gadi. 75 % pacientu bija 2.tipa CD, 19 % bija pirmā tipa CD un 6 % bija cita tipa CD. Atsaucoties uz FSFI 71 % sieviešu bija SSD. No visām *FSFI* anketas sekcijām visaugstāk novērtētais bija uzbudinājums (2, 97 punkti), sāpju līmenis (2, 84 punkti) un apmierinājums (2,82 punkti). Viszemākais punktu skaits bija seksuālajai vēmei (1, 61 punkti). Lubrkācija un spēja sasniegt orgasm bija novērtēta ar 2, 75 punktiem.

Secinājumi: CD ir nopietns SSD iemesls. Šī pētījuma rezultāts ar 71 % SSD CD pacientēm ir augsts salīdzinot ar citiem pieejamiem datiem. Lai gan sievietēm ir seksuālā disfunkcija, seksuālais apmierinājums un seksuālais uzbudinājums arī bija vienas no visaugstāk novērtētajām sekcijām. Viszemāk novērtētā sekcija ar nozīmīgu atšķirību no citām sekcijām, bija tieši seksuālā vēlme.

Introduction

Female sexuality reflects the reproductive organs of an individual and his/her properties as a human as well and, involves an individual's biological structure, learning experiences, attitudes, values and behaviors. The problems have occurred by a women in relation with her sexual life are influenced by her living conditions. But from the other side any change in sexual health affects an individual's life and general health (Rubin 2004: 119–125; Phillips 2009: 353–357).

Risk factors related with sexual dysfunction in women are: aging, diabetes mellitus, heart and blood vessel disorders, hypertension, urogenital disorders, psychological disorders, cancer and other chronic disorders (Doruk 2005: 1-6). Sexual dysfunction in women is a significant problem with a

very high percentage and, it affects the whole life of a women (Lutfey 2008: 514–527; Shifren 2008: 970–978; Ogbera 2009). According to Sexual Dysfunction Association, the percentage of sexual dysfunction in women increases with the age. Basically it affects one half of the women (Heiman 2014).

Approximately 285 million people are affected with diabetes mellitus worldwide. By the year 2030, 439 million people are expected to suffer from the disease. In addition, by 2025 the largest increase in diabetes mellitus prevalence will occur in the developing countries (Shaw 2009). Diabetes mellitus is known to cause different medical, psychological and sexual complications (Enzlin 2002). Sexual dysfunction can point on the beginning of diabetes mellitus (Miočić 2008: 35-42).

The causes of sexual dysfunction in women can be divided into psychological and organic. Between non-gynecological organic etiologies, hormonal abnormalities, autonomic neuropathies (parasympathetic nervous system releases endothelial nitric oxide synthase, ENOS) as complications of diabetes mellitus, along with vascular insufficiency due to atherosclerosis are of most importance (Miočić 2008: 35-42; Kendirci 2007). Somatic sensory system is affected by diabetes mellitus and introits vagina, labia minor and clitoris are the most deteriorated parts of genitalia in diabetic women. Although sexual complications are not present in all patients with diabetes mellitus, medications can be useful and improve blood flow in clitoris (Erol 2003; Caruso 2006) It is claimed that neuropathies, vascular impairments and psychological discomforts are the most recognized factors among the etiologies of sexual dysfunction in women with diabetes mellitus (Amaral 2008).

Materials and methods

The study included those women, who agreed to participate in the study, were over the age of 18, had no issues with reading, understanding and answering questions and had diabetes mellitus. An approval was obtained from the Riga Stradiņš University ethical committee to conduct the study.

Evaluation criteria were sexual desire, arousal, lubrication, ability to reach orgasm, sexual satisfaction and pain level. Each section consists of 5 points. Overall assessment 26,55 points and less of Female Sexual Function Index indicates sexual dysfunction. Data collection and statistical analysis was performed using SPSS 22.0 and Excel 2010 programs. The *Female Sexual Function Index* is a 19-item self-reported questionnaire for measuring sexual functioning in women. It was developed for purpose of assess sexual functioning. The questionnaire evaluate six aspects of sexual functions. These aspects are: desire, sexual arousal, lubrication, orgasm, satisfaction, pain. The *Female Sexual Function Index* is used in many clinical trials. However when using this

questionnaire the doctor needs to be careful and understand that it is not a measure of sexual experience, knowledge, attitudes, or interpersonal functioning in women.

Every respondent filled out an anonymous questionnaire. For every question there was one answer possible.

Results

In the study were included 100 women. All of the participants were aged between 24 and 75 years. The mean age of the women, who participated in the study, was 53,82 (±14,33) years. 75% (n= 75) of patients had type 2 diabetes, 19 % (n= 19) had type 1 diabetes and 6 % had other type of diabetes for example gestational diabetes. Most of participants (32% n= 32) were suffering from diabetes less than 5 years. 29 % (n= 29) had disease between 5 and 10 years, 23 % (n= 23) had between 10 and 20 years, 11 % (n=11) had it between 20 and 30 years and 5 % of participants (n=5) were suffering from diabetes more than 30 years. The average duration of their disease were between 10 and 20 years. 67 % (n= 67) of participants were in relationship but 33 % (n= 33) of them were not. According to the total FSFI scores, 71 % (n= 71) of the women had a total score less or similar to 26,55 what means that it is sexual dysfunction. Statistical tests showed that there is statistically significant correlation ($p< 0,05$) between sexual dysfunction and age.

Discussion

The fact that diabetes mellitus is an important cause of FSD and that the level of FSD for diabetes patients is high, has been already established by other researchers (Shifren 2008: 970–978). The rate of FSD among women with DM in different studies varies greatly - there are results that claim that only 26,4% of female diabetes patients have FSD (Rawa 2010: 179–185). But it is important to distinguish the patients with Type 1 and Type 2, because the pathogenetic patterns, that also influence the development of FSD, are different in these two types of the disease (Fig.1). Compared to Type 1 patients, the women with Type 2 DM have higher rates of FSD - studies, that investigate women with Type 2 DM, have found, that the FSD rate is from 49% (Taloyan 2010: 2-7) reaching even the level of 71% (Doruk 2005: 1-6). The highest result in the available researches is the same that is found in this study. So the result of this study of 71% female DM patients having SD is high comparing to other available data.

The current study also proves this fact, because the rate of 71% women having FSD is a very high result, if compared to healthy women, whose average FSD rate in the population is about 34% (Doruk 2005: 1-6). This result shows that the average FSD in women with Type 2 DM is almost twice as frequent as in healthy population. The cause of this remarkable difference can be the physiological consequences of DM – the damage of the small blood vessels, which can cause the disturbance of arousal and lubrication and also the damage of nerves also called neuropathy, which can explain the loss of sensation, reduced arousal and pain during penetration.

While the physiological causes certainly play an important role in the pathogenesis of FSD, the results of the conducted study emphasize also the psychological aspects of the development of FSD. As this study shows, the lowest rated section with a significant difference from other criteria was sexual desire (Fig.2). The brain as the most important sexual organ has been discussed in other available literature (Toledano 2006: 853-77). But in case of women it is even more powerful, because as other researches show, woman's sexual desire is directly linked to the viewpoint of herself and the norms of society (Shaw 2010). The physiological consequences of DM don't directly affect the central nervous system and other organs or hormones, which are directly connected with the psychological side of a person. So this fact arouses a discussion about the self – image and self – worth of a woman and the importance it has on reducing sexual desire.

Contradictory is the fact the satisfaction was rated as one of the highest criteria, because in society it has been accepted, that a normal quality of life component is sexual desire and sexual activity. But in the case of women with DM it is understandable that if the desire is low and they experience pain during sex, it can be desirable not to have this component of quality of life in order to avoid the unpleasant physical and psychological sensations.

Other explanation for the satisfaction with the sexual life in spite of the reduced quality of it can be age. The mean age of the participants of the survey was 54 years, which is the average age of menopause. The unstable and changing hormonal level along with other physical and sensational changes can affect the woman's body and mind. Menopause in most cases is associated with decrease of female hormones, elasticity of skin and also losing the reproductive function. The decrease in serum estrogen level with menopause affects sexual response. The decrease in estrogen level causes vaginal atrophy resulting in vaginal dryness and pain (Howard 2006: 355–367). So both the physical and the psychological changes during menopause can affect the sexual function of a women negatively.

Gender roles are also an important reason for the psychological causes of FSD. Because sexuality is associated with a woman's reproductive capability and also youth, aging women in society are perceived as less sexual, which can impact the possibility and quality of sexual relationships. In case of Type 2 DM, age is one of the risk factors and, as also this research shows, the patients with Type 2 DM are more frequently represented in the older groups of society.

This study is a good basis for further research. It would be significant to include other factors in this research such as heart and blood vessel disorders, hypertension, urogenital disorders, psychological disorders, cancer and other chronic disorders, social isolation, financial issues, unemployment status, lack of physical activities and religion.

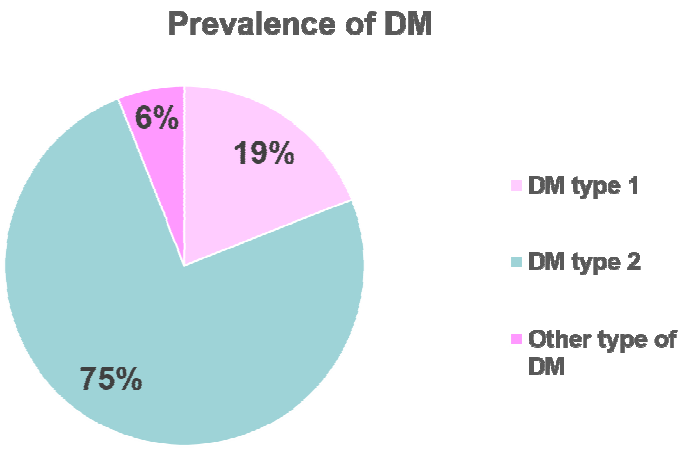

Figure 1. **Prevalence of diabetes mellitus**

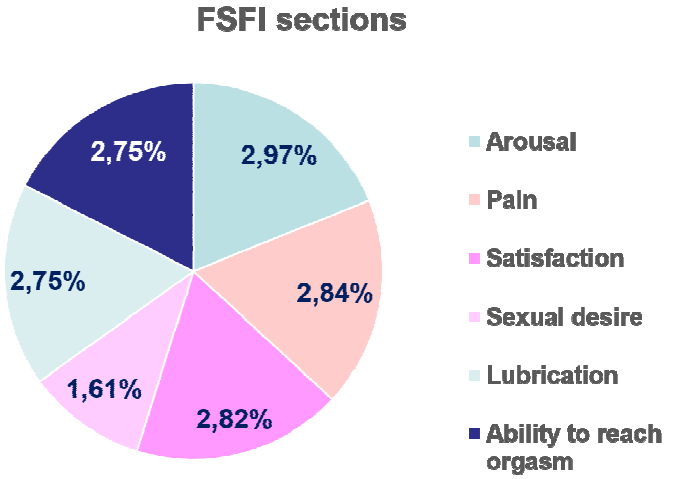

Figure 2. **Female sexual dysfunction index sections**

Conclusion

Prevalence of FSD among women with Type 2 DM is higher than in healthy population, thus Type 2 DM can be considered as important risk factor of the development of FSD. The impact on the development on FSD can be explained by physiological aspects of pathogenesis of Type 2 DM. But this research also emphasizes the psychosocial aspect of Type 2 DM as an important cause of FSD. If to include other factors in the research, this study represents a solid basis for further research.

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RESEARCH ON THE ASSOCIATION BETWEEN DYSPEPSIA, ANXIETY AND DEPRESSION

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Abstract
Key words: *Dyspepsia, anxiety, depression, somatisation, HADS*
Introduction: Dyspeptic syndrome includes symptoms such as epigastric pain, bloating, early satiation, fullness, epigastric burning, belching, nausea, and vomiting (Tack et al. 2016). Several pathophysiologic mechanisms have been suggested to underlie dyspeptic symptoms. One of them is somatization. It considers the psychological discomfort conversion into a physical symptom and is directly related to the gut-brain axis (Carabotti et al. 2015).
Aim: To research the prevalence and association of dyspeptic symptoms with affective disorders. Materials and methods. The questionnaire consists of sociodemographic information, questions concerning evaluation of dyspeptic symptoms prevalence and duration, Hospital Anxiety and Depression Scale (HADS). Data is statistically processed in Microsoft Excel and SPSS 20.
Results: There were 196 questionnaire respondents, 163 females (83,2%) and 33 males (16,8%). Minimal age 18 years, maximal age 47 years; median 23,45 years, moda 23. Spearman's rank correlation between the anxiety and epigastric pain (R= -0,299, p=0,000), nausea (R= -0,232, p=0,001), bloating (R= -0,247, p=0,000) established statistically significant reverse correlations. Spearman's rank correlation between the depression and dyspeptic symptoms did not establish statistically significant correlations.
Conclusion: Several dyspeptic symptoms are associated with anxiety, but the correlations are reversed. The more severe dyspeptic symptoms are, the lower the level of anxiety is.

Kopsavilkums
Atslēgas vārdi: *Dispepsija, trauksme, depresija, somatizācija, HTDS*
Ievads: Dispepsija ir medicīnisks jēdziens, kas apzīmē apgrūtinātu gremošanu. Dispeptiskie simptomi ir vēdera uzpūšanās, slikta dūša, sāpju sajūta un dedzināšana epigastrijā, ātra sāta sajūta, atraugas, vemšana, pilnuma sajūta (Tack et al. 2016). Dispepsijas pamatā ir vairāki patfizioloģiskie mehānismi. Viens no tiem ir somatizācija – psiholoģiskā diskomforta izpausme somatisko simptomu veidā. Šis mehānisms ir tieši saistīts ar zarnu-smadzeņu asi (Carabotti et al. 2015).
Mērķis: Izpētīt un noteikt saistību starp dispeptiskiem simptomiem, trauksmi un depresiju
Materiāli un metodes: Pētījumam tika sastādīta anketa ar sociodemogrāfiskiem jautājumiem, jautājumu bloks noteiktu dispeptisko simptomu ilguma un biežuma noteikšanai un Hospitālā trauksmes un depresijas skala (HTDS). Dati tika statistiski apkopoti Microsoft Excel un SPSS 20 datorprogrammās.
Rezultāti: Pētījumā piedalījās 196 respondenti, 163 (83,2%) ir sievietes, 33 (16,8%) ir vīrieši. Minimālais vecums 18 gadi, maksimālais 47 gadi, mediāna 23,45 gadi, moda 23. Spīrmena korelācijas koeficientu analīzē starp trauksmes līmeni pēc HTDS un sliktu dūšu (R=-0,232, p=0,001), sāpēm kuņģī (R=-0,299, p=0,000), vēdera uzpūšanos (R=-0,247, p=0,000) konstatēja statistiski ticamas korelācijas. Spīrmena korelācijas koeficientu analīzē starp depresijas līmeni pēc HTDS un dispeptiskiem simptomiem nekonstatēja statistiski ticamas korelācijas.
Secinājumi: Daži dispeptiskie simptomi ir asociēti ar paaugstinātu trauksmes līmeni, bet šī korelācija ir apgriezta: jo smagāki ir dispeptiskie simptomi, jo zemāks ir trauksmes līmenis.

Introduction

Dyspepsia (indigestion) includes multiple symptoms such as epigastric pain, bloating, early satiation, fullness, epigastric burning, belching, nausea, and vomiting (Tack et al. 2016). There is a clear association between psychosocial factors and gastrointestinal disorders confirmed in various studies.

The correlation between anxiety, depression and dyspepsia is widely studied and the comorbidity is high. Anxiety disorders are diagnosed 4-fold more often in patients with functional

dyspepsia compared with a general population. Among patients with co-morbid functional gastrointestinal disorders more commonly offers somatization (Wu JC 2012). In a recent study of the Swedish population is established that anxiety at baseline increased the risk for development of functional dyspepsia by 7,6-fold in the next 10 years, but depression is not associated with the higher FD risk. This prospective cohort study shows causation in the earlier found association between anxiety and dyspepsia and established that the anxiety state priors the dyspepsia. There is no data, how the anxiety level is changed among patients group that presents FD in 10-years (Aro et al. 2015).

The association between anxiety, depressions and dyspepsia also depending on the clinical subtype of dyspepsia. Thus, ulcer-like dyspepsia is linked to male gender but not to depression and anxiety. Dismotility-type dyspepsia is linked to female gender and anxiety or depression (Hofiman G. 2003).

The relationship between anxiety and gastric sensorimotor function in patients with FD was investigated in another study. In hypersensitive patients with FD, state anxiety measured with State-Trait Anxiety Inventory (STAI) is significantly and negatively correlated with discomfort threshold, pain thershold, and gastric compliance during barostat investigation with doble-lumen polyvinyl tube. The higher are levels of state anxiety, the lower discomfort and pain thersholds and gastric compliance are predicted during barostat investigation in hypersensetive patients with FD (Oudenhove et al. 2007).

Several pathophysiologic mechanisms have been suggested to underlie dyspeptic symptoms. One of them is somatization and it is directly related to the gut-brain axis. It considers the psychological discomfort conversion into a physical symptom. On the other hand the gut-brain axis consists of bidirectional communication between the central and the enteric nervous systems, linking emotional and cognitive centers of the brain with peripheral intestinal functions (Carabotti et al. 2015).

Dyspepsia is usually classified into two categories: organic (there is an organic lesion) and functional (FD), but if no examinations are done it is unexamined dyspepsia. Prevalence of dyspeptic complaints is 8-30% (Ghoshal et al. 2011). Referring reason of 70% of all fibrogastroscopies performed due to dyspeptic complaints is FD; only 10% are cases of peptic ulcer and 1% - gastroesophageal cancer (Talley et al. 2015). Most of all causes of dyspepsia are FD which according to the most recent Rome criteria IV is recommended to consider as disorders of interaction between brain and gastrointestinal system. This update was done because understanding of functional disorders also covers biosocial model and it is based on dysregulation of complex interaction between such factors as dysbiosis in guts, changed immune function of the mucous membrane, changed intestinal signalizing system (visceral hypersensitivity), as well as disturbed

ability of the central nervous system to regulate signalizing and motor function of the intestinal tract (Drossman et al. 2016).

Gut-brain axis concept exists in scientific literature, currently also gut-brain-microbiome concept is introduced. Gut-brain axis is bidirectional network connecting central neural system (CNS), vegetative neural system, enteric neural system and hypothalamic-pituitary-adrenal (HPA) axis. Vegetative neural system is divided into sympathetic and parasympathetic one, and it transmits both afferent signals from gastrointestinal lumen to CNS through enteric, spinal and vagal conduction paths and efferent signals from CNS to intestinal wall. HPA axis is considered as the main stress efferent axis coordinating adaptive responses to different stress factors. It is a part of limbic system, cerebral decisive zone involved mainly in memory and emotional responses. Environmental stress, as well as increased level of systemic pro-inflammatory cytokines activates this system through corticotropin-releasing factor from hypothalamus by stimulating secretion of adrenocorticotropic hormone (ACTH) from hypophysis which in turn affects cortisol release from the adrenal glands. Cortisol is the main stress hormone affecting many human organs, also the brain. Thus, both neural and hormonal communication paths are combined to allow the brain affecting action of the intestinal effector cells. However, on the other hand the same cells are influenced by intestinal microbiome which is examined actively in the current investigations. Some studies with germ-free animals showed decreased anxiety and increased response to higher ACTH and cortisol levels (Carabotti et al. 2015).

In this work, the term “anxiety” means negative emotion characterized for emotional distress, and not impetuous disorders or depression as psychiatric diagnosis.

Both psychological abilities to overcome stress, irritant threshold level and somatic reactions differ in different people. Anxiety is an individual psychological quality characterized by intensive worry about objectively irrelevant reasons, and anxiety for such people is frequent negative emotion. There are several studies showing both intrinsic and environmental causes on which the ability of each individual to react to different stress factors depends (Blackford et al. 2012).

Level if the individual anxiety is largely determined by development of the cerebral amygdale body and its interaction with higher associative centers (prefocal cortex) and other cerebral structures. Dysfunction of neurotransmitters in these regions leads to different mood disorders. There are evidences that that dopamine has significant role in anxiety modulation. Mesolimbic, mesocortical and nigrostrial dopaminergic systems are involved in this process and both D1 and D2 receptors participate in it. Activity of the dopaminergic system is regulated by GABA-ergic fibers in medial prefrontal cortex (mPFC) from the pedunculopontine and dorsolateral tegmental nuclei - inhibitory action (Zarrindast et al. 2015). There are data that anxiety is associated with lower

serotonin level in amygdala, and there is smaller volume of the adjacent prefrontal region (dorsal anterior cingulated cortex) (Mikheenko et al. 2015).

The higher associative centers responsible for cognitive functions (awareness of emotions occurs there) are located in the cerebral prefrontal cortex, as well as prefrontal cortex is closely connected with other structures and itself contains big amount of chemical synapses. This particularity may be considered as one of the possible bases in the inhibitory mechanism of anxiety impulsation because big amount of synapses may determine further divergence of afferent impulsation followed by delay of impetuous signal impulsing by GABA-ergic fibers located in it (Shin et al.2010), as well as inhibitory interneurons expressing 5-HT1A, 5-HT2A, or 5-HT3A receptors (Puig et al. 2011). GABA neuromediator is the most common inhibiting mediator providing postsynaptic inhibition that causes hyperpolarization in the postsynaptic space and thus interrupts further spread of the impulsation; serotonin also acts similarly (Byrne et al. 2014).

Serotonin [5- hydroxytryptamine (5-HT)] is important neurotransmitter involved in regulation of different psychological processes – emotions, consciousness, circadian and neuroendocrine rhythms. Attentions should be paid to serotonin transporter (5-HTT) gene determining serotonin reuptake in the cerebral synapse. Promoter of this gene (5-HTTLPR) may contain long or short allele. Long allele in the promoter of the serotonin transporter gene increases individual sensitivity to stress – these individuals feel bigger anxiety in stress situations (Ming et al. 2015).

There are evidences that basomedial amygdala (BMA) is the main ventral mPFC target in rodents brain; BMA recognizes safe and unsafe environment and its activation decreases sense of cold and strong anxiety associated with fear. It can be concluded that ventral mPFC descending BMA projections realize anxiety control (Adhikari et al. 2015). Thus, ventral mPCF plays critical role in the processes of inhibiting sense of fear and fear disappearance. Prefrontal cortex is connected to amygdale body in several regions. Primary interest is caused by γ-aminobutyric acid-ergic (GABA-ergic) neurons through which prefrontal cortex performs inhibiting action to the amygdale (Shin et al. 2010).

Overview of anxiety pathophysiologic mechanism, gut-brain-microbiome axis concept in scientific articles, big prevalence of dyspeptic complaints and biopsychosocial approach create interest to evaluate association between emotional condition and dyspeptic symptoms.

Material and methods

The questionnaire consists of sociodemographic information and variety of questions concerning evaluation of dyspeptic symptoms prevalence and duration, Hospital Anxiety and Depression Scale (HADS, Zigmond et al. 1983). Data is statistically processed in Microsoft Excel and SPSS 20 using Spearman's rank correlation coefficient and population descriptive statistics. All data were expressed in mean values with determination of 95% confidence interval. Rejection of

zero hypothesis and acceptation of alternative hypothesis was based on trustfulness level of the statistic hypothesis $p < 0.05$. The study was done by respecting regulations of the Helsinki Declaration and Human Rights Convention. Permission to conduct the study was received from Ethics Commission of the Rīga Stradiņš University.

Results

There were 196 questionnaire respondents, 163 females (83,2%) and 33 males (16,8%). Minimal age 18 years, maximal age 47 years; median 23,45 years, moda 23. Spearman's rank correlation between the anxiety and epigastric pain (R= -0,299, p=0,000), nausea (R= -0,232, p=0,001), bloating (R= -0,247, p=0,000) established statistically significant reverse correlations. Spearman's rank correlation between the depression and dyspeptic symptoms did not establish statistically significant correlations. 93,9% respondents had the same dyspeptic symptoms during the last 6 months. The most frequent symptoms were bloating and fullness, but the rarest ones – vomiting and epigastric burning; 144 respondents (73,5%) had bloating at least once during the last week, 131 respondents (66,8%) had fullness , but only 6 respondents (3%) had vomiting and 56 respondents (28,6%) had epigastric burning (Table 1).

Table 1. **Frequency of several dyspeptic symptoms during last week**

93.9 % respondents have the same dyspeptic complaints during the last 6 months ** symptoms that inversely correlate with anxiety*					
Dyspeptic symptoms	**None**	**Once a week**	**2-3 days a week**	**4-6 days a week**	**All days**
Fullness	32,99	30,96	25,38	9,64	1,02
Vomiting	96,95	3,05	0	0	0
Nausea*	**57,87**	**23,35**	**12,69**	**6,09**	**0**
Belching	37,56	15,23	23,35	13,20	10,66
Epigastric burning	71,57	11,68	12,18	3,55	1,02
Epigastric pain*	**54,31**	**25,38**	**15,23**	**4,06**	**1,02**
Bloating*	**26,40**	**23,35**	**31,47**	**12,69**	**6,09**
Early satiety	33,70	29,10	29,60	7,10	0,50

The anxiety level in the population is higher than depression. 19 respondents (9,7%) had normal anxiety level, 47 respondents (24%) had borderline scores and in 130 respondents (66,3%) the anxiety level assessed by HADS-A was detected as pathological. The mean score is 11,28, mediana 11,5, moda 13 for HADS-A (Fig.1.). The results for depression evaluated by HADS-D are as follows: 70 respondents (35,7%) had no depression, 101 (51,5%) had borderline scores, but significant depression level was detected in 25 (12,8%) respondents (Fig. 2.). The mean score for HADS-D is 8,17, mediana 8,00 un moda 8, also any statistically significant correlations between anxiety and depression in this population didn't establish.

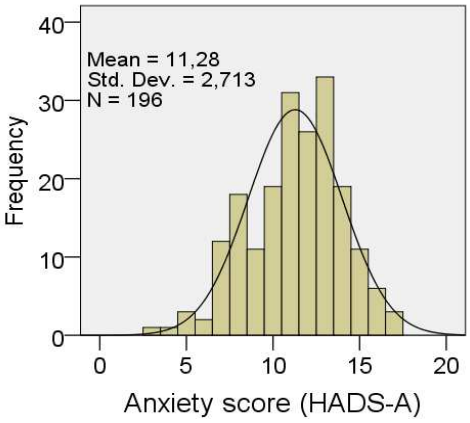

Figure 1. **Anxiety score among students**

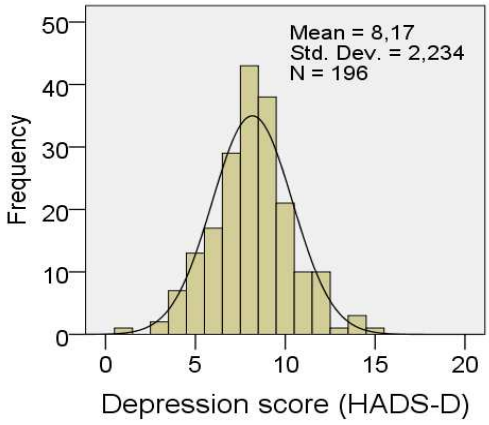

Figure 2. **Depression score among students**

The anxiety level is higher than depression level among all respondents. Scoring: 0-7 = Normal case, 8-10 = Borderline case, 11-21 = Abnormal case (Snaith et al. 2003).

Discussion

Study results align with results of several large studies that dyspepsia is closely associated with anxiety (Aro et al. 2015). Association with depression was not approved using HADS; there could be two reasons for it – weather HADS is not appropriate for evaluation of depression or this association really does not exist, what is in contradiction with several studies (Mak et al. 2012). Correlation study does not give picture of causality. It is interesting that opposite association is found for correlation between anxiety and dyspepsia that allows pose hypothesis that the cause could be somatization phenomenon that is manifestation of psychological distress in somatic symptoms. Somatization mechanism is very strong defensive mechanism against anxiety but it has almost not investigated at the level of pathophysiologic mechanisms (Busch 2014).

Conclusions

Several dyspeptic symptoms are associated with anxiety, but the correlations are inversed. The more severe dyspeptic symptoms are, the lower the level of anxiety is. Correlation does not imply causation. Presumably, some dyspeptic symptoms have a psychosomatic background and are caused due to anxiety somatization. Further studies needed to evaluate and confirm it.

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EVALUATION OF TENDENCIES FOR LABORATORY TESTINGS FOR CHILDREN FROM 3 MONTHS TILL 3 YEARS WITH INITIAL DIAGNOSIS: FEVER WITHOUT SOURCE

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Abstract

Evaluation of tendencies for laboratory testings for children from 3 months till 3 years with initial diagnosis: fever without source

Key words: *fever without source, children, laboratory testings*

Introduction. Fever is one of the main complaints of children seeking medical attention. Many have fevers without an apparent source (FWS) that requires further investigations to ascertain the diagnosis.

Aim. To assess the tendencies of done laboratory investigations and their values in children with FWS.

Materials and methods. The study incorporate children aged 3-36 months hospitalized at Children's Clinical University Hospital from 2014 - 2016 who presented with fever without obvious focus. Retrospective study data were compiled in Excel tables and processed with SPSS 16.0 data processing method.

Results. At the initial evaluation, there were 102 patients but valid were 30 according to definition of diagnosis**.** The median age was 21.5 months (min. - 3, max. - 35). The average temperature was 39.10^{o} C (min. – 37,7^{o} C, max. - 40^{o} C). Full blood count analysis were done in 100% (n = 30) patients. According to the age, leukocytosis had 33.33% (n = 10) patients, 19.99%(n = 6) had leukopenia and 46.67% (n = 14) had normal white blood cell count. Increased immature granulocyte count had only 9.99% (n = 3) of patients and generally this analysis were done to 96.57% (n = 29). C-reactive protein were done for 96.57% (n = 29) patients and it was increased above 40 mg/L for 16.65% (n = 5) patients, above 100mg/L - 3,33% (n = 1) patients. Il6 were done in 43.29% (n = 13) patients and median Il6 was 23.3(min.-2, max-275).Blood culture were done in 16.65%(n = 5) patients and it was negative for all patients. Inflammatory changes in urine determined for 6.66% (n = 2) of 89.91% (n = 27) patients. Lumbar puncture were done 6.66% (n = 2) children and the results were negative. 23,31% of patients had done fecal culturing but none of them were positive.

Conclusion. There is no relevance between doctors appointed examination in children with similar initial diagnosis.There is no single algorithm executed by all doctors. According to laboratory findings-various values differ in frequency.

Kopsavilkums

Laboratorisko izmeklējumu veikšanas izvērtējums bērniem no 3 līdz 36 mēnešu vecumam ar sākotnējo diagnozi: neskaidrs drudzis

Atslēgvārdi: *neskaidrs drudzis, bērni, laboratoriskie izmeklējumi*

Ievads. Drudzis ir biežākais iemesls dēļ kā bērnu vecāki meklē medicīnisko palīdzību. Daudziem bērniem ir drudzis bez iemesla (*fever without source),* kas prasa tālāku izmeklēšanu.

Mērķis. Novērtēt laboratorisko izmeklējumu veikšanas tendences un to vērtības bērniem ar sākotnējo diagnozi: neskaidrs drudzis.

Materiāli un metodes. Pētījumā tika iekļauti bērni no 3 - 36 mēnešu vecumam ar diagnozi - neskaidrs drudzis, kas stacionēti Bērnu klīniskajā universitātes slimnīcā no 2014. – 2016. gadam. Retrospektīvā pētījuma dati tika apkopoti programmā Excel un apstrādāti ar SPSS 16.0 datu apstrādes metodi.

Rezultāti. Pēc sākotnējas izvērtēšanas pētījumam atbilstoši bija 102 pacienti, bet pēc izslēgšanas kritēriju izvērtēšanas, pētījumam atbilstoši bija 30 pacienti. Mediānais pacientu vecumam bija 21.5 mēneši (min. – 3, maks. – 35). Vidējais temperatūras augstums bija 39.1 grāds pēc Celsija. (min. – 37.7^{0}C, maks. - 40^{0}C). Pilna asins aina tika veikta 100% (n = 30) pacientu. Atbilstoši vecumam noteiktajām normām, leikocitoze tika konstatēta 33.33% (n = 10) pacientu, 19.99% (n = 6) – leikopēnija, 46.67% (n = 14) – normāls leikocītu skaits. Paaugstināts nenobriedušo granulocītu skaits tika konstatēts tikai 9.99% (n = 3) pacientu un šis izmeklējums tika veikts 96.57% (29) pacientu. C reaktīvais proteīns tika veikts 96.57% (n = 29) pacientu, paaugstināts virs 40 mg/L tas bija 16.65% (n = 5) pacientu, virs 100 mg/L tas bija 3.33% (n = 1) pacientu. Il6 analīzes tika veiktas 43.29% (n = 13) pacientu un mediānā tā vērtība bija 23.3 pg/mL (min. – 2., maks. – 275). Asins uzsējums tika veikts 16.65% (n = 5) pacientu un visiem pacientiem rezultāts bija negatīvs. Iekaisīgas izmaiņas urīnā tika konstatētas 6.66% (n = 2) no 89.91% (n = 27) pacientu. Lumbālpunkcija tika veikta 6.66% (n = 2) bērnu un rezultāti bija negatīvi. 23.31% pacientu tik veikts fēču uzsējums, taču būtiskas atradne nevienam netika konstatēta.

Secinājumi. Pediatru vidū nepastāv vienota darbības principa, pēc kura ārsti vadītos veicot laboratoriskos izmeklējumus pacientiem ar vienādu sākotnējo diagnozi. Nav vienota algoritma pēc kura vadītos visi ārsti. Saskaņā ar laboratorijas izmeklējumiem – dažādas vērtības variē biežumā.

Introduction

Fever is body temperature increasing above 38^0C. It is the most common cause for parents looking for medical help. (Grope 2014) Most of the children, first fever episode is presented till three years. Fever consistute one third of the main reasons to visit pediatric practice. (Coburn 2017) It is proven that in 90 – 95% fever cause is uncomplicated viral etiology illnesses and only 5 - 10% cases fever causes bacterial diseases. (Grope 2014)

It is not always necessary to reduce temperature increase, because hypertermia is a normal body response reaction to possible initiator. The most common cause of hypertermia is uncomplicated viral diseases and the younger the child is, the more often they fall into these kind of illnesses. Children who attend kindergarten and school are the main group of children that suffer from infectious diseases. The norm is if children do have five till ten hypertermia episodes in a year, where two till three episodes takes place one after the other. (Myron 2014)

In literature fever is variously defined, but the most often used two terms are: fever without source (FWS) and fever unknown origin (FUO). Fever unknown origin is defined as fever above 38.3^0C that longs at least eight days and there is no diagnosis after anamnesis, initial physical and laboratory investigations. Fever without source ir defined as fever above 38^0C that longs till seven days and there is no diagnosis after anamnesis and initial physical investigation.

A large cohort-type study, which included children from 3 months to 3 years of age with a fever without source, was found that after the initial investigation, the diagnosis of bacterial infection was confirmed to 56% of patients, of which 90% was had middle ear inflammation. Specific infections such as croup, bronchiolitis, varicella and roseola were identified 4% of children. In a similar study at Boston Children's Hospital of 21,216 children aged 3 months to 36 months hospitalized with fever, six percent had recognizable viral infection, 47% had a specific bacterial infection and 47% of patients had a diagnosis of unexplained fever. (Coburn 2017)

Infection is the most common cause of fever unknown origin that is followed by rheumatologic diseases (lupus erythematosus, vasculitis etc. (Debra 2016) In 2011 there was done a systematic review of 18 studies, which included 1,638 children under 18 years of age with a diagnosis of fever unknown origin. The most frequent causes of this fever were: infection (51%, where 59% of these infections were bacterial nature), the initiator was found 23% of patients, rheumatologic diseases - 9% (most often - juvenile idiopathic arthritis), neoplastic diseases - 6% of patients (where most often - leukemia, lymphoma). (Chow 2011)

Worldwide children and adults most frequently die from infectious illnesses than from any other cause. The vast majority of deaths are in countries with low prevention level, medical care, and drug deficiency. (Longe 2011) In 2015 from infectious diseases worldwide died 5.97 million children under the age of five years, drawing 68% of all causes of death, where 18% died from

pneumonia, 15% from diarrhea, 8% from malaria. Based on the World Health Organization data, more than 800,000 children under five die each year annually from meningitis and pneumococcal pneumonia. There are six diseases that constitute 70% of children deaths: acute upper airway infectious where the main one is pneumonia (19%), diarrhea (18%), malaria (8%), measles (4%), HIV/AIDS (3%) and asphyxian in delivery and infectious diseases (37%). Looking for the causes of fever cannot forget about oncology, autoimmune, connective tissue diseases etc.

In different countries different laboratory investigations are made to detect inflammation. The aim of this study was to evaluate the tendencies for laboratory testings for children from 3 months till 3 years with initial diagnosis: fever without source.

Worldwide the most commonly measured laboratory investigations to detect inflammation are: cell blood count, erythrocyte sedimentation rate, C-reactive protein, procalcitonin. Also immature granulocyte count and Interleukin 6 can be used. To detect inflammatory process in urinary tract, urine analysis can be done as well

After anamnesis and initial physical investigation there must be concrete plan about further investigations and treatment in children with fever. In different countries tactics differ, it also depends on country geographical position. There must be one algorithm that is applied by all doctors who have patient with fever.

One of countries where is implemented fever algorithm is USA. In that algorithm children are grouped in 3 age classes: 1) newborns with temperature above 37.5^0C 2) 1-3 months old infants with temperature above 38^0C and 3) children above 3 months and with temperature above 38^0 C.

Initially children above 3 months till 3 years were evaluated objective. Doctor have to evaluate children's behaviour and look. Healthy child is interested in things that happen around, communicate and behaves healthy. Toxic child is pale, with blood perfusion disturbances, lethargic, with hypoventilation or tachycardia. If there are any doubts about childrens condition, it is recommended to evaluate children by risk scale. If the child after evaluation and with temperature 38^0C is documented as sick than doctor have to do following investigations:

1) Full blood count, urea, creatinine, CRP, blood culture;
2) Urine analysis un urine culture (with "clean catch"or catheterization method);
3) Consider chest radiography necessity depending on symptomatology
4) Consider lumbar puncture necessity
5) Evaluate repeatedly patient. Evaluation can be done also by AVPU parameters. (A-patient is awake, V – patient replies on verbal stimulus, P – patient replys on painfull stimulus, U – patient is unresponsive.

Further patients therapy consists of:

1) Intravenous antibacterial therapy depending on the causative agent. Empirically antibacterial therapy usually start with ceftriaxone 50mg/kg, if there is suspected CNS engagement than vankomycin 15mg/kg can be added.
2) Consider hydratation 0,9% NaCl 20ml/kg, repeat if there is shock signs
3) Paracetamol 15mg/kg every 4-6 hours, maximum 80mg/kg/day for children above 3 months
4) Ibuprofen 10mg/kg every 6-8 hours, maximum 40mg/kg/day together with food.

If patient is evaluated as healthy than patient undergoes urine analysis and every hour patient is evaluated by AVPU scale. If urine testings shows urinary tract infection than antibacterial therapy is recommended. If patients urine analysis is without pathology than patient is posted at home and family doctor visit is recommended after 24 hours. In risk group are children from three till six month old because this group of children have not done full vaccination.

Material and methods

In this retrospektive descriptive research were included boys and girls, aged 3 – 36 months which were hospitalised at Children's Clinical University Hospital with fever from 2014 – 2016 who do not have related illnesses, congenital or acquired immunodeficiency, metabolic diseases, immunosuppressive therapy, children who do have fever longer than a week and do not have a reaction to antibacterial therapy.

Initially patients were evaluated by systemic inflammatory response syndrome (SIRS) criteria. To evaluate systemic inflammatory response syndrome there must be the presence of two criteria of the following four: 1) temperature above 38^0C or under 36^0C 2) tahycardia (above 2 Standart Deviations from age norm) or bradicardia for children younger than one year (under 2 Standart Deviations from age norm) 3) breathing frequence > 2 Standart Deviation from age norm 4) white blood cell count increased or decreased under norm according to certain age norms or >10% of immature granulocytes.

After evaluation of SIRS, children were divided into precautionary levels: high, medium, low. If children was SIRS positive, he was attributed to high precautionary level and futher he was evaluated by activity, hidration, skin color and elements after which he had done futher investigations. If children was SIRS negative further he was evaluated by activity, hidration, skin color and elements and was divided into medium of low precautionary level. According to doctors diagnosis and clinical findings, further children had laboratory and radiological investigations.

Data were compiled in special database using the programm Excel. Patient data were encrypted in giving patients the identification numbers and do not reflect patients personal data.

Data were proceeded with SPSS 16.0 data processing method. In patient data analysis were used descriptive statistical methods.

Results

Initially, there where 102 patients selected in Andromed system with diagnosis R50 (fever without source) but after the evaluation of exclusion criteria, in the study were included only 30. The median patient age was 21.5 months (min. - 3 max.- 35). Of the total number of inpatient children: 36.3% (n = 11) were boys, 63.27% (n = 19) - girls. Most of the children were hospitalized in June - 19.98% (n = 6), in July, in March - 16.65% (n = 5). Hospitalization frequency in each of the months shown in the graph. (Figure 1)

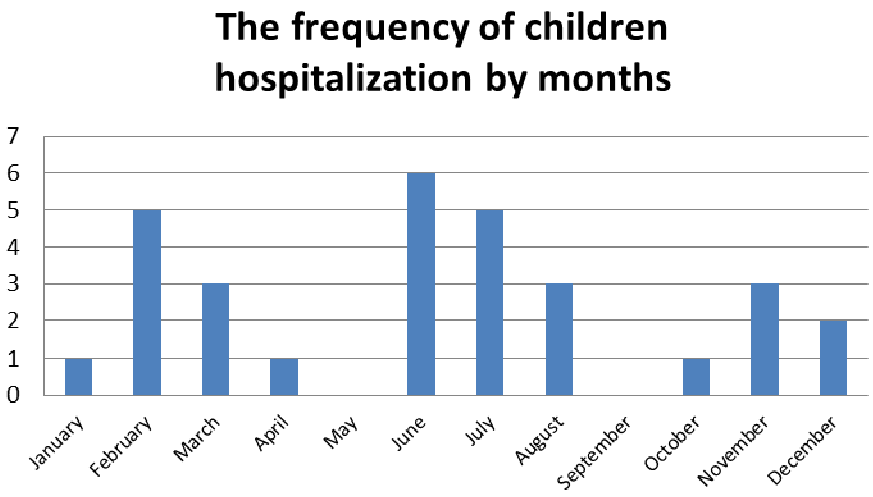

Figure 1.

The average height of the fever in hospitalized children was 39.1^0 C (min -. 37.7^0 C maks.- 40^0 C). After summarizing the results of history data it is clear that the average disease duration till the patient enters the hospital were 6.2 days, median - 3.5 days. The average temperature duration in prehospital care were 5.7 days but median - 3 days. The average day count after which patients were looking for medical care were five days. The median hospital stay were three days (min.-1, max – 20.). The average hospital stay were 4.1 days (min - 0.5, max.- 13).

From al hospitalized children 66.66% (n = 20) patients have undergone the complete vaccination course, 16.65% (n = 5) - partially, 3.33% (n = 1) – have not vaccinated.

Normal white blood cell count was observed in 46.66% (n = 14) patients, where the minimal white blood cell count was 22.8 x 10^3 / uL, maximal - 13.8 x 10^3 / uL and median - 11.12 x 10^3 / uL. 19.98% (6) patients had leukopenia, where the minimal white blood cell count amounted to 4.83 x 10^3 / uL, maximal – 5.53 x 10^3 / uL, median - 5.29 x 10^3 / uL. Leukocytosis was admitted to 33.33% (10) patients with a minimum - 5.14 x 103 / uL, maximum - 33.80 x 10^3 / uL, median value - 19.89 x 10^3 / uL.

C reactive protein is one of the laboratory examinations, which are carried out most often in children hospitalized with fever - this study is carried out in 96.66% (n = 29) of patients.

The minimal C reactive protein amount was 0 mg/L, maximal – 102.32 mg/L , median – 16.99 mg/L. There are two C reactive protein values with are considered to be clinically significant - under 40mg/L and under100mg/L. In the following graph are showed borderlines to prominently display how many and which patients C reactive protein value was elevated.

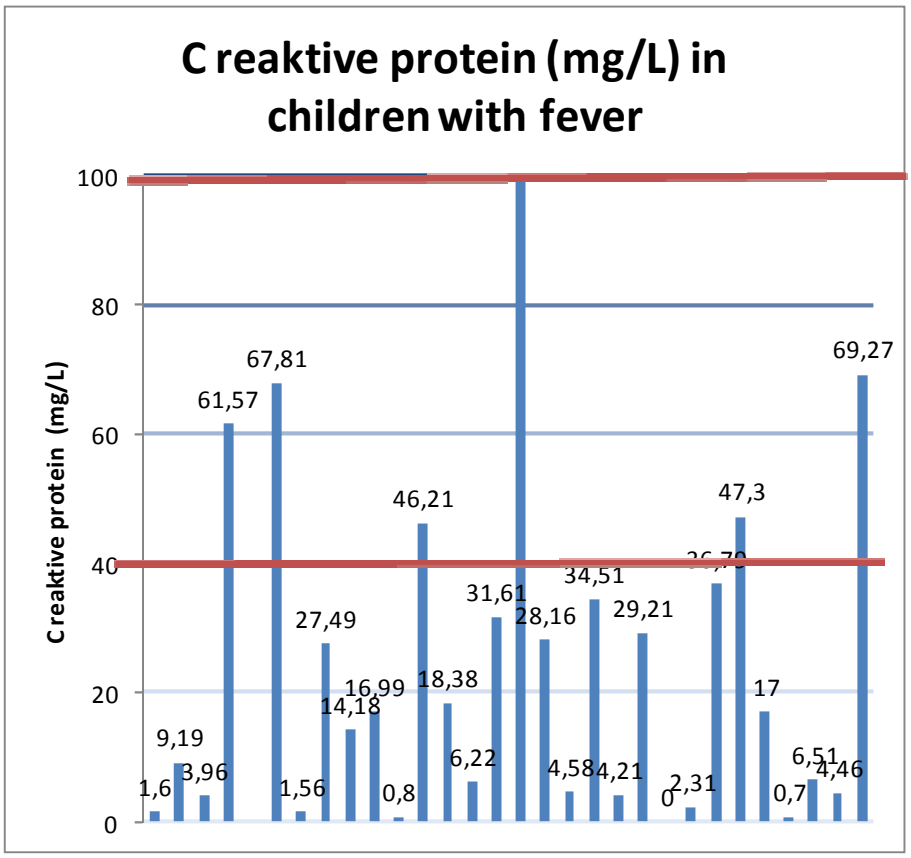

Figure 2.

In the graph (Figure 2) there is seen than C reactive protein in clinically significant borders (40 - 99mg/L), is increased for 16.65% (n = 5) patients and only 3.33% (n = 1) of patients C reactive protein was under 100mg/L.

It is really important to remember that C reactive value is not incread only in infectious diseases but also in rheumatological diseases, autoimmune vasculitis, inflammatory bowel diseases (Crohn's disease, Ulcerative colitis), cancer, surgeries and cardiological diseases. (Pavāre 2011)

Increased immature granulocyte count had only 9.99% (n = 3) of patients and generally this analysis were done to 96.57%(n = 29). Il6 were done in 43.29% (n = 13) patients and median Il6 was 23.3(min.-2, max-275)

Correlation calculation between C-reactive protein and white blood cells are not demonstrated statistical significance (p> 0.05). The reliability of statistics, has not shown the correlation between CRP and Il-6 (P> 0.05).

Blood culture were done in 16.65%(n = 5) patients and it was negative for all patients. Inflammatory changes in urine determined for 6.66% (n = 2) of 89.91% (n = 27) patients.

Lumbar puncture were done 6.66% (n = 2) children and the results were negative. 23,31% of patients had done fecal culturing but none of them were positive.

Discussion

Testing in febrile children 3 to 36 months of age has been used to screen for the risk of bacterial infection as well as to diagnose specific infections. The decision to perform laboratory tests depends upon a variety of factors including age, immunization status, and obvious findings of infection. (Coburn 2017) It is clear that in our study the majority of doctors perform laboratory tests that indicates infammation (white blood cell count, C reactive protein, Il-6 etc) . Preliminary evidence suggests that elevations in levels of inflammatory mediators may be better markers of secundar bacterial infection than white blood cell count in children at significant risk for bacterial infection. (Coburn 2017)

In this study correlation between C-reactive protein and white blood cells are not demonstrated statistical significance ($p > 0.05$). The reliability of statistics, has not shown the correlation between CRP and Il-6 ($P > 0.05$). Opposite correlation rates in children with fever have shown in other researches (Pavāre 2011). A statistically reliable correlation cannot be obtained due to the limited number of cases in the study.

After summarizing and analyzing all the results it is clear that there is no single algorithm executed by all doctors for laboratory investigations in children with diagnosis: fever without source. In other countries there are developed and implemented algorithms for pediatrics how to manage, investigate and treat children with fever. (Hamilton J. 2013) Implementing a fever management tool in Latvia there can be used foreign algorithms.

Conclusions

- There is no relevance between doctors appointed examination in children with similar initial diagnosis: fever without source.
- There is no single algorithm executed by all doctors.
- According to laboratory findings-various values differ in frequency.

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SURVIVAL PREDICTORS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA UNDERGOING TRANSARTERIAL CHEMOEMBOLISATION

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Abstract

Survival predictors in patients with hepatocellular carcinoma undergoing transarterial chemoembolisation

Key words: *hepatocellular carcinoma, survival, sodium, TACE, BCLC*

Introduction: Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer deaths worldwide. When surgical resection is not an option transarterial chemoembolization (TACE) is a possible treatment but there is still no consensus on factors affecting survival after TACE.

Aims: To assess overall survival (OS) and identify independent survival risk factors in patients with HCC before undergoing TACE.

Materials and methods: Over a five-year period (2011-2015), 34 unique patients undergoing TACE in Clinical University Hospital were retrospectively assessed before their first TACE. Data included patients sex, age, previous therapy, presence of liver cirrhosis, distant metastases, hepatitis, oesophageal varices, ascites, diabetes, number of nodules, diameter of largest nodule, Barcelona Clinic Liver Cancer (BCLC) stage, MELD score and laboratory values before treatment (ALAT, ASAT, total bilirubin, alkaline phosphatase, albumin, INR, alpha fetoprotein). Data were analysed with SPSS v.20.0.

Results: Out of 34 patients, 64.7 % were male and 35.3 % – female. Median age was 65.5 ± 14.5. Median OS was 15.00 ± 6.47 months. Independent survival risk factors on Cox regression univariate analysis were hepatitis B infection (p=0,044, HR=5.722), diameter of the largest nodule ≥5cm (p=0,015, HR=7.214), sodium level of ≥140 mEq/L (p=0,012, HR=0,175). ASAT and alkaline phosphatase had no effect on survival (p<0.05; HR=1,00). Kaplan-Meier analysis showed that absence of distant metastases, stage B tumour (BCLC) and patients with previous liver surgery had higher OS but it was not statistically significant (p>0.05).

Conclusions: A factor associated with higher OS was serum sodium level of ≥140 mEq/L and with lower OS – presence of hepatitis B infection, diameter of largest nodule ≥5cm. ASAT, alkaline phosphatase, previous liver surgery, presence of distant metastases and BCLC stage (B or C) had no significant effect on OS when performing TACE.

Kopsavilkums

Dzīvildzi ietekmējošie faktori pacientiem ar hepatocellulāru karcinomu pirms transarteriālas ķīmijembolizācijas veikšanas

Atslēgas vārdi: *hepatocellulāra karcinoma, dzīvildze, nātrijs, TACE, BCLC*

Ievads: Hepatocellulāra karcinoma (HCC) starp audzējiem ir trešais biežākais nāves cēlonis pasaulē. Kad ķirurģiska rezekcija nav iespējama, kā ārstēšanas metodi var izmantot transarteriālu ķīmijembolizāciju (TACE), lai gan nav vienprātības par to, kuri faktori ietekmē pacientu dzīvildzi pēc TACE.

Mērķis: Darba mērķis ir novērtēt pacientu dzīvildzi pēc HCC ārstēšanas ar TACE un noskaidrot, kādi riska faktori ietekmē pacientu izdzīvošanu.

Materiāli un metodes: Piecu gadu periodā (no 2011. līdz 2015. gadam) 34 pacienti tika ārstēti ar TACE Klīniskās universitātes slimnīcā un retrospektīvi analizēti. Ievāktie dati bija pacientu dzimums, vecums, iepriekšēja terapija, tika fiksēts vai pacientiem bija aknu ciroze, distālas metastāzes, hepatīts, barības vada varikozas, ascīts, diabēts. Tika fiksēts mezglu skaits, lielākā mezgla diametrs, *Barcelona Clinic Liver Cancer* (BCLC) stadija, MELD skalas rezultāts un laboratorie rezultāti (ALAT, ASAT, kopējo bilirubīnu, nātriju, sārmaino fosfotāzi, albumīnu, INR, alfa fetoproteīnu). Visi iegūtie dati tika apstrādāti SPSS v.20.0.

Rezultāti: No 34 pacientiem 64.7% bija vīrieši un 35.3% bija sievietes. Mediānais vecums bija 65.5±14.5. Mediānā dzīvildze pēc ārstēšanas bija 15.00 ± 6.47 mēneši. Kā neatkarīgos riska faktorus *Cox* regresijas *univariate* analīze uzrādīja hepatīta B infekciju (p=0,044, HR=5.722), lielākā mezgla diametru ≥5cm (p=0,015, HR=7.214), nātrija līmeni serumā ≥140 mEq/L (p=0,012, HR=0,175). ASAT un sārmanā fosfotāze neietekmēja pacientu dzīvildzi (p<0.05; HR=1,00). *Kaplan-Meier* analīze uzrādīja, ka iepriekš operētiem pacientiem un tiem, kam nav distālu metastāžu, kā arī BCLC stadijas B audzēju grupā, bija lielāka kopējā dzīvildze, bet šis rādītājs nebija statistiski ticams (p>0.05).

Secinājumi: Faktori, kas saistās ar lielāku dzīvildzi, bija nātrija līmenis serumā ≥140 mEq/L un faktori, kas saistījās ar zemāku dzīvildzi bija hepatīts B infekcija un lielākā audzēja mezgla diametrs ≥ 5 cm. ASAT, sārmainā fosfotāze, iepriekšēja aknu operācija, distālas metastāzes un BCLC stadija (B vai C) statistiski ticami neietekmēja pacientu dzīvildzi pēc TACE.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of death amongst all oncologic diseases. HCC represents 90% of all primary liver malignancies (Gomaa et al. 2008).

Incidence of primary liver malignancies in Latvia per 100 000 people is 1.8 for female gender and 4.6 for male gender (EASL-EORTC 2012). Men are typically two to three times more likely to develop HCC. One year survival rates for local disease is around 67%, but with distant metastases around 15% (Altekruse et al. 2009).

Amongst all HCC patients approximately 78% have a chronic hepatitis B or C infection, 53 % and 25 %, respectively. (Perz Jet al. 2006)

One way of staging patients with HCC is using The Barcelona Clinic Liver Cancer (BCLC) staging system. BCLC looks at tumour status (size, number, vascular invasion, lymph nodes, distant metastases), liver function (Child–Pugh scale) and patient performance status. These are used as predictive factors to group patients in five stages (0, A, B, C, and D) according to their prognosis and treatment options. For patients with local small tumors the best approach is surgical resection. Unfortunately within five years 70% of patients with HCC will have a recurrence. (EASL-EORTC 2012)

Transarterial chemoembolization (TACE) is a treatment option for BCLC stage B patients that are not suitable for surgical treatment and for those patients who have a disease recurrence. The aim of the treatment is to cut of the blood supply of the tumour and to induce necrosis, that in turn lessens the tumor burden and decrease tumor markers. TACE is usually used as a palliative treatment for BCLC stage B tumors to increase patient survival. (Shin SW 2009)

Because the main objective of this treatment is to extend the patients live there have been a lot of discussions about prognostic factors that affect patient survival. Some of the proposed factors are Child–Pugh class, tumour size (> 5 cm), multinodular disease (more than three nodules), the level of serum sodium (≥ 140 mEq/L), alkaline phosphatase, albumin (< 30 g/l), total bilirubin (> 2 mg/dl), alpha fetoprotein and hepatitis virus B infection, presence of ascites and portal vein thrombosis. (Biolato et al. 2014; Dhanasekaran et al. 2010; McGlynn et al. 2011)

We aimed to assess overall survival rates and to identify survival predictors in patients with HCC before undergoing TACE.

Materials and Methods

Over a five year period (between January 2011 and December 2015) a retrospective study was done in Clinical University Hospital. In total 34 patients were included who met the following criteria:

- patients with diagnosis “Hepatocellular carcinoma” (HCC);
- had at least one TACE session.

Data were obtained from patients medical records and was entered into Microsoft Excel 2007 and later analysed with IBM SPSS v.20.0:

1. patients demographic data (sex, age);
2. number of TACE sessions and previous therapy;
3. etiology and other conditions (virus hepatitis B or C, presence of liver cirrhosis, oesophageal varices, ascites, diabetes mellitus);
4. tumor burden (number of nodules, diameter of largest nodule, bilobarity, presence of distant metastases) and Barcelona Clinic Liver Cancer (BCLC) stage of the tumor;
5. laboratory values before treatment (ALAT, ASAT, total bilirubin, alkaline phosphatase, albumin, INR, alpha fetoprotein) and Model for end stage liver disease (MELD) score.

Data about survival was obtained from Latvian Center for Disease Prevention and Control (LCDPC) database. Survival was analysed using Kaplan-Meier method (p values were assessed with Log Rank and Breslow test) and independent risk factors – using Cox proportional regression model in univariate analysis. Laboratory values were expressed as mean value ± standard deviation. Survival was assessed using its' mean and median values. Results with p value of <0.05 were found to be statistically significant.

Results

Out of 34 patients, 22 (64.7%) were male and 12 (35.3%) – female. Median age was 65.5 ± 14.5 years. Mean survival was 19.37 ± 2.78 months and median survival was 15.00 ± 6.47 months. The 6-, 9- and 12-month survival rates were 67%, 61% and 53%, respectively. There were no differences in terms of survival among male and female patients ($p = 0.90$) and among elderly and younger patients ($p = 0.98$).

Mean number of TACE sessions was 2.8 ± 1.7 (ranging from one to seven). There were no survival rate differences in patients who had more or less TACE sessions.

Twenty-eight patients (82.4 %) had no previous therapy as tumors were unresectable but 6 patients (17.6 %) underwent surgical resection previously and TACE was used because of tumor recurrence. Mean survival in patients who had unresectable HCC was 18.53 ± 3.01 months but in patients with recurrence after surgery it was higher (21.25 ± 5.65 months) however this difference was not statistically significant ($p = 0.76$ in Log Rank test). Mean disease free survival (from surgery till first TACE session) in patients with recurrence was 8.00 ± 1.23 months.

Among etiology of the tumor, most commonly patients had virus infection. In 16 patients (47.1 %) it was hepatitis C virus infection, in 2 patients (5.8 %) it was hepatitis B virus infection and for 16 patients (47.1 %) etiology was other (e.g., alcochol use) or unknown. Among other conditions, diabetes mellitus was present in 7 patients (21.2 % of cases), liver cirrhosis – in 16 patients (57.1 % of cases), oesophageal varices in 11 patients (34.4 % of cases) and ascites in 6

patients (18.2 % of cases). From above mentioned factors, only hepatitis B virus infection was found to be statistically significant survival predictor (p = 0.044; hazard ratio (HR) = 5.722; 95 % confidence interval (CI): 1.04 – 31.91), where in these patients mean survival was lower (6.50 ± 5.50 months) than in patients without hepatitis B virus infection (27.72 ± 4.10 months).

Tumor burden (number of nodules and diameter of the largest nodule) is shown in Figure 1. Mean number of nodules was 1.9 ± 0.96 (ranging from one to four). Patients were divided in two groups: group A with only one nodule and group B with multinodular disease. Mean survival in group A was higher (20.85 ± 3.84 months) than in group B (18.27 ± 3.96 months) but it was not statistically significant. Mean diameter of the largest nodule was 5.74 ± 2.39 cm. These patients were also divided in two groups: patients with largest nodule diameter < 5 cm (group C) and largest nodule diameter of ≥ 5 cm (group D). Mean survival was higher in group C (32.83 ± 2.98 months) than in group D (11.15 ± 2.87 months) and it was statistically significant (p = 0.006 in Log Rank test).

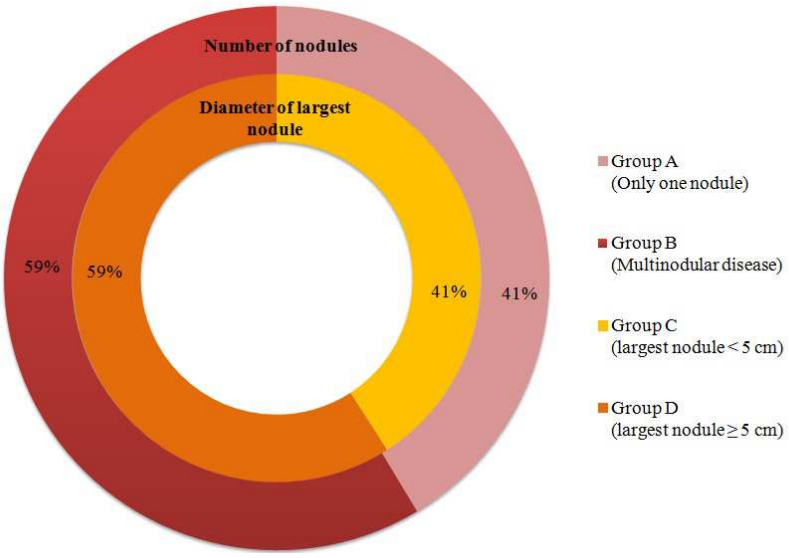

Figure 1. **Distribution of tumor burden groups amongst patients with hepatocellular carcinoma undergoing transarterial chemoembolisation**

Only three patients (8.8 %) had nodules in both lobes (bilobarity). Their mean survival was lower (7.00 ± 2.45 months) than in patients with nodule in one lobe (19.42 ± 2.85 months), but it was not significant (p = 0.94). Distant metastases (TNM classifications) were present in 5 patients (29.4 % of cases). Mean survival was higher in patients with no metastases (20.31 ± 4.57 months) than in those with metastases (9.60 ± 4.76 months) but again it was not significant (p = 0.247).
BCLC stages were evaluated in only 15 patients due to lack of information about portal invasion and lymph node metastases. There were only stage B (8 patients) and stage C (7 patients) tumors in our study. Mean survival in patients with stage B tumor was 24.13 ± 5.53 months but with stage C tumor – 10.43 ± 3.99 months. This difference was not statistically significant (p = 0.194). It is shown in Figure 2.

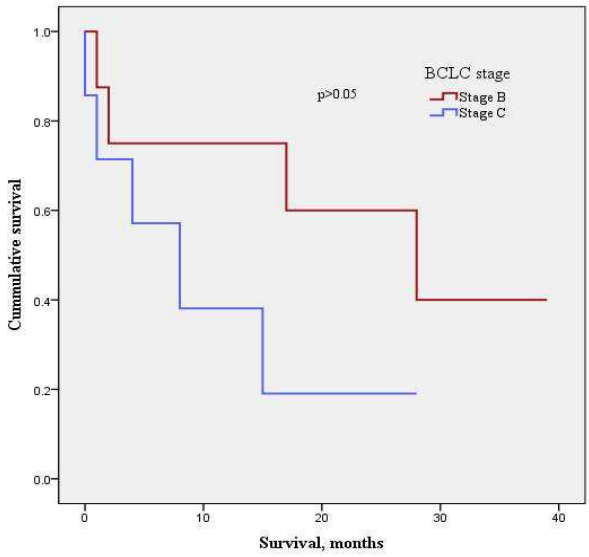

Figure 2. **Survival function depending on BCLC classification amongst patients with hepatocellular carcinoma undergoing transarterial chemoembolisation (*Kaplan-Meier* analysis)**

Laboratory values and results from Cox proportional regression model univariate analysis are shown in Table 1. Two values were further evaluated from a determined cut-off level. For serum sodium it was 140 mEq/l as it was the lowest value when it still had statistical significance. For alpha fetoprotein (AFP) the cut-off value was 20 ng/ml. This value was chosen because of its' association with poorer prognosis in literature.

Table 1. **Baseline laboratory values and survival predictors in *Cox* proportional regression model univariate analysis**

	Mean ± standard deviation	**p value[3]**	**Hazard ratio**	**95 % confidence interval**	
				Upper	**Lower**
Alanine aminotransferase (U/l)	67.68 ± 46.93	NS	-	-	-
Aspartate aminotransferase (U/l)	148.92 ± 323.14	.028	1.002	1.000	1.003
Total bilirubin (mmol/l)	36.74 ± 45.13	NS	-	-	-
Alkaline phosphatase (U/l)	195.85 ± 177.45	.039	1.003	1.000	1.006
Albumin (g/l)	37.66 ± 6.57	NS	-	-	-
Creatinine (μmol/l)	67.98 ± 19.72	NS	-	-	-
Serum sodium (mEq/l)	140.32 ± 3.25	.011	.715	.553	.926
Serum sodium ≥140 mEq/l	-	.012	.175	.045	.679
International normalised ratio	1.12 ± 0.30	NS	-	-	-
Alpha fetoprotein (ng/ml)	141.76 ± 172.67	NS	-	-	-
Alpha fetoprotein ≥20 ng/ml	-	NS	-	-	-

Four laboratory values proved to be significant for survival. Changes in aspartate aminotransferase and alkaline phosphatise levels do not predict survival (hazard ratio = 1.00). Higher serum sodium levels were associated with higher OS (see figure 3). In our study, we determined the cut-off at 140 mEq/l. Patients with serum sodium under cut-off value had mean

[3] NS – not significant

survival of 11.55 ± 4.73 months whereas patients with serum sodium level of ≥140 mEq/L had mean survival of 30.11 ± 3.96 months (p = 0.005). Also, MELD score was calculated and mean value in our patients was 10 ± 3 points. This value had no significance in predicting survival.

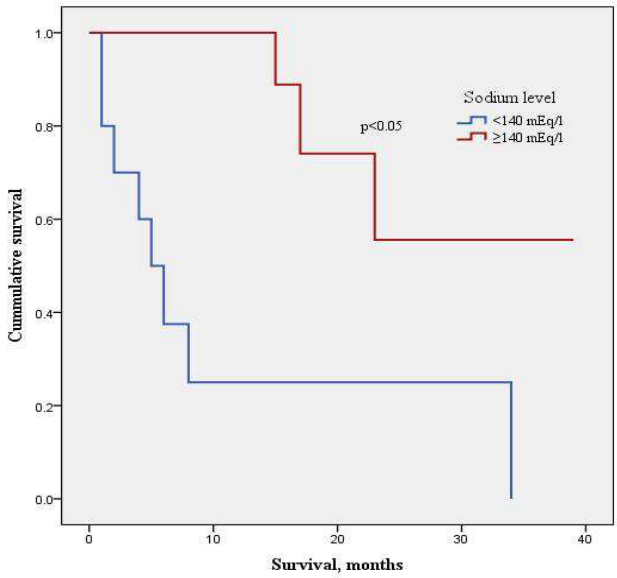

Figure 3. **Survival function depending on serum sodium level amongst patients with hepatocellular carcinoma undergoing transarterial chemoembolisation (*Kaplan-Meier* analysis)**

Discussion

Our study found several significant factors for predicting survival aswell as some factors that might not be taken into account when predicting survival before performing TACE. Some of the factors had already been established in other studies (hepatitis B virus infection and diameter of largest nodule) and our study double-proved their significance for predicting survival (Biolato et al. 2014).

Many studies had approached the question of alpha fetoprotein specificity in predicting prognosis and survival in patients with HCC. The diagnostic values of this marker vary according to the chosen cut-off values. In cirrhotic patients, when the cut-off value is 20 ng/mL, its specificity can be even 90% (Hsu et al 2015; Wang et al. 2012). Our study showed no specificity in predicting survival at this cut-off level. On contrary, reduction of AFP by 20 % correlated with median OS in patients undergoing TACE in a different study (Lee et al. 2012). In our study, patients with lower AFP levels had higher OS but it was not statistically significant.

Another interesting finding was the role of higher serum sodium level in predicting better overall survival. There are many studies that agree with our findings and also suggest hyponatriemia to be a factor for higher complication rates and lower patient performance status, (Zhang et al. 2014; Hiroki Nishikawa et al, 2015). Latter study included more than 1000 patients

and 5 year survival rates were 48.2 % in patients with higher serum sodium than in patients with lower serum sodium (25 %). Also, we need to take into consideration that MELD criteria in 2016 was updated and serum sodium was included as important prognostic factor for predicting survival and eligibility for liver transplantation.

There is no consensus on BCLC staging system and its usefulness in predicting candidate patients before TACE. It is recommended for stage B cancers to be treated with TACE. Our study showed that TACE can be done in stage B aswell as stage C tumors by not having a significant difference in terms of survival. In another study BCLC staging system was considered only second top-ranking staging system and was not helpful in predicting survival (Zhang et al. 2014).

Alongside above mentioned factors, patients with distant metastases had lower OS rates. Although this finding was not statistically significant, other studies showed (Zhang et al. 2014) similar OS rates, but they were significant in predicting survival. Therefore, even though our study did not show significance we should take into consideration presence of distant metastases before choosing TACE as an alternative treatment option.

Conclusions

A factor associated with higher OS was higher serum sodium level and with lower OS – presence of hepatitis B infection, larger nodule diameter.

ASAT, alkaline phosphatase, previous liver surgery, presence of distant metastases and BCLC stage (B or C) had no significant effect on OS when performing TACE and they might not be taken into account in terms of survival when choosing TACE as an optional treatment for patients with HCC.

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SURVIVAL PREDICTORS IN PATIENTS WITH UNRESECTABLE PERIHILAR CHOLANGIOCARCINOMA UNDERGOING PALLIATIVE BILIARY STENTING

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Abstract

Survival predictors in patients with unresectable perihilar cholangiocarcinoma undergoing palliative biliary stenting

Key words: *perihilar cholangiocarcinoma, survival, tumor markers, stenting, palliative therapy*

Introduction: Perihilar cholangiocarcinoma (PCCA) is a rare bile duct malignancy. Only 30% of them are resectable. The rest can be managed by biliary stenting but there is still no consensus on factors before this procedure that affect survival.

Aim: To find out prognostic survival factors in patients with unresectable PCCA before undergoing palliative biliary stenting.

Materials and methods: This retrospective study included 36 patients from 2011-2015 with unresectable PCCA who underwent palliative biliary stenting in Clinical University Hospital. Data included patients sex, age, patient co-morbidities, method of stenting, stent material, laboratory values, tumor markers CEA, CA19-9, MELD criteria, size of the tumor, presence of metastases and *Bismuth-Corlette* classification. Data were analysed by SPSS v.20.0 (Kaplan-Meier method for survival, Cox regression univariate analysis for independent risk factors assessement).

Results: Of 36 patients 47.2 % were female and 52.8 % – male. Mean age was 67.33 ± 18.25 ranging from 45 till 89. Mean overall survival (OS) was 6.43 months. Minority of patients (22.2 %) had endoscopic and 77.8 % - percutaneous stenting. In 54.8 % plastic stent was used and in 45.2 % - metal stent. Metal stent group was associated with higher OS compared with plastic stent group (p=0.041). Patients with MELD score of ≥23 had statistically lower OS (p=0.033). Independent risk factors were presence of oesophageal varices (p=0.043; HR=2.973), extrahepatic metastases (p=0.039; HR=4.112), albumin (p=0.035; HR=0.887), INR ≥1.4 (p=0.025; HR=3.069), CA19-9 ≥200 U/ml (p=0.049; HR=3.261), CEA ≥14 U/ml (p=0.005; HR=5.014).

Conclusions: Patients in metal stent group had better OS rates than those in plastic stent group. Most important prognostic factors before stenting were presence of oesophageal varices, albumin level, INR, CA19-9, CEA, MELD score and presence of extrahepatic metastases.

Kopsavilkums

Dzīvildzi ietekmējošie faktori pacientiem ar nerezecējamām perihilārām holangiokarcinomām pirms paliatīvas žultsceļu stentēšanas

Atslēgas vārdi: *perihilāra holangiokarcinoma, dzīvildze, audzēju marķieri, stentēšana, paliatīva aprūpe*

Ievads: Perihilāras holangiokarcinomas (PCCA) ir reti, ļaundabīgi žults ceļu audzēji. Tikai 30% no tām ir rezecējamas. Pārējie pacienti ir kandidāti paliatīvai terapijai, piemēram, žults ceļu stentēšanai, tomēr joprojām nav konkrētu faktoru, kas ietekmētu dzīvildzi pirms šīs procedūras uzsākšanas.

Mērķis: Identificēt dzīvildzi ietekmējošus faktorus pacientiem ar PCCA pirms paliatīvas žultsceļu stentēšanas.

Materiāli un metodes: Šis retrospektīvais pētījums iekļāva 36 pacientus laika periodā no 2011. līdz 2015. gadam ar nerezecējamu PCCA, kuriem pirmo reizi tika veikta paliatīva žultsceļu stentēšana Klīniskā Universitātes slimnīcā. Tika analizēti šādi dati: dzimums, vecums, blakusstāvokļi, stentēšanas metode un izmantotais materiāls, laboratorie rādītāji, audzēju marķieri (CEA, CA19-9), MELD skalas kritēriji, audzēja izmērs, metastāžu klātbūtne un *Bismuth-Corlette* klasifikācija. Dati tika analizēti ar SPSS v.20.0 (*Kaplan-Meier* metode dzīvildzes analīze un *Cox* regresijas proporcionālā modeļa *univariate* analīze neatkarīgo riska faktoru identificēšanai).

Rezultāti: No 36 pacientiem 47.2 % bija sievietes un 52.8 % – vīrieši. Vidējais vecums bija 67.33 ± 18.25 gadi (no 45 līdz 89 gadiem). Vidējā kopējā dzīvildze (OS) bija 6.43 mēneši. Mazākajai daļai pacientu (22.2 %) veica endoskopisku, stentēšanu bet 77.8 % - perkutānu stentēšanu. Biežāk (54.8 %) izmantots tika plastikāta stents, bet retāk (45.2 %) – metāla stents. Pacienti ar implantētu metāla stentu uzrādīja augstāku OS nekā pacienti ar implantētu plastikāta stentu (p = 0.041). Pacientiem ar ≥23 punktiem pēc MELD skalas bija zemāka OS (p=0.033). Netakarīgie riska faktori bija barības vada vēnu varices (p=0.043; HR=2.973), ekstrahepatiskas metastāzes (p=0.039; HR=4.112), albumīna līmenis (p=0.035; HR=0.887), INR≥1.4 (p=0.025; HR=3.069), CA19-9 ≥200 U/ml (p=0.049; HR=3.261), CEA ≥14 U/ml (p=0.005; HR=5.014).

Secinājumi: Pacientiem ar implantētu metāla stentu bija lielāka kopējā vidējā dzīvildze nekā pacientiem ar plastikāta stentu. Svarīgākie dzīvildzi ietekmējošie faktori pirms stentēšanas bija barības vada vēnu varices, albumīna līmenis, INR, CA19-9, CEA, punkti pēc MELD skalas un ekstrahepatisku metastāžu klātbūtne.

Introduction

Perihilar cholangiocarcinoma (PCCA), is a rare malignancy (2 – 4 : 100 000) that originates from the epithelial cells of the bile duct. It is the most common tumor amongst all bile duct tumors (46 % - 97 %) and the second most common primary malignant tumor of the liver with rising incidence and poor survival prognosis. (Valero et al. 2012)

It is localised anywhere between confluence of both hepatic ducts (biliary confluence) and above the site of cystic duct origin. Only 30% of them are resectable due to late diagnostics. The rest are managed palliatively. (Razumilava et al. 2013)

Perihilar cholangiocarcinomas can be further classified using *Bismuth-Corlette (B-C)* classification which is used in practice for more than 40 years. It is helpful in choosing the best treatment option (surgical resection, transplantation or palliative treatment). It is based on the exact location of tumor and has five types – I, II, IIIa, IIIb, IV, respectively. (Plentz et al. 2015)

Biliary stenting is a palliative treatment option in order to relieve symptoms of obstruction such as jaundice, and to improve quality of life. There are two techiques used for stenting: endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTCA). The choice between these two techniques is based upon *B-C* classification. ERCP is recommended for B-C type I and II, but PTCA – for type III and IV. Comparing both methods, technical success rate is higher using PTCA. There is also a choice between stent materials: plastic or self-expandable metal stent. Self-expandable metal stent is recommended in case if patients' survival is going to be more than 3 months, otherwise it is recommended to use plastic stent. (Goenka et al. 2014)

There are no established factors that could predict survival in patients before palliative biliary stenting. However, there are some proposed factors that have predictive role in all PCCA patients, such as early tumor stage, tumor location, albumin, alanine aminotransferase and gamma-glutamyltransferase levels. (Yusoff et al. 2012; Coelho et al. 2017)

Also, tumor markers have an informative role in predicting survival but there are no clear levels that indicate a poorer prognosis. However, carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) have been shown to correlate with tumor stage, unresectability and overall survival. (Malaguarnera G et al. 2011)

The aim of this study was to find out prognostic survival factors in patients with unresectable PCCA before undergoing palliative biliary stenting.

Materials and Methods

Over a five year period (between January 2011 and December 2015) a retrospective study was done in Clinical University Hospital. In total 36 patients were included who met the following criteria:

- patients with diagnosis “Perihilar cholangiocarcinoma” (PCCA);
- underwent planned biliary stenting (endoscopic or percutaneous);
- patient had no previous history of biliary stenting

Confirmation of the PCCA diagnosis was made by using radiological findings (computed tomography) and biopsy specimens from the tumor. The B-C classification initially was applied using CT imaging but confirmed only after performing stenting procedure, using ERCP or PTCA data. Also, none of these patients had cholangitis at the time of performing stenting procedure.

Other data were obtained from patients medical records, was entered into *Microsoft Excel 2007* and later analysed with *IBM SPSS v.20.0*:

1. patients demographic data (sex, age);
2. method of stenting (ERCP or PTCA) and stent material (plastic or metal);
3. patient co-morbidities (virus hepatitis B or C infection, presence of liver cirrhosis, oesophageal varices, ascites, diabetes mellitus);
4. tumor burden (size of the tumor, presence of metastases and portal vein thrombosis) and *Bismuth-Corlette* classification;
5. complication rate after stenting procedures;
6. laboratory values before treatment (ALAT, ASAT, alkaline phosphatise, GGT, total bilirubin, albumin, creatinine, sodium, INR) and Model for end stage liver disease (MELD) score;
7. tumor markers CEA, CA19-9.

Data about survival was obtained from Latvian Center for Disease Prevention and Control (LCDPC) database. Survival was analysed using Kaplan-Meier method (p values were assessed with *Log Rank* and *Breslow* test) and independent risk factors – using *Cox* proportional regression model in univariate analysis. Laboratory values were expressed as mean value ± standard deviation. Survival was assessed using its’ mean and median values. Results with p value of <0.05 were found to be statistically significant.

Results

Of 36 patients 17 (47.2 %) were female and 19 (52.8 %) – male. Mean age was 67.33 ± 18.25 years (ranging from 45 till 89). Mean survival from the date of procedure was 6.43 ± 1.39 months (95 % CI: 3.70 – 9.15). 3-, 6- and 12-month survival rates were 47.7 %, 30.6 % and 16.7 %, respectively. There were no differences in terms of survival among male and female patients ($p = 0.82$) and among elderly and younger patients ($p = 0.99$).

Distribution between stenting method and materials are shown in Figure 1. PTCA was done more frequently than ERCP. Mean survival was a little higher after PTCA (6.54 ± 1.53 months) than it was after ERCP (5.13 ± 2.66 months) but it was not significant ($p = 0.703$ in Log Rank test).

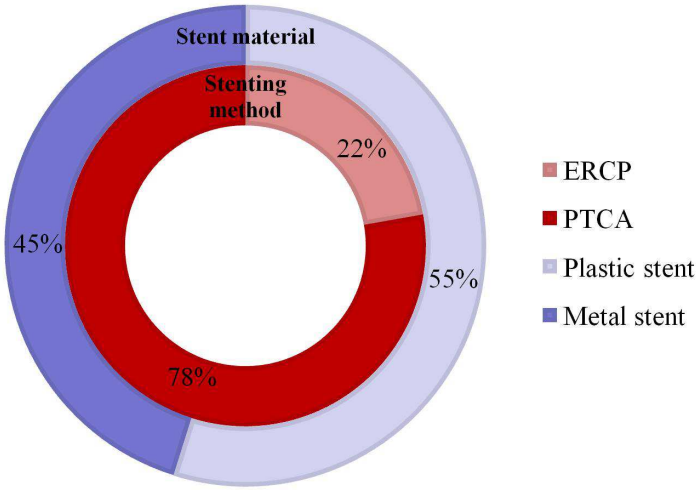

Figure 1. **Distribution between stenting method and stent material amongst patients with perihilar cholangiocarcinoma before biliary stenting**

Only one patient had a complication after performing stenting – iatrogenic pancreatitis after ERCP. Patients' survival in this case was 1 month and it was lower than the mean and median survival rates in the group but it was not included in statistical analysis because of only one case present.

Distribution between stent material (plastic or self-expandable metal stent) was similar (see Fig.1). Metal stent group was associated with higher survival compared with plastic stent group ($p = 0.041$). Mean survival in plastic stent group was 3.65 ± 1.31 months but in self-expandable metal stent group it was 10.07 ± 2.69 months (Figure 2).

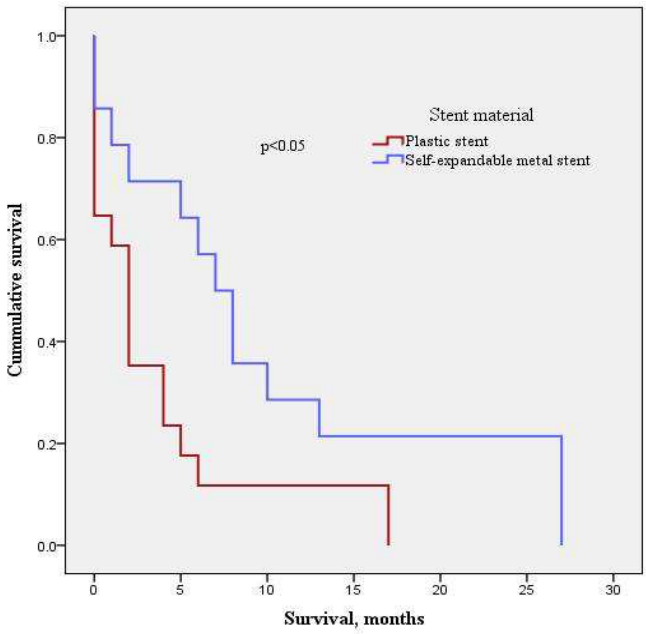

Figure 2. **Survival function and stent material amongst patients with perihilar cholangiocarcinoma before biliary stenting (*Kaplan-Meier* analysis)**

Distribution amongst other patient co-morbidities is shown in Figure 3. Most commonly patients presented with oesophageal varices (5 patients). None of the patients were diagnosed with hepatitis C virus infection.

Only presence of oesophageal varices was found to be statistically significant independent survival predictor ($p = 0.043$; hazard ratio (HR) = 2.973; 95 % confidence interval (CI): 1.033 – 8.557), where in these patients mean survival was lower (1.40 ± 1.17 months) than in patients without oesophageal varices (7.60 ± 2.07 months).

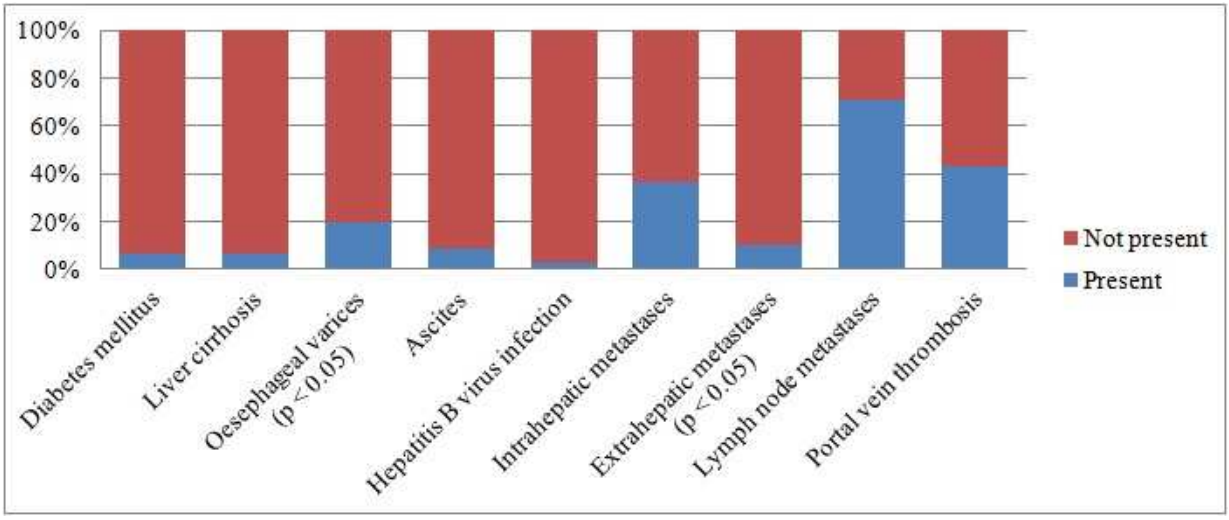

Figure 3. **Co-morbidities and tumor burden amongst patients with perihilar cholangiocarcinoma before biliary stenting and their significance in predicting survival**

Distribution amongst tumor burden (presence of distant metastases and portal vein thrombosis) is shown in Figure 3. Most commonly, patients presented with lymph node metastases. Mean survival in these patients was 3.08 ± 0.95 months. There were also 3 patients with portal vein thrombosis (mean survival of 4.67 ± 3.71 months), 11 patients with intrahepatic metastases (mean survival of 4.00 ± 1.50 months) and 3 patients with extrahepatic metastases (mean survival of 0.33 ± 0.33 months). Only presence of extrahepatic metastases were associated with significantly lower survival rates ($p = 0.011$). It was also found to be an independent survival predictor ($p = 0.039$; HR = 4.112; 95 % CI: 1.074 – 15.736). Tumor size was also evaluated. Mean tumor size was 4.53 ± 3.53 centimetres but it was not prognostic for survival.

Bismuth-Corlette classification was assessed in 27 of 36 patients due to lack of radiological information. All types were present in these patients. Most commonly patients presented with type IV lesion (33.3 %). Type I was present in 18.5 %, type II – in 25.9 % and type III – in 22.2 %. Lowest mean survival was in patients with type IIIa and IIIb lesions (3.00 ± 1.67 months), whereas for type I lesions it was the highest (8.00 ± 3.85 months). However, this association was not significant.

Laboratory values and results from Cox proportional regression model univariate analysis are shown in Table 1. Four values were further evaluated from a determined cut-off level. For INR it was 1.4, for albumin it was 28.0 g/l and for CEA it was 14 U/ml when they still had statistical significance. Because CA 19-9 was not significant independent prognostic factor we used a cut-off level of 200 U/ml because of its' association with poorer prognosis in literature.

Table 1. **Baseline laboratory values and survival predictors in *Cox* proportional regression model univariate analysis**

	Mean value ± standard deviation	**p value[4]**	**Hazard ratio**	**95 % confidence interval**	
				Upper	**Lower**
Alanine aminotransferase (U/l)	124.22 ± 103.71	NS	-	-	-
Aspartate aminotransferase (U/l)	118.25 ± 85.83	NS	-	-	-
Total bilirubin (mmol/l)	257.19 ± 154.55	NS	-	-	-
Alkaline phosphatase (U/l)	573.25 ± 327.99	NS	-	-	-
Gamma-Glutamyl Transferase (U/l)	916.80 ± 762.60	NS	-	-	-
Albumin (g/l)	26.06 ± 5.86	.035	.887	.794	.991
Albumin ≥ 28 g/l	-	.042	.195	.041	.940
Creatinine (μmol/l)	70.83 ± 36.16	NS	-	-	-
Serum sodium (mEq/l)	138.38 ± 3.59	NS	-	-	-
International normalised ratio (INR)	1.27 ± 0.57	.034	1.959	1.054	3.642
INR ≥ 1.4	-	.025	3.069	1.153	8.171
CEA level (U/ml)	59.28 ± 146.84	.023	1.004	1.001	1.008
CEA ≥ 14 U/ml	-	.005	5.014	1.617	15.552
CA 19-9 level (U/ml)	990.82 ± 2073.37	NS	-	-	-
CA 19-9 ≥ 200 U/ml	-	.049	3.261	1.005	10.579

Two laboratory values proved to be significant survival predictors. Higher albumin levels were associated with higher survival rates. In our study, we determined the cut-off at 28 g/l. Patients with albumin level under cut-off area had mean survival of 10.17 ± 3.09 months whereas patients with albumin level level of ≤ 28 g/l had mean survival of 2.90 ± 0.82 months (p = 0.019). INR ≥ 1.4 was associated with lower survival rates (mean survival of 1.50 ± 0.81 months).

Higher CEA levels (≥ 14 U/ml) were associated with poorer mean survival (2.70 ± 1.17 months) and for CA 19-9 it was 200 U/ml (mean survival of 3.73 ± 1.09 months). See Figure 4.

[4] NS – not significant

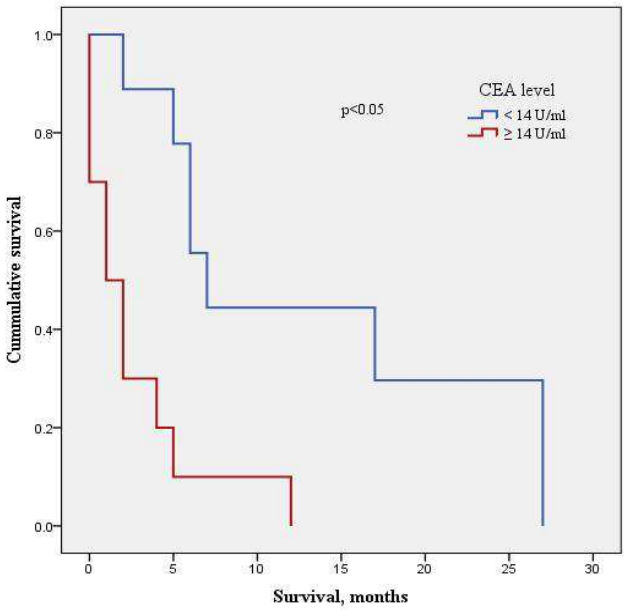

Figure 4. **Survival function depending on CEA level in patients with perihilar cholangiocarcinoma before biliary stenting (*Kaplan-Meier* analysis)**

Also, MELD score was calculated and mean value in our patients was 19.15 ± 5.13 points. This value had significance in predicting survival if the score was ≥ 23 and associated with lower survival rates (p = 0.033).

Discussion

Our study showed that mean and median survival rates in patients with PCCA before palliative biliary stenting are indeed, low. In recent study median survival for PCCA patients was 13.9 months, which was higher than in our study. This study, however included other treatment methods (Waseem et al. 2017). In another study a mean survival of 17.1 months in 24 patients with cholangiocarcinoma undergoing palliative stenting was shown (Vasilieva et al. 2016). This raises the need for early diagnostics and precise location of the disease.

Comparing stenting techiques, our study showed that PTCA is used more commonly than ERCP and this is a good practice that should be used in patients with PCCA as it is associated with higher technical success rate in other studies (Goenka et al, 2014).

In our study, the ratio between self-expandable metal stent and plastic stent usage was 1:1. It should be noted that metal stents are associated with better survival rates than plastic stents not just in our study but in other studies aswell where patients with metal stents had OS of 5 months compared with plastic stents where OS was 1.5 months. (Sangchan et al. 2012) However, we also need to take into consideration that plastic stent can be changed in case of dysfunction whereas this cannot be done in case of a metal stent.

Bismuth-Corlette classification showed no prognostic value in terms of survival. Similar findings have been published in recent studies. Therefore, it should be used only when choosing the most appropriate technique of the treatment. (Goenka et al. 2014)

Amongst laboratory values albumin, INR and MELD score (calculated from creatinine, serum sodium, total bilirubin and INR) proved to be significant for survival. We need to take into account that in Year 2016 MELD criteria was revised and PCCA was added as an exception with automatically assigning MELD score of 22. We analysed MELD score despite this exception but our findings were justified as they suggest its predictive role when MELD score is ≥ 23 points. (Kamath 2016)

Both CA 19-9 and CEA can be found in malignant biliary tract obstruction. Recent studies suggest that CEA has high specifity and it correlates with poor overall survival at cut-off level of 2.8 U/ml (Liska V et al. 2017). Another study showed that CEA level at 400 U/ml is just as specific as it is at 100 ng/ml in diagnosis of PCCA (Chalasani N et al 2000). In our study cut-off level for CEA was 14 U/ml and it had prognostic significance in overall survival. Elevated CA 19-9 levels (> 1000 U/ml) correlate with advanced disease and poor survival. (Juntermanns B et al. 2010) In our study patients with advanced disease were associated with poorer survival at cut-off level of 200 U/ml. This raises the probability of low CEA and high CA 19-9 level roles in predicting survival.

This study clearly indicated factors that have that do not have high relevance in order to choose the best treatment option for PCCA patients. However, this study had also some limitations – PCCA is a rare disease and in order to evaluate it more thoroughly, studies in larger cohorts and larger periods should be done.

Conclusions

Patients in metal stent group had better survival rates than those in plastic stent group.

Most important prognostic factors before stenting were presence of oesophageal varices, presence of extrahepatic metastases, albumin level, INR, MELD score.

Tumor marker CEA has predictive role in survival already at low levels, wheras for CA 19-9 it is only at high levels.

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POSTNATAL FACTORS ASSOCIATED WITH ANAEMIA OF PREMATURITY AND NEED FOR RED BLOOD CELL TRANSFUSION

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Abstract
Key words: *Anaemia of prematurity, transfusion of red blood cells*
Introduction: Anaemia is a common multifactorial issue in very premature infants hospitalised in Neonatal Intensive Care Unit. A lot of different factors and their combinations may trigger development of anaemia and consequently a transfusion of red blood cells (RBC).
Aim: The aim of this study was to determine the most common possible postnatal causes that may exacerbate anaemia of prematurity and to detect their connection with the need of RBC transfusion.
Materials and methods: A retrospective medical record review was done for 70 preterm neonates who were admitted to Neonatal Intensive Care Unit at Children's Clinical University Hospital from September 2014 till November 2016. The first four weeks of hospitalisation were analysed and included neonates with birth weight <1.500g or gestational age <32 weeks.
Results: In total 79% (n=55) of neonates had anaemia, 36% (n=25) of neonates received transfusion of RBC. The most common triggers were identified: blood loss due to phlebotomy or various bleeding, surgical manipulations and infections. Blood loss due to phlebotomy expierenced 100% (n=70) of neonates. The average blood volume collected per four weeks was 14.7 ml/kg (0.53 ml/kg/day) or around 14.7 % of total blood volume. Altogether 40% (n=28) of neonates had loss of blood ≥10% of total blood volume. We were comparing data between two groups: neonates who underwent RBC transfusion and neonates who did not. Results show that those who underwent RBC transfusion lost on average 20.23 ml/kg due to blood sampling per four weeks. Those who did not undergo RBC tranfusion – 9.62 ml/kg. Blood loss due to other causes were found in 70% (n=49), the most frequent type of bleeding was intraventricular hemorrhage – 66% (n=46) of all neonates. 80% (n=20) of them who underwent transfusion of RBC had some type of bleeding simultaneously and 64% (n=29) of neonates who did not undergo transfusion. Surgical manipulations experienced 10% (n=7) of neonates. 49% (n=34) of neonates were diagnosed with infection. Among those neonates who underwent transfusion of RBC 60% (n=15) had infection, among those who did not undergo transfusion 40% (n=19) had infection. 56% (n=14) of neonates who underwent transfusion of RBC had all three main triggers simultaneously: phlebotomy, various bleeding and infection.
Conclusions: Three most common triggers were identified: blood loss due to phlebotomy, bleeding and infections. All these triggers were found more often between those neonates who underwent transfusion of RBC. And very often they have affected neonate at the same time.

Kopsavilkums
Atslēgvārdi: *Priekšlaikus dzimuša bērna anēmija, Eritrocītu masas transfūzija*
Ievads: Anēmija ir multifaktoriālas etioloģijas hematoloģiska saslimšana, kas ir bieži sastopama priekšlaikus dzimušiem bērniem, kuri ir stacionēti Jaundzimušo intensīvās terapijas nodaļā (JITN) Dažādi faktori un to kombinācijas var veicināt anēmijas attīstību un sekojošu nepieciešamību pēc eritrocītu masas transfūzijas.
Mērķis: Noskaidrot biežāk sastopamos postnatālos priekšlaikus dzimuša bērna anēmijas pastiprinošos faktorus un noskaidrot to saistību ar anēmiju un eritrocītu masas transfūziju.
Materiāli un metodes: Tika veikts retrospektīvs pētījums, ievācot un analizējot datus no BKUS arhīva medicīniskajām kartēm. Pētījumā tika atlasīti 70 jaundzimušie ar svaru zem 1 500 gramiem vai ar gestācijas laiku zem 32 nedēļām, kuri iestājušies BKUS JITN nodaļā laika posmā no 2014. gada septembra līdz 2016. gada novembrim. Analizētas pirmās četras nedēļas slimnīcā.
Rezultāti: Pētījuma rezultāti rāda, ka anēmija attīstījusies 79% (n= 55) jaundzimušo, eritrocītu masas transfūzija veikta 36% (n=25) jaundzimušo. Visbiežākie anēmijas izraisošie faktori tika identificēti: asins zudums asins analīžu veikšanas laikā, dažāda veida hemorāģijas, infekcijas un ķirurģiskas operācijas. Asins zudumu analīžu laikā pieredzēja 100% (n=70) jaundzimušo. Vidējais noņemtais asins daudzums vienam bērnam četru nedēļu laikā ir 14,68 ml/kg (0,5 ml/kg/dienā) jeb aptuveni 14,68% no kopējā cirkulējošā asins tilpuma. Visās četrās nedēļās kopā vairāk kā 10% asins tilpuma zaudējuši 40% (n=28) jaundzimušo. Bērnam, kuram ir veikta eritrocītu masas pārliešana vidējais paņemtais asins tilpums pirmajās četrās nedēļās ir vairāk kā divas reizes lielāks nekā bērnam, kuram nav veikta EM transfūzija - 20,23 ml/kg pret 9,62 ml/kg. Asins zudums dažāda veida asiņošanas laikā tikai atrasts 70% (n=49) jaundzimušo,

visbiežāk atrastais asiņošanas veids ir intraventrikulāra hemorāģija – 66% (n=46) jaundzimušo. Jaundzimušo grupā, kurā tika veikta eritrocītu masas transfūzija – 80% (n=20) bērnu atrasta dažāda veida asiņošana. Grupā, kurā netika veikta eritrocītu masas transfūzija – 64% (n=29) bērnu atrasta dažāda veida asiņošana. Ķirurģiskas operācijas tika veiktas 10% (n=7) jaundzimušo. Infekcijas tika diagnosticēta 49% (n=34) jaundzimušo. No tiem, kuriem veikta eritrocītu masas transfūzija- 60% (n= 15) diagnosticēta infekcija. No tiem, kuriem nav veikta eritrocītu masas transfūzija – 40% (n=19) diagnosticēta infekcija. Visi trīs galvenie anēmijas pastiprinošie faktori – asins zudums analīžu laikā, dažādu veidu asiņošana un infekcijas- vienlaicīgi tika atrasti 56% (n=14) jaundzimušo, kuriem veikta eritrocītu masas transfūzija.
Secinājumi: Visbiežākie anēmijas pastiprinošie faktori tika identificēti: asins zudums asins analīžu veikšanas laikā, dažāda veida asiņošanas un infekcijas. Visi šie faktori biežāk tiek atrasti jaundzimušo grupā, kurā veikta eritrocītu masas transfūzija un ļoti bieži šie faktori skar jaundzimušo vienlaicīgi.

Introduction

Anaemia of prematurity (AOP) is the most common haematological complication in preterm infants that typically occurs during 4th – 8th week of life from a variety of physiological and pathological factors. In preterm neonates anaemia is a pathologic process, usually symptomatic and requires frequent red blood cell (RBC) transfusions. And because of AOP critically ill newborns in the NICU are among the most heavily transfused patient groups – various studies have shown that around 80% of neonates in NICU receive transfusion of RBC. (Martin 2010, Widness 2008).

Various triggers of anaemia can be divided in three groups: blood loss, decreased RBC production and increased RBC destruction. All these factors may act on a newborn prenatally, intranatally and postnatally. Specifically preterm neonates have physiological factors that contribute anaemia – decreased synthesis of erytropoietin, shortened erytrocytes lifespan and decreased amount of iron. All additional triggers of anaemia should be clarified and prevented to improve the state of neonate and avoid transfusion of RBC. (Macdonald 2015).

Materials and methods

A retrospective medical record review was done for 70 preterm neonates who were admitted to Neonatal Intensive Care Unit at Children's Clinical University Hospital from September 2014 till November 2016. The first four weeks of hospitalisation were analysed and included neonates with birth weight <1.500g or gestational age <32 weeks. Data about anaemia, transfusion of RBC, diagnosis, performed blood tests and their volumes was mainly obtained. The data was gathered over the time span of two months (from November 2016 until December 2016). Results were summarized and statistically processed by *Microsoft Excel* and *IBM SPSS*. Mainly descriptive statistics were used and statistically significant result was considered when $p < 0.05$.

Results

Gestation time of neonates ranged from 24 to 31 weeks. The mean gestation time – 28 weeks. 51% (n=36) of neonates were boys, 49% (n=34) - were girls. Average birth weight – 1255 (650 – 1980) grams.

In total 79% (n=55) of neonates had anaemia, 36% (n=25) of neonates received transfusion of RBC. Anaemia and necessity of RBC transfusion is inversely proportional to birth weight. 94% of

neonates with extremely low birth weight expierenced anaemia and 47% of them received transfusion of RBC. 60% of neonates with low birth weight developed anaemia and 26% of them received transfusion of RBC.

The most common triggers were identified: blood loss due to phlebotomy or various bleeding, surgical manipulations and infections.

Blood loss due to phlebotomy expierenced 100% (n=70) of neonates. The average blood volume collected per four weeks was 14.7 ml/kg (0.53 ml/kg/day) or around 14.7 % of total blood volume. Altogether 40% (n=28) of neonates had loss of blood ≥10% of total blood volume – more than maximum recommended blood loss due to blood sampling. More than 20% blood loss had 19% of neonates – in this case we can say that they have secondary iatrogenic anaemia. We were comparing data between two groups: neonates who underwent RBC transfusion and neonates who did not. Results show that those who underwent RBC transfusion lost on average 20.23 ml/kg due to blood sampling per four weeks. Those who did not undergo RBC tranfusion – 9.62 ml/kg (p=0.000).

Blood loss due to other causes were found in 70% (n=49), the most frequent type of bleeding was intraventricular hemorrhage – 66% (n=46) of all neonates. Anaemia was diagnosed in 84% of neonates with some type of bleeding. 80% (n=20) of them who underwent transfusion of RBC had hemorrhage simultaneously and 64% (n=29) of neonates who did not undergo transfusion.

Surgical manipulations experienced 10% (n=7) of neonates.

49% (n=34) of neonates were diagnosed with infection. Anaemia was diagnosed in 88%(n=30) of neonates with some type of infection. Among those neonates who underwent transfusion of RBC 60% (n=15) had infection, among those who did not undergo transfusion 40% (n=19) had infection.

56% (n=14) of neonates who underwent transfusion of RBC had all three main triggers simultaneously: phlebotomy, various bleeding and infection.

Discussion

The findings of this study are supported by similar studies that have been described in the international scientific literature.

All studies confirms the high frequency of anaemia in preterm infants – around 80% of neonates. In our study aneamia was found in 79% of neonates.

The frequency of RBC transfusion varies between the studies, in our study it was less frequent than generally. For example in some Dutch study which was carried out in year 2008 transfusion of RBC received 53% of neonates, in our study 36% of neonates received it. The reason for the difference might be the diversity in transfusion guidelines. (Hack 2008).

Various studies have shown that blood loss due to blood sampling is greater than recommended. (Howie 2010) It varies 10 – 25 ml/kg in their first weeks of hospitalisation. In our study it is 14,7 ml/kg – exceeds the recommended maximum as well. (Bell 1977).

Conclusions

Three most common postnatal triggers of anaemia were identified: blood loss due to blood sampling, bleeding and infections;

All these triggers were found more often between those neonates who underwent transfusion of RBC;

More than half of neonates who underwent transfusion of RBC all three main triggers have affected simultaneously.

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LUNG TRANSPLANTATION PATIENT IN LATVIA – LONG TERM RESULTS

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Abstract

Lung transplantation patient in Latvia – long term results

Key words: *pulmonary hypertension (PH), idiopathic pulmonary arterial hypertension (IPAH), lung transplantation, complications, immunosuppressive therapy, side effects*

Introduction. PH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest. There is a pathogenetic therapy available for a pulmonary arterial hypertension (PAH) patients. For those who fail on drug treatment and remain in WHO functional class III-IV, lung transplantation is a treatment option to increase survival and gain a good quality of life.

Case report description. A 32-year-old female with anamnesis of IPAH for 3 years is in high risk group – predicted one year mortality >10%. According to the medical reports patient is a potential candidate for transplantation procedure. A double lung transplantation was performed on April 2014.

On follow-up visits after transplantation patient is in a good general condition. On follow-up visit (17.03.2015.) there are some side effects of immunosuppressive therapy present– chronic kidney disease (CKD) 3A (creatinine 121µmol/l; GFR 54.9 ml/min/m^2), anemia (hemoglobin 98 g/l), hepatotoxicity (AlAT 47 U/l), hypercholesterolemia (total cholesterol 7,0 mmol/l).On follow-up visit (12.01.2017.) there are no side effects of immunosuppressive therapy or other complications present.

The aim of my research is to evaluate, whether the lung transplantation as a treatment method has increased survival and quality of life for the patient with idiopathic pulmonary arterial hypertension (IPAH).

Conclusion. Lung transplantation procedure has improved survival and quality of life for patient with WHO functional class IV IPAH. Significant complications after transplantation have not developed, but side effects of immunosuppressive therapy (tacrolimus, everolimus, prednisolone) are present a year after transplantation, but after two years there are no evidence of their presence.

Summary. The case report demonstrates a 32-year-old female with WHO functional class IV IPAH. A double lung transplantation was performed. Patient is in a good general condition a year and 3 years after transplantation. Significant complications have not developed, and during the last follow-up visit there is no evidence of side effects of immunosuppressive therapy.

Kopsavilkums

Plaušu transplantācija paciente Latvijā – ilgtermiņa rezultāti

Atslēgvārdi: *pulmonāla hipertensija (PH), idiopātiska pulmonālā arteriālā hipertensija (IPAH), plaušu transplantācija, komplikācijas, imūnsupresīvā terapija, medikamentu blakusefekti*

Ievads. PH ir definēta kā vidējā pulmonālā arteriālā spiediena (mPAP) paaugstināšanās ≥25 mmHg miera stāvoklī. PH grupai – pulmonālai arteriālai hipertensijai (PAH) – ir pieejama patoģenētiskā terapija. Gadījumos, kad medikamentozā terapija kļūst neefektīva un pacienta stāvoklis atbilst PVO PAH III-IV funkcionālai klasei, plaušu transplantācija ir terapijas metode, kas var uzlabot pacienta dzīvildzi un dzīves kvalitāti.

Gadījuma apraksts. 32 gadus vecai sievietei tika veikta plaušu transplantācijas operācija gala stadijas IPAH dēļ (paciente pieskaitāma augsta riska grupai – paredzamā viena gada mirstība >10%). Ņemot vērā pacientes rādītājus un kontrindikāciju neesamību, paciente ir potenciāla kandidāte plaušu transplantācijas operācijai. 2014.gada 15.aprīlī pacientei tika veikta bilaterāla plaušu transplantācija.

Plānveida izmeklēšanu laikā pēc plaušu transplantācijas pacientes vispārējais veselības stāvoklis ir labs. Izmeklējumi, kas veikti 17.03.2015. norāda, ka ir attīstījušās imūnsupresīvās terapijas blaknes – hroniska nieru slimība 3A (seruma kreatinīns 121µmol/l; GFĀ (glomerulu filtrācijas ātrums) 54.9 ml/min/m^2), anēmija (hemoglobīns 98 g/l), hepatotoksicitāte (AlAT 47 U/l), hiperholesterolēmija (kopējais holesterols 7.0 mmol/l). Plānveida izmeklēšanas laikā pēc pusotra gada (12.01.2017.) izmeklējumi nenorāda uz imūnsupresīvo medikamentu blakņu vai citu komplikāciju esamību.

Secinājumi. Es secinu, ka pacientes vispārējais veselības stāvoklis ir labs gadu un trīs gadus pēc plaušu transplantācijas. Smagas komplikācijas nav attīstījušās. Plaušu transplantācijas operācija ir uzlabojusi pacientes ar IPAH dzīvildzi un dzīves kvalitāti.

Kopsavilkums. Gadījuma apraksts ir par 32 gadus vecu sievieti ar PVO IV funkcionālās klases PAH, kurai veikta bilaterāla plaušu transplantācija. Pacientes vispārējais veselības stāvoklis ir labs gadu un trīs gadus pēc plaušu transplantācijas. Nozīmīgas komplikācijas nav attīstījušās un pēdējās plānveida izmeklēšanas laikā nav datu par imūnsupresīvo medikamentu blakņu esamību.

Introduction

PH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest. Pulmonary arterial hypertension (PAH) is uncommon type of pulmonary hypertension (prevalence in developed countries: 15-50 cases per 1 million) – it is included in a group of rare diseases. PAH is a severe disease that has a negative impact on survival and quality of life (Pulmonary Hypertension Association). Though there is a pathogenetic therapy available for PAH patients (according to ESC/ERS Guidelines, 2015). For those who fail on drug treatment and remain in WHO functional class III-IV, lung transplantation is a treatment option to increase survival and gain a good quality of life (Hachem et al. 2015). The overall survival for IPAH patients is 2.8 years without lung transplantation done (O`Callaghan, Humbert 2012; Benza et al. 2010).

Common problems to be prepared for when deciding to undergo lung transplantation procedure are shortage of donors, adequate recipient selection and limitation of survival of graft and recipient (Broaddus et al. 2016).

Current 1-, 5-, and 10-year survival rates following lung transplantation are 82%, 55%, and 33%, respectively. Survival rates have steadily improved over time, as indicated by an increase in median survival from 3.9 years in 1990–1997 to 6.1 years in 2005–2012. Disease-specific differences in survival are apparent but may be confounded by differences in severity of illness, comorbidities, and average age among these populations. In descending order, median survival is 8.3 years for cystic fibrosis (CF), 6.4 years for alpha $_1$ -antitrypsin deficiency, 5.7 years for sarcoidosis, 5.5 years for chronic obstructive pulmonary disease (COPD) and IPAH, and 4.7 years for idiopathic pulmonary fibrosis (IPF) (Broaddus et al. 2016).

An improvement on effectiveness and safety of immunosuppressive therapy has the biggest contribution on increase in survival rates after lung transplantation because of less complications and side effects. Despite the progress, still there is a high risk for development of complications (graf versus host disease, infections) (Jani et al. 2017; Mandanas 2015; Sims, Blumberg 2014; Vos, Blondeau, Vanaudenaerde et al. 2008) and side effects of imunosuppressants (diabetes mellitus, renal injury, arterial hypertension, thrombocytopenia, osteoporosis, hypercholesterolemia, myopathies, infections etc.) (Scheffert, Raza 2014).

To maximize the effectiveness of lung transplantation procedure, to gain best possible quality of life, it is important to do follow-up visits to diagnose complications and start therapy early. It is also very important for recipients to receive prophylaxis against commonest infections. Strategy described can help to reach the highest cost-effectiveness.

Case report description

A 32-year-old female with anamnesis of idiopathic pulmonary arterial hypertension (IPAH) for three years is unable to carry out any physical activity without symptoms; dyspnea and fatigue

are even present at rest. Patient is in high risk group – predicted one year mortality >10% (based on these findings: progression of symptoms, clinical signs of right heart failure, repeated syncope, WHO functional class IV PAH, BNP plasma level ~5000 pg/ml, right atrium area 42 cm^2, pericardial effusion, right atrial pressure 125 mmHg). mPAP 64 mmHg as assessed by right heart catheterization.

According to the medical reports patient is a potential candidate for transplantation procedure – patient meets the requirements and has no contraindications.

Patients' indications regarding lung transplantation procedure (Whitson 2015):

- Clinically and physiologically severe disease – idiopathic pulmonary arterial hypertension WHO functional class IV.
- Limited life expectancy due to lung disease.
- Ineffective medical therapy. Patient receives combination pathogenetic therapy - Revatio (sildenafil) 20mg 4x a day, Volibris (ambrisentan) 5mg in morning, Ventavis (iloprost) 7-8 inhalations per day. Supportive therapy – Spirix (spironolactone) 25mg 2x a day, Coaxil (tianeptine) 1tab in morning, Patoprazole (pantoprasole) 20mg in morning, Digoxin (digoxin) ½ tab every other day, Orfarin (orfarin) 4.5mg in evening, Hypothiazide (hydrochlorothiaside) 20mg in morning, Trifas (torasemide) 120mg in morning. Despite the maximal medical therapy patients' condition becomes more severe, symptoms progress rapidly.

A double lung transplantation under ECMO support was performed on 15th of April 2014. Patient has to use immunosuppressant drugs for life (tacrolimus, everolimus, prednisolone).

On follow-up visits a year and 3 years after transplantation patient is in a good general condition, no complaints present. Patient is completely independent doing daily activities, no limitations are noticed. Significant complications (severe infections or graft versus host disease) have not developed. Spirometry shows normal lung ventilation function (FEV1=85.8%; FEV1/FVC=103.8%). It is important to control lung ventilation function due to risk of bronchiolitis obliterans syndrome which is a major cause of lung allograft dysfunction. Echocardiography shows normal heart function and there are no data about PH (right ventricular systolic pressure ~ 30 mmHg, inferior cava diameter 19 mm with inspiratory collapse >50%, right atrial area 15 cm^2).

On follow-up visit (17.03.2015.) there are some side effects of immunosuppressive therapy present– chronic kidney disease 3A (creatinine 121µmol/l; GFR 54.9 ml/min/m^2 (Cockroft-Gault)), anemia (hemoglobin 98 g/l), hepatotoxicity (AlAT 47 U/l), hypercholesterolemia (total cholesterol 7.0 mmol/l).

On follow-up visit (8.12.2016.) there are no side effects of immunosuppressive therapy or other complications present.

Discussion

Patient has to use immunosuppressive therapy for life after lung transplantation to suppress immune reactions - avoid allograft rejection, which can be hyperacute, acute or chronic (bronchiolitis obliterans syndrome) (Jani et al. 2017; Mandanas 2015; Sims, Blumberg 2014). Maintenance therapy consists of triple drug therapy with a calcineurin inhibitor (tacrolimus), antiproliferative agent (everolimus) and corticosteroids (prednisolone). It is very important to control plasma levels of tacrolimus and everolimus monthly to adjust doses that reduce the rate of rejection. While it is not possible to manage patients after transplantation without immunosuppressive therapy, these medications have significant side effects. The most common are considered to be opportunistic infections (Gandhi, Khanna 2004; Humar, Snydman 2009), malignancy and drug-specific toxicities. Common drug – specific toxicities for triple therapy are diabetes mellitus, renal injury, arterial hypertension, thrombocytopenia, osteoporosis, hypercholesterolemia, myopathies (Scheffert, Raza 2014). All these require regular control and prophylaxis (especially against opportunistic infections. Medications used: valganciclovir, amphothericin B and trimetoprim/sulphametoxazole).

It is necessary to evaluate patients' general condition lifelong (spirometry, full blood count, plasma biochemistry, coagulogram, chest x-ray and CT, ECG, ECHO and tacrolimus, everolimus plasma levels) as these complications mentioned above may manifest hereafter.

Considering that there is only one lung transplantation patient in Latvia by now, it would be useful to compare results, treatment and medical care tactics with experience from other patients from different countries.

Conclusions

1. PAH is one of the PH groups and it is rare and severe disease that limits life expectancy and worsens quality of life. Though there is a pathogenetic therapy available for PAH patients and in case of end stage disease – lung transplantation is an effective treatment option.
2. Before lung transplantation patients' general condition is difficult: WHO functional class IV PAH, bedrest-cure and permanent oxygen dependence. By analyzing medical reports, I conclude that patient has an increased one year mortality risk - >10%.
3. A year and 3 years after lung transplantation patient is in a good general condition with no complaints. A year after transplantation side effects of immunosuppressive therapy have developed – CKD 3A, anemia, hepatotoxicity and hypercholesterolemia. 3 years after transplantation these complications are not present.
4. Hypothesis has been approved – lung transplantation as a therapy method has improved life expectancy and quality of life for a patient with former IPAH.

Acknowledgement

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DEPRESSION AND ANXIETY SEVERITY DEPENDING ON HEROIN ADDICTION FOR PATIENTS WITH WITHDRAWAL OR REMISSION

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Abstract
Key words: *Heroin addiction, depression, anxiety severity*
Introduction: Affective disorders have a high prevalence among opioid users both during the withdrawal and the remisson (Maremmani et al. 2015). There is not much information about the difference of affective sphere for patients with abstinence syndrome in comparison to patients who have achieved a clinically-stable remission during the opioid replacement therapy.
Aim: To detect the association between the heroin addiction and depression, anxiety for the patients with withdrawal or remission.
Materials and methods: Sociodemographic information, Addiction Severity Index (ASI), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A). Data is statistically processed in SPSS 20 using Spearman's Rank Correlation Coefficient, Independent Samples t-test and descriptive statistics.
Results: 108 patients, 39 females (36.1%) and 69 males (63.9%). Minimal age 19, maximal – 45, mean - 32 years. All patients are devided into groups: there are 57 patients in opioid withdrawal in the first group, who intook heroin at least one time during the last 10 days; there are 51 patients in remission, who didn't intake heroin from 1 - 3 years. Spearman's rank correlation between the addiction severity index and depression (R=0.856, p=0.000), addiction severity index and anxiety (R=0.898; p<0.0001) both established statistically significant correlations. The Independent Samples t-test established statistically significant difference between the patients group with the withdrawal and the patients group with the remission, the difference between two means of addiction severity index - 4.83 points, the difference between two means of depression severity - 15.59 points, the difference between two means of depression severity - 16.33 points, all differences are statistically significant (p<0.0001) and all means are higher in the group of patients with the withdrawal. For patients in remission the mean addiction severity rate - 7.93 points, the mean depression rate - 21.68 points, the mean anxiety rate - 20.68 points. For patients in remission the mean addiction severity - 3.1 points, the mean depression rate - 6.1, the mean anxiety rate - 4.35.
Conclusion: There are strong correlations between the addiction severity, depression and anxiety. Remission, achieved by the methadone or buprenorphine programs, shows a significant addiction severity, depression and anxiety decrease.

Kopsavilkums
Atslēgas vārdi: *Heroīna atkarības, depresijas, trauksmes līmenis*
Mērķis: Noteikt saistību starp heroīna atkarības smagumu pacientiem ar abstinences sindromu vai remisiju un depresijas, trauksmes līmeni.
Materiāli un metodes: Sociodemogrāfiskie jautājumi, Addiction Severity Index (ASI) heroīna atkarības smaguma izvērtēšanai, Hamilton Depression Rating Scale (HAM-D) depresijas smaguma izvērtēšanai, Hamilton Anxiety Rating Scale (HAM-A) trauksmes smaguma izvērtēšanai. Respondentu anketēšana veikta tiešas saskarsmes veidā pēc sastādītajiem anketas jautājumiem. Datu apstrāde veikta SPSS 20 datorprogrammā, izmantojot Spīrmena korelācijas koeficientu, T-tests divu neatkarīgu izlašu vidējo rādītāju salīdzināšanai un aprakstošo statistiku.
Rezultāti: 108 pacienti, 39 sievietes (36,1%) un 69 vīrieši (63,9%). Jaunākais pacients 19, vecākais - 45 gadus vecs. Vidējais vecums - 32 gadi. Pacienti ir iedalīti divās grupās: pirmajā grupā ir 57 pacienti ar abstinences sindromu, kuri ir lietojuši heroīnu vismaz vienu reizi pēdējo 10 dienu laikā, otrajā grupā - 51 pacients, kas atrodas remisijā un nav lietojuši heroīnu vismaz 1 – 3 gadus. Spīrmena korelācijas koeficients starp heroīna atkarības smagumu un depresiju (R=0.856, p=0.000), heroīna atkarības smagumu un trauksmi (R=0.898, p=0.000) uzrādīja statistiski ticamu korelāciju. T-tests divu neatkarīgu izlašu vidējo rādītāju salīdzināšanai uzrādīja statistiski ticamu atšķirību starp pacientiem ar abstinences sindromu un pacientiem remisijā, atšķirība starp šīm abām grupām vidējam heroīna atkarības smaguma indeksam ir 4.83, depresijas smagumam – 15.59, trauksmes smagumam – 16.33 punkti, visas atšķirības ir statistiski ticamas (p=0.000), respektīvi, atkarības, depresijas un trauksmes smaguma rādītāji ir augstāki pacientiem ar abstinences sindromu. Pacientiem ar abstinences sindromu vidējais heroīna atkarības smagums ir 7.93, vidējais depresijas smagums - 21.68, vidējais trauksmes smagums - 20.68 punkti. Pacientiem ar remisiju vidējais heroīna atkarības smagums - 3.1, vidējais depresijas smagums - 6.1, vidējais trauksmes smagums - 4.35 punkti.
Secinājumi: Ticama korelācija starp heroīna atkarības smagumu, depresiju un trauksmi. Remisija, iegūta ar opiātu aizvietojošās (uzturošās) programmas metadonu vai buprenorfīnu, uzrāda ticamu heroīna atkarības smaguma, depresijas un trauksmes pazemināšanos.

Introduction

Drug addiction is a global socially economic problem. Drug users are mainly people of working age (Bartoli et al. 2014). According to the British statistics, almost half of youngsters (48%) try drugs, third of them start to use them regularly, every tenth become chronic drug addict (Utināns 2015). Drug addiction affects general human health, including psychic, contributes to criminality and mortality due to overdose among young people. It is characterized by decrease in personality level, respectively, loss of interests and concentration only to getting drugs, working abilities worsen, there is emotional indifference (Semple et al. 2014).

In Latvia the most used opioid is heroine (Osis 2006). After reaching the brain heroine transforms to 6-monoacetilmorphine and morphine (Пятницкая et al. 2008). Endorphins usually act on opiate receptors that relieve pain in natural conditions. Using of opioids artificially actives endorphin system and under regular irritation it is exhausted causing disorders of monoamine system activity. Desire, anxiety, dysphoria develops. After all it does not create euphoria but only relieves abstinence (Aberberga et al. 2007). Abstinence starts 6 - 24 hours after a dose and lasts for up to 5-7 days with a peak in day 2-3 (Semple et al. 2013). Post-abstinence may remain for 2-6 months with depression, anxiety, dysphoria. At this time there is very high possibility of spontaneous relapses. While gradually physical disorders decrease, emotional background improves and desire is not so actual (Sadock et al. 2014). Two years after stopping affective fluctuations remain. Remission can be considered stabile enough only after abstinence of 3-5 years. Alcohol abstinence, psycho traumas, insufficient understanding of one's disease leads to relapse (Olatunji et al. 2010). When drugs are not used during abstinence, post-abstinence or remission, anxiety, depression and dysphoria develops (Chen et al. 2017).

Affective disorders are part both of addiction development and remission (Мохначев et al. 2001). There is also statement that affective disorders are rare before use of drugs, are not cause of using but forms during narcotization process – lability of the emotional sphere develops (Винникова et al. 1999). Causality of depression and anxiety due to drug addiction however makes us think, respectively, that the main aim of drug addicts is to avoid tension and not derive pleasure. Theoretic thought in understanding of drug addiction pays too big attention to simple searching for pleasure, desire to feel ecstasy, upsurge or euphoria, but desperate desire to escape from-non-specific tension is underestimated. Drug addiction may be considered as adaptive behavior with the aim to relieve pain caused by affects and temporary increase ability to control yourself (Hasse et al. 2011). Correction of affective disorders increases efficiency of the therapy and an important part of the relapse prevention (Минко et al. 2003). Treatment involves opiate substitutional programs – use of methadone and buprenorphine – based on replacement of highly dangerous narcotic substance to seemingly less dangerous one. Using less dangerous opiate, disappearance of opiate famine can be

achieved; gradual decrease in substitutional dose may lead to complete withdraw from drugs (Andrēziņa et al. 2015).

Work actuality is to find out how strongly heroin use correlates to the level of depression and anxiety. In my work I tried to gather and analyze this subject.

Materials and methods

Sociodemographic information, Addiction Severity Index (ASI) (4-7=moderate, 8-10=severe) (Илюк et al. 2012), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A) (15-23= moderate severity; >23=highly severe) (Zimmerman et al. 2013).

Data is statistically processed in SPSS 20 using Spearman's Rank Correlation Coefficient, Independent Samples t-test and descriptive statistics. Rejection of zero hypothesis and acceptation of alternative hypothesis was based on trustfulness level of the statistic hypothesis $p < 0.05$. T-test was used for comparison of mean values of two independent selections.

Results

There are patients, 39 females (36.1%) and 69 males (63.9%). Minimal age 19, maximal – 45, mean - 32 years.

79 patients (72%) have started using drugs up to the age of 18 years, 28 (26%) – up to the age of 14 years. Marihuana was the first narcotic substance for several years (2-3 years) before trying heroin in 87 patients (78.5%), among them 66 (60%) parallel added amphetamine, 17 patients (15.5%) started with amphetamine. When starting use heroin everybody has mono-drug-addiction of this opioid. 63 patients (58%) started to use drugs at the age of 16-21 years; mean heroin experience was 4 years. The main motives of starting use heroin: interest – 64 patients (58%), anxiety relieve – 13 patients (12%), influence of social environment – 31 patients (30%). 55 patients (50%) continue to use heroin to improve mood, 27 patients (25%) – because of fear of abstinence syndrome , 27 patients (25%) to forget about daily care. Some family member of 16 patients (15%) had drug addiction, 13 patients (12%) live with some drug addict. In case of heroin addiction, poly-drug-addiction with tranquilizers (more often Clonazepam), opioid analgesics (more often Tramadol) to enhance the effect or relieve abstinence syndrome was found in all patients. All patients sometimes substitute heroin with illegal methadone, buprenorphine for relieving abstinence syndrome.

All patients are devided into groups: there are 57 patients in withdrawal in the first group, who intook heroin at least one time during the last 10 days; there are 51 patients in remission, who didn’t intake heroin from 1 - 3 years.

Spearman's rank correlation between the addiction severity index and depression ($R=0.856$, $p<0.0001$), addiction severity index and anxiety ($R=0.898$; $p<0.0001$) both established statistically significant correlations. The Independent Samples t-test established statistically significant

difference between the patients group with the withdrawal and the patients group with the remission, the difference between two means of addiction severity index - 4.83 points, the difference between two means of depression severity - 15.59 points, the difference between two means of depression severity - 16.33 points, all differences are statistically significant ($p<0.0001$) and all means are higher in the group of patients with the withdrawal (Table 1). For patients in withdrawal the mean addiction severity rate - 7.93 points, the mean depression rate - 21.68 points, the mean anxiety rate - 20.68 points (Fig. 1, 3, 5). For patients in remission the mean addiction severity - 3.1 points, the mean depression rate - 6.1, the mean anxiety-4.35 (Fig. 2, 4, 6).

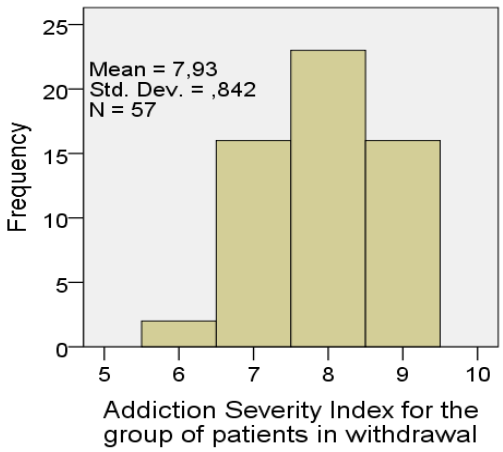


Figure 1. **ASI score among patients in withdrawal**

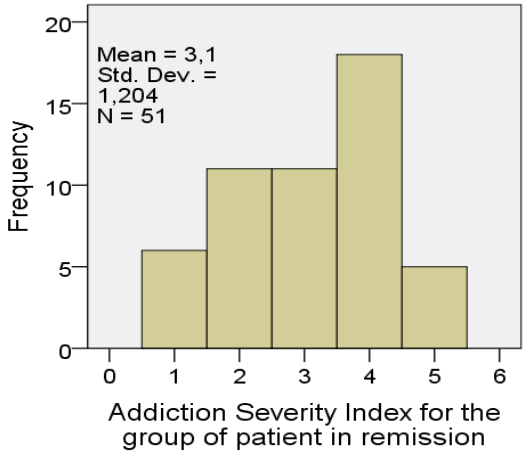


Figure 2. **ASI among patients in remission**

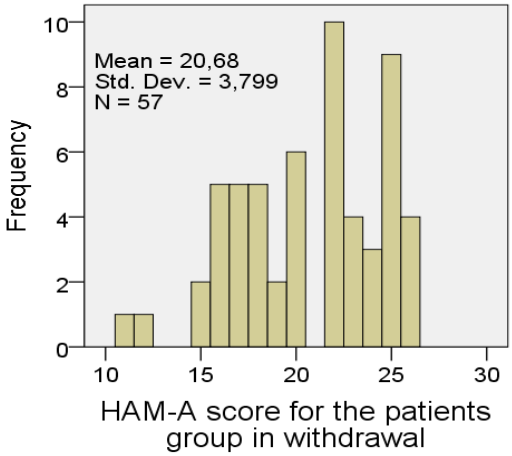


Figure 3. **Anxiety score among patients in withdrawal**

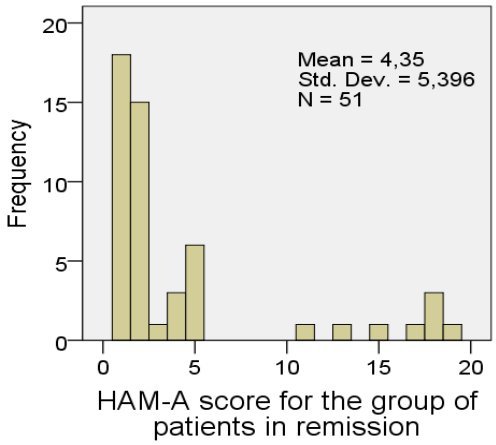
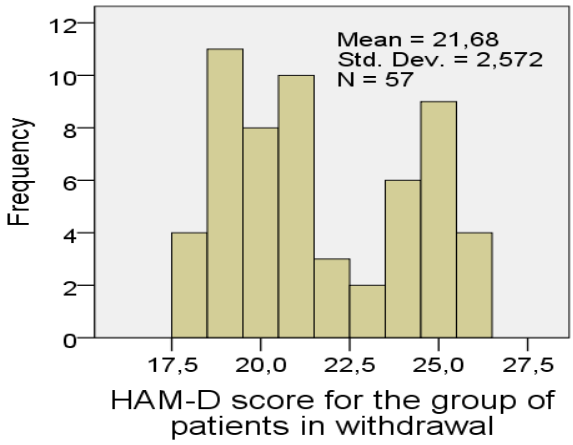
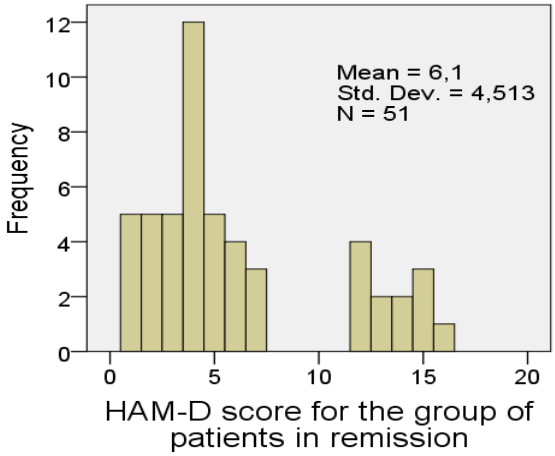


Figure 4. **Anxiety score among patients in remission**

The optimal HAM-A score ranges: mild anxiety (8-14); moderate (15-23); severe (≥ 24) (Matza et al. 2010)





The optimal HAM-D score range: no depression (0-7); mild depression (8-16); moderate depression (17-23); and severe depression (≥24) (Zimmerman et al. 2013)

Figure 5. **Depression score among patients in withdrawal**

Figure 6. **Depression score among patients in remission**

Table 1. **Independent Samples T-test analysis**

	The mean score among patients in withdrawal	**The mean score among patients in remission**	**The difference between means in both groups of patients (Independent Samples T-test)**	**T-test significance level**
ASI	7.93	3.1	4.83	***p<0.0001***
HAM-D	20.68	4.35	15.59	***p<0.0001***
HAM-A	21.68	6.1	16.33	***p<0.0001***

Discussion

Study results align with data from several studies (Taurah et al. 2014) that severity of heroin addiction in abstinence or remission is associated with depression and anxiety. Two groups are turning out very clearly – patients of abstinence syndrome and remission. In abstinence the patients more often have symptoms of depression and anxiety that in remission, so it can be concluded that remission achieved by methadone or buprenorphine of the substitutional therapy shows credible decrease in depression and anxiety.

The most discussable question is about causality, respectively, whether there was depression and anxiety already before beginning of use or it appeared afterwards as a response. 80% of the patients convincingly reply that they have not felt symptoms of depression and anxiety before started to use drugs, however after asking more precisely about any psychotraumatic events it seems objectively that depression or anxiety developed due to life conditions. Discussable question is also about the fact that drug addicts maybe cannot understood very well their emotions and feelings and probably it has led to escaping from reality with the help of drug use, or comparing with the current severe depression of abstinence anxiety emotional experience of that time seems irrelevant.

The study gives an idea about the problem actuality and helps to determine direction of the further studies.

Conclusions

There are strong correlations between the addiction severity, depression and anxiety. Remission, achieved by the methadone or buprenorphine programs, shows a significant addiction severity, depression and anxiety decrease. The main motives of starting use heroin: interest – 64 patients (58%), anxiety relieve – 13 patients (12%), influence of social environment – 31 patients (30%). The main discussable question still remains causality - there was depression and anxiety already before beginning of use or it appeared afterwards as a response.

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CHRONIC DISEASES AND WOMEN COMPLIANCE PARTICIPATING IN NATIONAL CANCER SCREENING PROGRAM

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Abstract

Chronic diseases and women compliance participating in National Cancer Screening program

Key words: *Chronic diseases, women health, Cancer Screening, General Practitioner*

Introduction: Non - communicable diseases (NCDs) are leading cause of death globally. WHO data shows, that every year, 16 million people die before the age of 70 from NCDs. Worldwide cancer morbidity and mortality remains high. In Latvia there are state funded preventive opportunities such as prophylactic visit with GP and three cancer screenings – for breast, colorectal and cervical cancer. Women 50 – 70 years of age are included in all of them.

Aim: The aim of this study is determine if and how chronic diseases, age and BMI (body mass index) affects women compliance participating in National cancer screening program.

Material and methods: This study took place in 5 different, randomly chosen GP practices in Riga. Data from National cancer screening data base were used to select every third women in each GP practice, who had to receive Mammography invitation letter in 2015. Additional data were taken from participants' ambulatory cards, questionnaires and objective investigation.

Results: 208 women with average age of 60.1 ± 5.7 years and average BMI of 27.77 ± 4.63 kg/m^2 were included in this study. Only 9 of them participated in all State funded prophylactic opportunities. Better cancer screening coverage in all three cancer screenings was registered in group with chronic diseases.

Conclusions: The results of this study show that women with one or more chronic diseases more actively participated in National cancer screening program. Women with chronic diseases more often have prophylactic visit with GP, therefore more often visits with GP can result in better compliance and better cancer screening coverage.

Kopsavilkums

Hronisku slimību esamības ietekme uz sieviešu līdzestību piedalīties Valsts organizētā vēža skrīninga programmā

Atslēgvārdi: *Hroniskas saslimšanas, sieviešu veselība, vēža skrīnings, ģimenes ārsts*

Ievads: Vadošais nāves cēlonis pasaulē ir hroniskās neinfekciozās slimības (HNS). PVO dati rāda, ka katru gadu HNS dēļ priekšlaicīgi, nesasniedzot 70 gadu vecumu, mirst 16 miljoni cilvēku. Saslimstība ar vēzi un vēža mirstība saglabājas augsta visa Pasaulē. Valsts nodrošinātā profilakse Latvijā iekļauj profilaktisko apskati pie ĢĀ un trīs vēža skrīningus – krūts, kolorektālajam un dzemdes kakla vēzim. Sievietes vecumā no 50 līdz 70 gadiem ir iekļautas visas trīs skrīninga programmās.

Mērķis: Šī pētījuma mērķis ir noskaidrot vai un kā hronisku slimību esamība, vecums un ĶMI (ķermeņa masas indekss) ietekmē sieviešu līdzestību piedalīties Valsts organizētā vēža skrīninga programmā.

Materiāli un metodes: Pētījums norisinājās 5 dažādās, nejauši izvēlētās ĢĀ praksēs Rīgā. Lai atlasītu katru trešo sievieti katrā ĢĀ praksē, kam 2015.gadā bija jāsaņem mamogrāfijas skrīninga vēstule, tika izmantota Nacionālā veselības dienesta vēža skrīningu datubāze. Papildus nepieciešamie dati tika iegūti no dalībnieku ambulatorajām kartēm, aptaujas anketām un objektīvās izmeklēšanas.

Rezultāti: Pētījumā tika iekļautas 208 sievietes ar vidējo vecumu 60.1 ± 5.7 gadi un vidējo ĶMI 27.77 ± 4.63 kg/m^2 . Tikai 9 no šīm sievietēm piedalījās visas valsts nodrošinātajās profilakses iespējās (ĢĀ profilaktiskā apskate un visi 3 vēža skrīningi). Labāka vēža skrīningu aptvere visiem trīs skrīningiem tika reģistrēta sievietēm ar hroniskām saslimšanām.

Secinājumi: Šī pētījuma rezultāti rāda, ka sievietes ar vienu vai vairākām hroniskām saslimšanām aktīvāk piedalās Valsts organizētā vēža skrīninga programmā. Sievietes ar hroniskām saslimšanām biežāk ierodas uz profilaktisko apskati pie ĢĀ. Biežākas vizītes pie ĢĀ var uzlabot pacientu līdzestību piedalīties organizētā vēža skrīninga programmās un skrīningu aptveri.

Introduction

One of the leading causes of death globally is cancer. As population expands, ages and adopt unhealthy lifestyle behaviors cancer cases and deaths is expected to increase rapidly. In 2012 an

estimated 14.1 million new cancer cases and 8.2 million cancer deaths occurred worldwide (Torre et al 2016). With increased life expectancy of population more people are at risk to develop chronic non – communicable diseases (NCDs). Main groups of NCDs are cardiovascular diseases, cancer, chronic pulmonary diseases and diabetes. Recent studies shows that approximately 50.0% of adults aged 60 years and more have at least one chronic non – communicable disease and about one – third of them has at least two (Sazlina 2015). Current burden of NCDs are high, World Health Organization (WHO) data shows that each year 16 million people die prematurely before the age of 70 from NCDs. Therefore one of the WHO aims is to reduce premature deaths from NCDs at least by one – third by 2030 (WHO 2015).

Armaroli et al in 4th Edition of European Code against Cancer shows the main cancer epidemiology and screening tendencies in European Union (EU). There are successful screening programs in EU for colorectal, breast and cervical cancer. Third most common cancer and the second leading cause of cancer deaths in EU is colorectal cancer with more than 345 000 new cases and 150 000 deaths in 2012. People diagnosed with colorectal cancer usually are older than 60 years (about third of them). The risk of dying from this type of cancer (about half of people diagnosed with colorectal cancer will die from it) is lower if the cancer is detected with screening (Armaroli et al 2015). Like in rest of the world breast cancer is the most common cancer in EU for women and the most common cause of death due to cancer for women with about 365 000 new cases and 91 000 deaths per year (Armaroli et al 2015). Among EU countries incidence for certain types of cancer may differ. Armaroli et al study talks about higher cervical cancer incidence in the countries that acceded to the EU after 2003 and lack of adequate organized cervical cancer screening programs in these countries. In 2012 there were about 34 000 new cases and more than 13 000 deaths due to cervical cancer in EU (Armaroli et al 2015).

In 2015 there were diagnosed 11 123 new cancer cases (562.5 per 100 000 population) in Latvia and 20.5% of them were in stage IV. Most commonly diagnosed cancer for women in Latvia was breast cancer: 1163 new cases (108.7 per 100 000 population), second place - skin cancer (non – melanoma): 658 new cases (61.5 per 100 000 population) and third – colorectal cancer: 565 new cases (52.8 per 100 000 population) (DPCCL 2016). Main causes of death for women in Latvia in 2015 were cardiovascular diseases (893.8 per 100 000 population), cancer (264.7 per 100 000 population). Leading cause of cancer deaths for women in Latvia was breast cancer (41.6 per 100 000 population) and colorectal cancer (36.6 per 100 000 population) (SYHCL 2016).

Screening is application of suitable diagnostic tests in asymptomatic patients. The aim of screening is to determine those who have a condition and can benefit from early detection and diagnosis and those who do not. Detection of disease at an early, asymptomatic stage is crucial as disease at this stage can be potentially more amenable to treatment (Gates 2014).

In every country screening and other preventive strategies differs. There are prophylactic state funded opportunities in Latvia – prophylactic visit with GP once a year and three cancer screening programs (for breast, cervical and colorectal cancer). Women age 50 – 70 are included in all three cancer screening programs. Breast cancer screening in Latvia includes invitational letter from state to screening mammogram and mammography every two years for women from 50 to 69 years of age. Cervical cancer screening consists of state sent invitational letter to cervical cancer screening and Pap smear every three years for women from 25 to 70 years of age. Colorectal cancer screening consists of fecal occult blood test (given by GP) every year for everyone from 50 to 74 years of age.

Mammography is a standard screening method for breast cancer globally. It has a 77 – 95% and 94 – 97% of sensitivity and specificity and this method for breast cancer screening are associated with reduction in breast cancer mortality (Warrier et al 2016).

Cervical cytology or Papanicolaou test or Pap smear is globally preferred cervical cancer screening test. And this method has shown to reduce invasive cervical cancer incidence by up to 80%. This test also has a high specificity of 90 – 99%, but data has shown that the sensitivity of a single Pap smear to be as low as 51% (Aggarwal 2014).

Screening for colorectal cancer using fecal occult blood test (FOBT) can detect this disease at an earlier stage than symptomatic presentation and significantly decrease mortality from this malignancy (Triantafillidis et al 2017). Standard fecal occult blood test requires sampling from three separate following stools. The impact of this screening on colorectal cancer incidence and mortality has been prospectively assessed in several, large randomized trials. These trials demonstrated that repeated (once per year or two years) fecal occult blood test screening reduces CRC – related mortality by approximately 32 – 233 and 6 – 18%, respectively (Schreuders et al 2016).

In Latvia screening fulfillment is low. From National Health Service data – in 2015 only 35% of women fulfilled breast cancer screening and 25% - cervical cancer screening. Colorectal cancer screening fulfillment in 2015 was only 10%.

As we need to understand reasons for non – compliance in National cancer screening program and ways to improve cancer screening coverage we created our quantitative cross - sectional study to see if there is difference between women who fulfills cancer screenings and those who do not fulfill them.

Aim

The aim of this study is determine if and how chronic diseases, age and BMI (body mass index) affects women compliance participating in National cancer screening program.

Material and Methods

This study took place in 5 different, randomly chosen GP practices in Riga. Data from National cancer screening data base were used to select every third women in each GP practice, who had to receive Mammography invitation letter in 2015.

Ethical approval for this study was given by Ethical committee of Rīga Stradiņš University.

For first phase of this study data about all three cancer screenings were collected using National cancer screening data base and information in each GP practice about Colorectal cancer screening coverage (this information does not appear in National cancer screening data base). For women who agreed to participate in second stage of this study additional data were taken from their ambulatory cards, questionnaires and objective investigation.

From ambulatory cards information about their glucose level (mmol/l/), Total cholesterol level (mmol/l) and low – density lipoprotein level (mmol/l) in last 18 months were taken. In objective investigation measurements of their blood pressure (mmHg), pulse (heartbeats per minute), weight (kg) and height (m) were recorded. Measurements of their height and weight were used to calculate Body mass index (BMI = body mass (kg) divided by the square of the body height (m)).

All data were analyzed using IBM SPSS 22.0 program. To calculate results independent T – test Mann Whitney test and Pearson's chi-square tests were used.

Results

208 women with average age of 60.1 ± 5.7 years and average BMI of 27.77 ± 4.63 kg/m^2 were included in this study. Only 9 of them (0.5%) participated in all State funded prophylactic opportunities (prophylactic visit with GP, all 3 cancer screenings). 60 women (28.8%) had done nothing.

108 women (51.9%) performed mammography, 27.8% of them had normal mammogram (R1), 58.3% had potentially benign finding (R2) and 19.9% had suspected pathology (R3). Age and BMI didn't have statistically significant difference ($p > 0.05$) between women who did or didn't conduct breast cancer screening. Cervical cancer screening had to be done for 197 women (11 out of all women had been eliminated because of underlying conditions). 58 (29.4%) women had Pap smear done and 91.8% of them had normal Pap smear (A1) and 8.2% had atypical squamous cells of unknown significance (A2). Women who had cervical cancer screening were younger ($p <0.05$), but there was no difference in BMI ($p > 0.05$). Only 33 women (19.9%) had colorectal cancer screening, 93.9% of them had negative fecal occult blood test result and 6.1% had positive test result. Women conducting colorectal cancer screening were older ($p < 0.05$), but there was no difference in BMI ($p > 0.05$).

162 women (77.9%) were included in second phase of study, 113 (69.8%) of them had one or more chronic diseases. Women with chronic diseases were older and had higher BMI ($p < 0.05$). (See Table 1)

Table 1. **Parameters of women with and without chronic diseases**

Parameters	With chronic diseases	Without chronic diseases	P value
Age	60.6 ±5.6	58.6 ±5.6	p <0.05*
BMI (Body mass index)	28.6 ±4.9	25.8 ±3.2	p <0.05*
SBP (systolic blood pressure)	128.5 ±13.9	125.4 ±15.7	p >0.05*
DBP (diastolic blood pressure)	79.5 ±8.0	76.4 ±8.1	p >0.05*
P (pulse)	72.3 ±7.0	71.7 ±9.7	p >0.05*
GLC (glucose)	5.7 ±1.3	5.4 ±0.7	p >0.05*
TC (total cholesterol)	5.9 [5.0;6.8]	5.7 [5.3;6.2]	p >0.05**
LDL (low density lipoprotein)	3.5 [2.8;4.4]	3.4 [2.7;3.9]	p >0.05**

* Independent T Test
** Mann Whitney test

61.1% of women with chronic diseases had prophylactic visit with GP and only 38.8% of women without chronic diseases had prophylactic visit at GP ($p < 0.05$). There was no difference in age or BMI between both groups ($p > 0.05$).

Table 2a. **Cervical cancer screening fulfillment in study population**

Group	Fulfilled screening (%)	Did not fulfill screening (%)
With chronic diseases	39.8	60.2
Without chronic diseases	24.4	75.6
	p <0.05*	

* Pearson's chi-square tests

Table 2b. **Breast cancer screening fulfillment in study population**

Group	Fulfilled screening (%)	Did not fulfill screening (%)
With chronic diseases	61.9	38.1
Without chronic diseases	57.1	42.9
	p <0.05*	

* Pearson's chi-square tests

Table 2c. **Colorectal cancer screening fulfillment in study population**

Group	Fulfilled screening (%)	Did not fulfill screening (%)
With chronic diseases	22.1	77.9
Without chronic diseases	16.3	83.7
	p <0.05	

* Pearson's chi-square tests

Better cancer screening coverage in all three cancer screenings was registered in group with chronic diseases. 61.9% of women with chronic diseases had mammography done and 57.1% of women without chronic diseases had ($p < 0.05$). 39.8% of women with chronic diseases had Pap smear and 24.4% of women without chronic diseases had ($p < 0.05$). 22.1% of women with chronic diseases had done fecal occult blood test, 16.3% of women without chronic diseases had ($p < 0.05$).

Discussion

Participating in screening programs has impact on cancer incidence and mortality; this has been assessed in many studies for colorectal cancer (Schreuders et al 2016), breast cancer (Warrier

et al 2016) and cervical cancer (Aggarwal 2014). In recent studies there are found many factors that impacts cancer screenings. Study in UK showed that attending breast cancer screening at least once reduced mortality risk by 35%. Attending in the last 3 years (prior to the case's date of diagnosis/pseudo diagnosis) resulted in around 60% reduction in mortality (Massat et al 2015). Many studies shows that there is difference in screening attendance in different ethnic groups, different income groups and in groups with different educational level (Jack et al 2014, Labeit et al 2017, Chang et al 2017). Study in Great Britain showed that past screening behavior influences actual behavior. Past uptake of the same type of screening examination increases the chances of recent uptake for a breast or cervical cancer. This study also agreed with other studies, that a GP visit in the last year leads to higher uptake of breast and cervical cancer screening (Labeit et al 2015). GP endorsement also increases overall screening uptake in colorectal cancer screening (Raine et al 2016, Pornet et al 2014). Other studies shows that individual approach, team care and education about cancer and cancer screenings benefits cancer screening uptake (Acera et al 2017, Ashtarian et al 2017, Kurtinaitiene et al 2016, Fisher et al 2016, Rennie et al 2015, Thompson et al 2014).

In our study we found that women with one or more chronic diseases had better participation in cancer screening program for all three screenings (for breast, cervical and colorectal cancer), our results contradicts some other studies. Jensen et al in their study found that likelihood of non – participation in breast cancer screening increased with the number of co – existing diseases. However authors agreed that association between chronic diseases, multimorbidity and non – participation in breast cancer screening has not been studied sufficiently. Some studies found that multimorbidity increased non – participation, but Heflin et al. in their study had similar results as we. This study demonstrated that three or more conditions increased the propensity to participate (Jensen et al 2015). Sarfati et al in their article expresses an opinion, that comorbidity may result in increased contact with health services resulting in more opportunities for screening and early diagnosis and the impact of comorbidity on the diagnosis of cancer depends on factors that include those related to the type of cancer, the type and severity of comorbidity, and the health care system (Sarfati 2016).

Recent studies shows association between high BMI and increased risk for breast and colorectal malignancies (Chen et al 2016, Sebastiani et al 2016, Suchanek et al 2016, Simone et al 2016). In our study we didn't find statistically significant difference in BMI between women who participated or didn't in cancer screenings. Also we did not find statistically significant difference in age between both groups, but that may be due to small age group chosen.

Results for screenings in our study were in – between the normal range or had suspected pathology. Considering high breast and colorectal cancer incidence we can assume that women who did not participate in screenings have high possibility for these malignancies.

Comparing our study group with general cancer screening fulfillment in Latvia we had better results, maybe it's due to our study geographic limitations (rural areas has less availability to GP's and medical care).

Some studies of patients given choice how to do screenings have shown some positive results. In Liang et al 3 – year follow – up of randomized trial they compared adherence to colorectal cancer screening comparing different screening strategies. Results showed that participants offered a choice between fecal occult blood test (FOBT) and colonoscopy or just colonoscopy continued to have relatively high adherence, whereas adherence in FOBT group was significantly lower (Liang et al 2016). Also study in Germany showed, that patients given chance to choose screening test improved adherence to screening (Adler et al 2014). Australian study showed importance of team care to improve cervical cancer screening uptake. In this study they compared how cervical cancer screening uptake can improve if women have the chance to do screening at GP office by the nurse. (Rennie et al 2015).

Limitations of the study included limited geographical setting (Riga, Latvia) and limited GP (two out of 7 invited GP refused to participate in this study) and therefore a broader national study should be done. Also we did not compare how the number or type of chronic diseases affects compliance to the screenings.

In our study we didn't include results for FOBT from one GP because the tests were made in laboratory and only one time (FOBT includes tests from three following stools).

Conclusions

State funded prophylactic opportunities in Latvia are poorly used. Only 0.5% of our study participants used them all (prophylactic visit with GP once a year and three cancer screening programs (for breast, cervical and colorectal cancer)). Compliance for colorectal and cervical cancer is rather low. The results of this study show that women with one or more chronic diseases have better compliance participating in National cancer screening program. Women with chronic diseases more often have prophylactic visit with GP, therefore more often visits with GP can result in better compliance and better cancer screening coverage. To improve cancer screening compliance we need to educate the patient, use team care at GP practice and more individual approach to each patient.

We need to do qualitative study to understand more about reasons for non – compliance in cancer screenings.

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PARENTS ROLE IN DEHYDRATION TREATMENT IN THE CASE OF PEDIATRIC ACUTE GASTROENTERITIS IN CHILDREN'S CLINICAL UNIVERSITY HOSPITAL

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Abstract

Parents role in dehydration treatment in the case of pediatric acute gastroenteritis in Children's Clinical University hospital

Key words: *Dehydration, parental knowledge, gastroenteritis, pediatrics*

Introduction: pediatric acute gastroenteritis is often considered a benign disease but according to World Health Organization data it remains a leading cause of morbidity and mortality in children younger than 5 years old or roughly 15% of all child deaths.

Aim: the aim of the study was to evaluate parental knowledge and attitude of dehydration treatment in the case of pediatric acute gastroenteritis and to figure out if guideline-based rehydration treatment is used in emergency settings in Children`s Clinical University Hospital (CCUH).

Materials and methods: a questionnaire consisting of 16 questions was completed by child`s parent in the Emergency Department in CCUH and a questionnaire consisting of 8 closed-ended questions was fulfilled by the attending physician. Data were also compared with objective signs and information in medical charts.

Results: all together 81 questionnaires were collected. Only 4% (n=3) of all children had severe dehydration, 26% (n=21) of them had moderate and 70% (n=56) had mild dehydration. Surprisingly, 10% of the parents answered that child should not drink more fluids as usual. Almost two thirds of parents answered that the most effective way how to replace the fluid loss is by intravenous rehydration meanwhile only one third were sure that oral rehydration is the most effective way. Only 11% (n=9) of parents answered correctly to the question how much their child should drink fluids every day according to their age. The second part of the study was to find out if guideline-based rehydration therapy is used in emergency settings in CCUH. While there were 70% children with mild dehydration only half of them received oral rehydration and nobody received rehydration through nasogastric tube. Mostly, children in CCUH received intravenous rehydration (64% all together).

Conclusions: the study proved that parental knowledge about rehydration treatment of pediatric acute gastroenteritis is far from being satisfactory and further parental education should follow. More targeted and guideline-based rehydration therapy should be applied in CCUH emergency settings and also the role of rehydration through the nasogastric tube should be considered more often.

Kopsavilkums

Vecāku loma dehidratācijas ārstēšanā bērniem akūta gastroenterīta gadījumā Bērnu Klīniskās Universitātes slimnīcā

Atslēgas vārdi: *Dehidratācija, vecāku zināšanas, pediatrija*

Ievads: Bieži bērnu akūts gastroenterīts tiek uzskatīts par labdabīgu slimību, bet saskaņā ar Pasaules Veselības organizācijas datiem vēl aizvien ir galvenais iemesls saslimstībai un mirstībai bērniem, kas jaunāki par 5 gadiem, vai aptver aptuveni 15% no visiem bērnu nāves iemesliem.

Mērķis: Pētījuma mērķis bija izvērtēt vecāku zināšanas un attieksmi pret dehidratācijas ārstēšanu akūta gastroenterīta gadījumā, un noskaidrot, vai vadlīnijās balstīta rehidratācijas terapija tiek lietota Bērnu klīniskās universitātes slimnīcas Neatliekamās medicīniskās palīdzības un observācijas nodaļā.

Materiāli un metodes: Pacienta pavadošais vecāks aizpildīja anketu, kura sastāvēja no 16 jautājumiem, un pacienta ārstējošais ārsts - anketu ar 8 slēgta tipa jautājumiem. Tāpat dati tika iegūti no pacienta medicīniskās dokumentācijas.

Rezultāti: Kopā tika savākta 81 anketa. No visiem bērniem tikai 4% (n = 3) bija smaga dehidratācija, 26% (n = 21) bija vidēja un 70% (n = 56) bija viegla dehidratācija. Pārsteidzoši, bet 10% no vecākiem atbildējuši, ka bērnam nav nepieciešams dzert vairāk šķidruma akūta gastroenterīta gadījumā, kā ikdienā. Gandrīz divas trešdaļas vecāku atbildēja, ka visefektīvākais veids kā kompensēt šķidruma zudumu, ir intravenoza rehidratācijaa, bet tikai viena trešdaļa bija pārliecināti, ka orāla rehidratācija ir visefektīvākā akūta gastroenterīta gadījumā. Tikai 11% (n = 9) no vecākiem atbildēja pareizi uz jautājumu, cik daudz viņu bērnam jāizdzer šķidrums atbilstoši vecumam. Otrā pētījuma daļa bija noskaidrot, vai vadlīnijās balstīta dehidratācijas terapijas tiek lietota BKUS NMPON. No 70% bērnu ar vieglu dehidratāciju tikai puse saņēma orālu rehidratāciju, un neviens nesaņēma rehidratāciju caur nazogastrālo zondi. Galvenokārt, bērni BKUS NMPON saņēma intravenozu rehidratāciju (64% kopā).

Secinājumi: Pētījums pierādīja, ka vecāku zināšanas par rehidratācijas terapiju bērnu akūtu gastroenterīta gadījumā ir tālu no vēlamā un jāturpina tālāka vecāku izglītošana. BKUS NMPON būtu jālieto mērķtiecīgāka un uz vadlīnijām balstīta rehidratācijas terapija, tāpat biežāk būtu jāapsver rehidratācijas terapijas nodrošināšana caur nazogastrālo zondi.

Introduction

Although pediatric acute gastroenteritis is considered to be a mild and self-limiting disease**,** according to the World Health Organization (WHO) acute gastroenteritis (GE) all over the world remains the leading cause of morbidity and mortality in children less than 5 years old with an average of 15% of all causes of death of children (Elliott 2007). For most children acute GE case is easy to be treated with an adequate fluid intake. Therefore, it is possible to easily achieve a successful treatment at home, if the parents have the necessary knowledge about oral rehydration therapy (ORT) in case of acute GE (Aviner 2013).

Acute GE symptoms are a frequent cause of hospitalization in Children`s Clinical University Hospital (CCUH) Emergency Department. According to CCUH statistics in 2016 Emergency Department 5334 patients were admitted with acute symptoms of GE, which is an average of 445 patients per month. Parents often visit CCUH Emergency Department due to the lack of knowledge about acute GE treatment on an outpatient basis. Although in Europe there is a lot of guidelines for the treatment of acute dehydration in case of GE, as well as there are internal CCUH recommendations, but there is often missing link between the guidelines and the information availability in the intelligible form for parents (Matson 2017).

The aim of the study was to find out and evaluate parents' knowledge and attitude towards dehydration treatment of acute gastroenteritis, as well as to figure out whether the rehydration therapy that is applied in CCUH is based on international guidelines and recommendations. Similar studies of parental knowledge and treatment of dehydration treatment in the case of acute GE have not been done in Latvia so far and only one study has been done worldwide (Nir 2013). Scientific research included those patients who were admitted in CCUH Emergency Department in the time period from January to March 2017 having a diagnosis of acute gastro-enteritis and acute gastroenteritis symptoms.

Material and Methods

The study design was prospective. In order to achieve the study goals and tasks and to obtain the necessary data the questionnaire was given to patient`s parent in the time period from January to March 2017. The questionnaire consisted of 16 closed-ended questions or issues with selection options. Another questionnaire was given to attending physician and it consisted from 7 closed-ended questions. Further the data were also obtained from the patient's medical charts. Only that parent was interviewed whose child besides acute gastroenteritis specific symptoms was also having a diagnosis of acute gastroenteritis and furthermore was admitted to CCUH Emergency Department. Patients were enrolled prospectively and on a voluntary basis. Ethics committee permission was received from both the university and the hospital.

For all the results to be able to make a summary and to calculate the necessary statistical data statistical processing program Microsoft Excel and IBM SPSS Statistics version 23.0 were used.

Results

Scientific research was carried out by analyzing all completed questionnaires both – by the 81 patients' parents or other accompanying persons, as well as by 81 patients' treating physicians. Also patients' medical documentation was analyzed. Survey covered the period from January to March 2017. In the *Figure 1* age distribution in months is represented. It is seen that age is not in normal distribution and the peak is at the age of 50 months and it is approximately at the age of 4 years. Mostly in Emergency Department children till the age of 100 months (approximately at the age of 8 years) are admitted.

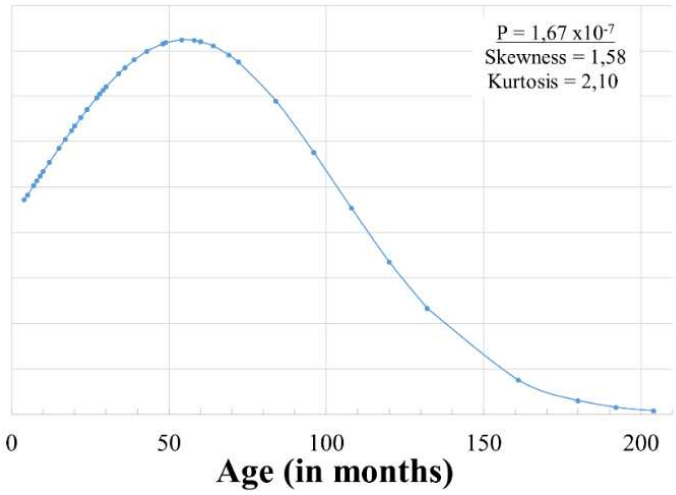

Figure 1. **Age distribution in months**

Patients' distribution by age - infant, preschool, school-age and adolescent (age group distribution in *Figure 2*) was also analyzed. *Figure 2* shows that the largest age group that has been admitted in Emergency Department with acute gastroenteritis diagnosis is a preschool patients (from 2 to 5 years), but the smallest age group that has been admitted in Emergency Department is adolescent patients (at the age from13 to 18 years). Also in this case, the age group distribution is not statistically reliable or in a normal distribution because group frequency is not equal.

Analyzing the 81 patients' distribution by gender (*Figure 3*), it is evident that the group distribution is statistically significant and in a normal distribution because group frequency is equal. Among all the patients included in the study, 44% (n = 35) were girls and 56% (n = 46) were boys.

A total of 81 patients' parents and also doctors that provided treatment for children in CCUH Emergency Department were interviewed. In one of the questions in questionnaire the attending physician also rated the degree of dehydration by objective signs and symptoms. Those data were also compared with information in medical documentation.

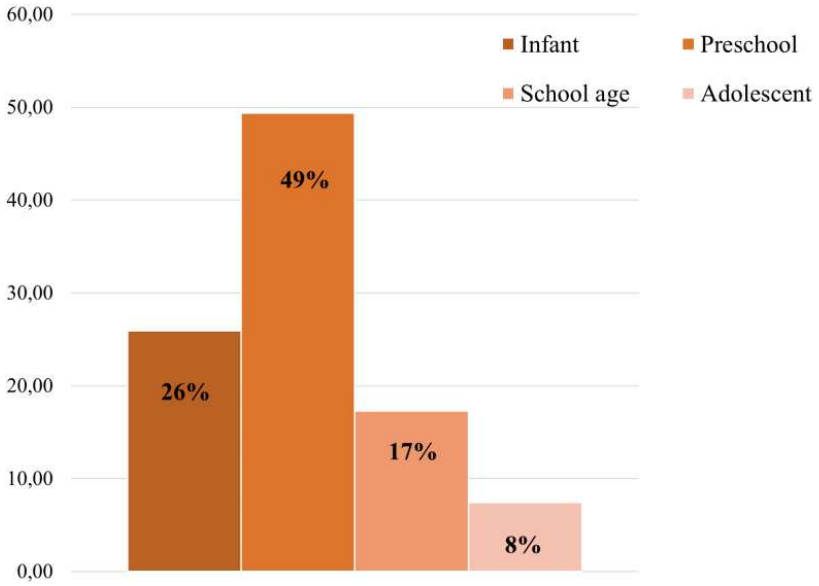

Figure 2. **Age distribution by age groups**

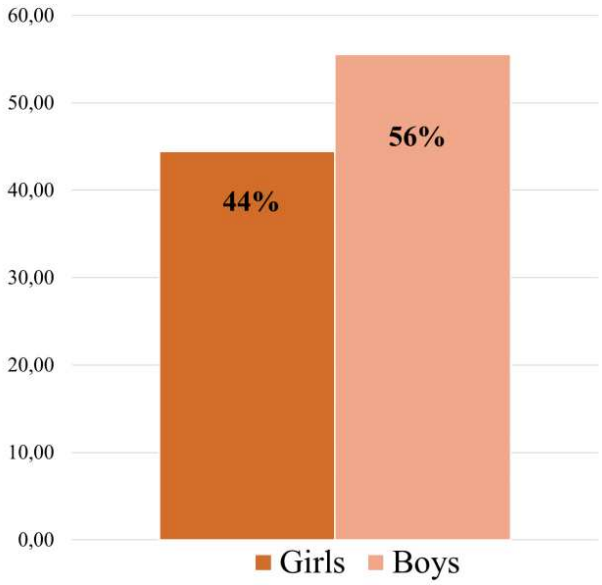

Figure 3. **Gender distribution**

Analyzing both the parents and the doctor replies, it was concluded that the main part (70% (n=56)) of children who visited CCUH Emergency Department was with mild dehydration degree, with moderate dehydration degree were 26% (n=21) of all cases, but with severe dehydration degree were only 4% (n=3), but none of the patients has been identified with a diagnosis of shock (*Figure 4*).

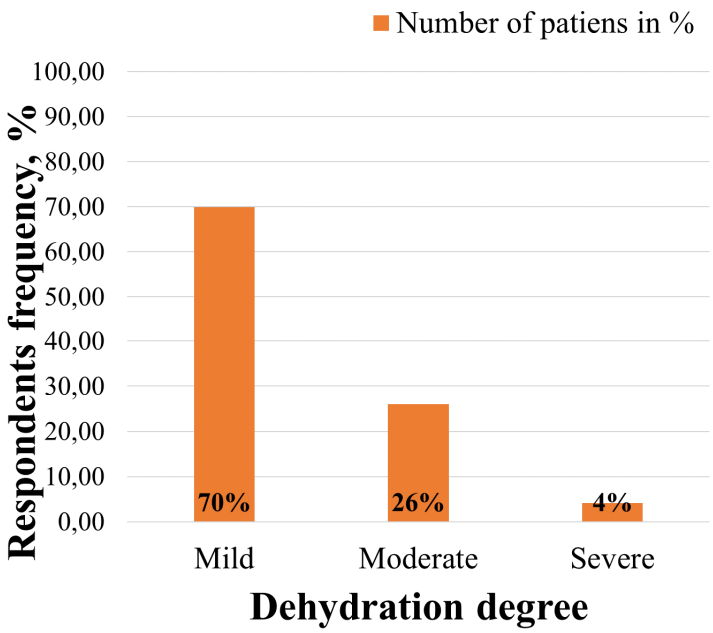

Figure 4**. Dehydration degree**

Further analyzing the information, a statistically significant correlation was not found between the patient`s fever status and the dehydration degree, the vaccine status against Rota virus, as well as if the patient had/had not previously visited the family doctor and the degree of dehydration. Also, no correlation was found between the age of patient or age group and dehydration degree. However, a statistically significant difference (p< 0, 05) was found between the vomiting and / or diarrhea count in the day of hospitalization and the degree of dehydration (*Figure 5*) but there was no statistically significant difference (P>0.05) between the vomiting and/or diarrhea count during whole illness period and dehydration degree.

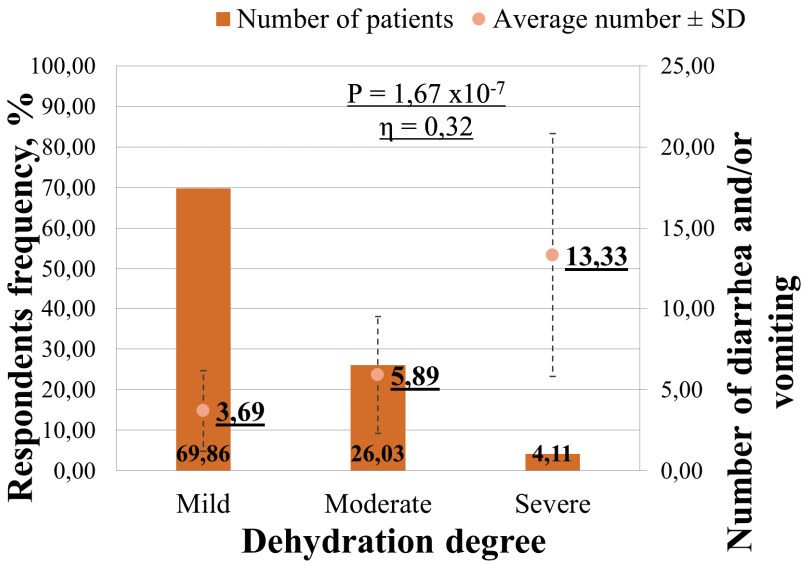

Figure 5. **Dehydration degree correlation with number of diarrhea and/or vomiting in the day of hospitalization**

In CCUH Emergency Department is observed that most of the patients or 64 % (n=52) of all cases received intravenous rehydration therapy (IVRT), oral (p/o) rehydration (ORT) was used in only 35% (n=28) of patients, but rehydration therapy by nasogastric tube was not used in any of the cases (*Figure 6*). It has been concluded that there is a correlation between the degree of dehydration and the chosen therapy and this correlation is statistically significant (P <0.05), but 50% (n=28) of patients with mild dehydration received IVRT and none of the patients with moderate dehydration received ORT. No correlation was found between the age of patient or age group and chosen approach of therapy.

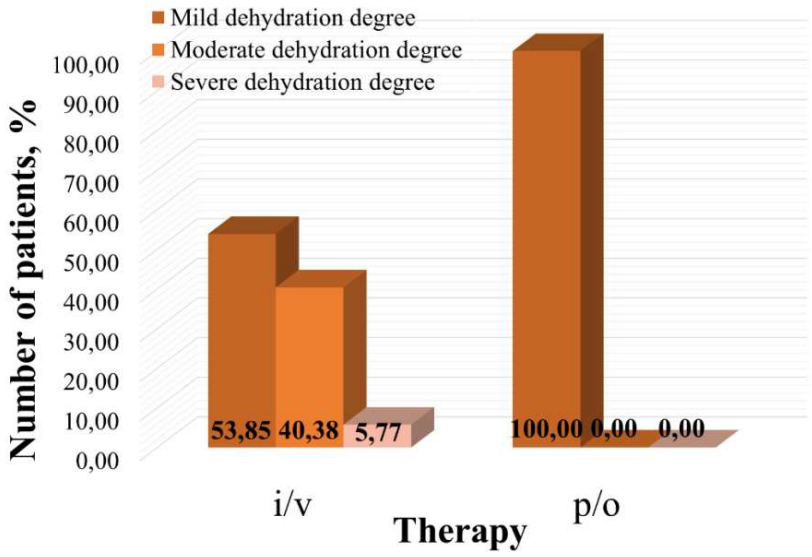

Figure 6. **The form of dehydration therapy**

Various manipulations and investigations were carried out in 73% (n=59) of patients, and on average 4 manipulations were done for each of these patients. The manipulations and procedures that were analyzed in the study were as follows - urine analysis, full blood count, blood biochemical studies, X-ray, US, i/v injections and medications, fecal test to bacteria and viruses. Mostly for patients full blood count and blood biochemical studies were performed. These manipulations were carried out in 92% (n=54) of patients who received at least one manipulation. It has been also concluded that there is no correlation between the selected types of manipulation for patients and the degree of dehydration (P> 0.05). But statistically significant correlation was found between the selected types of manipulation for patients and the day of ongoing illness (*Figure 7*).

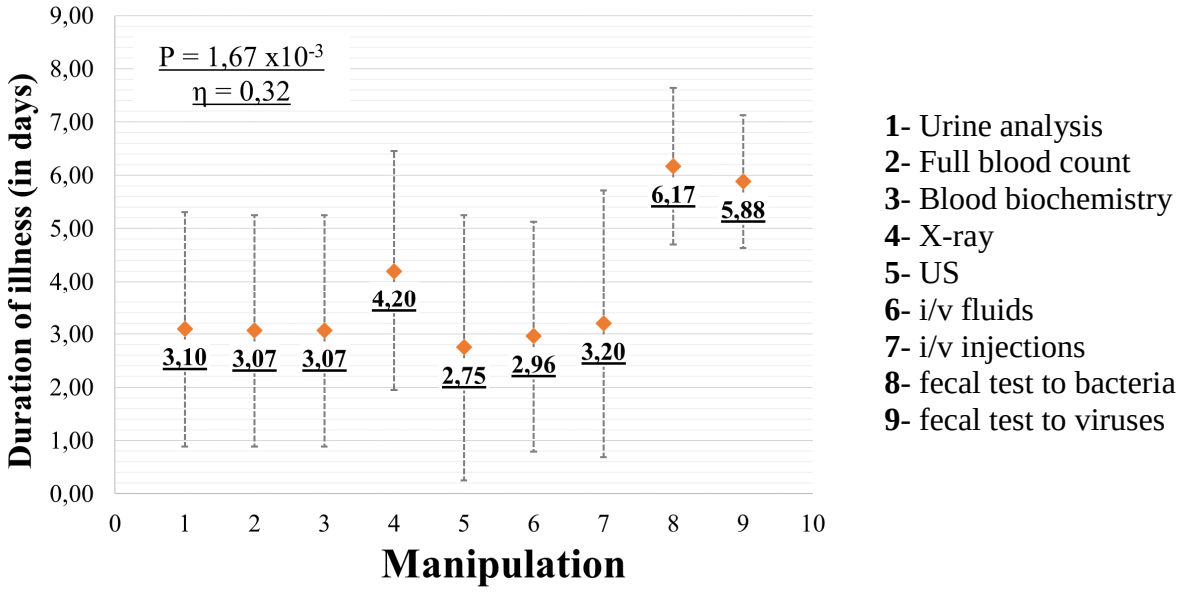

Figure 7. **Manipulation correlation with the duration of illness**

Parental knowledge and attitudes toward dehydration treatment in the case of acute gastroenteritis were assessed with 16 closed-ended questions or questions with multiple-choice. The questionnaire had questions about an illness episode anamnesis data, about fluid intake quantity and nature in the case of exact illness episode and everyday life. Also, the questionnaire included questions about the rehydration therapy and fluid compensation in the case of acute gastroenteritis, as well as the most effective rehydration types in the parents believe.

The parents and the treating physician's questionnaire data were compared and it was found out that the estimated number of days of illness in 68% (n=55) of all cases were the same in parents and doctor's questionnaire, but in the question about vomiting and / or diarrhea only 1 out of 81 patients answered the same as physician. Only 11% (n=9) patients received fluid in the amount of required norms of the day after the *European Food Safety Authority (EFSA) 2010* according to the age groups. However, there was no correlation between the degree of dehydration, and whether the patient receives adequate daily fluid intake according to child`s age group. Also, there was no correlation between the dehydration degree and the fluid intake amount in the last 24 hours.

Water as the fluid to compensate the fluid loss in the case of acute gastroenteritis, has been used in 90% (n=73) of patients. However, only in 4% (n=3) of all cases *Rehidrons (*oral rehydration salts) has been used. Other options that parents use to compensate the fluid loss for children were juice, tea, fresh milk, *Coca-Cola*, broth and infant formula. 90% (n=73) of parents believe that in the case of vomiting and / or diarrhea child needs to drink more fluids than usual, and the average volume in milliliters for each vomiting and / or diarrhea episode is 418.81 ± 517.19 (CI 95% 288.56…549.06) with an interval from 20 to 2000 ml. But surprisingly 10% (n=8) of the parents

believe that child should not drink more fluids in the case of acute gastroenteritis than in the everyday life.

According to the results it was concluded that 63% (n=51) of parents believe that the most effective way of rehydration is intravenous infusion and only 17% (n=14) of parents would agree to an insertion of nasogastric tube. The other answers included that there is no need to do rehydration therapy in the case of acute gastroenteritis and the combination between the other forms of rehydration therapy. As the main reason for admitting the child to CCUH Emergency Department, 44% (n=36) of parents mentioned was the first time the child was having so severe vomiting and / or diarrhea episode. Also, 21% (n=17) of parents admitted that they do not have enough information to achieve an adequate rehydration therapy at home. Other answers that parents were giving for the question why they were admitted to Emergency Department were that they come to Emergency Department every time the child is having a diarrhea and/or vomiting, that is the very first time when the child is having diarrhea and/or vomiting or the family doctor recommended to have a consultation in CCUH Emergency Department.

The main limitation of this study is that only parents who failed to successfully cope with the treatment of acute GE at home were interviewed. Thus it would be necessary to do the survey for control group, to compare the parent`s knowledge with those parents who were able to successfully treat acute GE in outpatient settings.

Discussion

Even though acute gastroenteritis can be adequately treated in an outpatient basis, it is still a frequent cause of hospitalization for children (Aviner 2013). According to CCUH data in 2016 with acute gastroenteritis symptoms in Emergency Department 5334 children were admitted, which is an average of 445 patients per month. Therefore, we can conclude that the parents are lacking knowledge how to treat acute gastroenteritis in an outpatient setting. More than 65% (n = 53) of patients that were included in study recognizes that it was the first time when they presented with so severe vomiting and / or diarrhea episode and did not know how to treat a particular illness episode in an outpatient setting.

From the literature, it can be concluded that guidelines for the treatment of acute gastroenteritis are introduced in Europe and around the world, but there is a missing link between the guidelines and the information provided for parents (Guarino *et al.* 2008).

Analyzing rehydration therapy tactics in CCUH Emergency Department it can be concluded that too often intravenous rehydration therapy (IVRT) is used. It’s estimated that IVRT was applied in 64% (n = 52) of all patients, and in 50% (n = 28) patients with mild dehydration. One of the reasons why doctors choose IVRT in case of mild dehydration could be the impact of parents

(Leung 2006). 63% (n = 51) of parents believe that IVRT is the most effective type of dehydration therapy in case of acute gastroenteritis.

In CCUH it would be necessary to emphasize the importance of rehydration therapy by nasogastric tube, because it was not used in any of cases. Only 17% (n = 14) of parents would agree to provide rehydration by nasogastric tube and 1% (n = 1) of parents mentioned it as the most effective type of rehydration therapy. However, several guidelines and CCUH recommendations also mentions that a nasogastric tube is the method of choice if ORT has failed (Zavadska *et al.* 2013; NICE *et al*. 2009).

The main limitation of the study is the lack of control group. The study included only patients and their parents, who have not been able to successfully cope with rehydration therapy in an outpatient setting. Therefore, it would be necessary to compare the parents' knowledge to those parents who have been able to successfully treat dehydration in a case of acute gastroenteritis in outpatient settings.

Conclusions

No correlation between the degree of dehydration and fever status, the age of patient and age group, as well as vaccination against Rota virus was found.

The correlation between vomiting and/or diarrhea total number in the day of hospitalization and dehydration degree was found.

The most often used type of rehydration is intravenous fluids administration in CCUH, which is also used in 50% of cases for patients who have mild dehydration degree. That is not according to international guidelines or CCUH practical recommendations.

Patients' parents have poor knowledge of the required amount of liquid, which their child should use on a daily basis, taking into account the child's age group. Also the parents have the lack of knowledge about the specialized rehydration solutions. More than half of the parents still believe that the most effective way how to compensate the fluid loss in case of dehydration is with intravenous system.

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VACCINE PREVENTABLE DISEASES IN CHILDREN'S CLINICAL UNIVERSITY HOSPITAL IN THE TIME PERIOD FROM 2005 TO 2016 AND THE MAIN REASONS FOR VACCINATION REFUSAL

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Abstract

Vaccine preventable diseases in Children's Clinical University hospital in the time period from 2005 to 2016 and the main reasons for vaccination refusal

Key words: *pediatrics, children, vaccine, vaccine preventable disease, vaccination*

Introduction: The National Immunization Program (NIP) is successful example of effective preventive care for children. The NIP helps to reduce morbidity and mortality of vaccine preventable diseases (VPD) but despite that parents more and more often choose to skip or partly skip the vaccination.
Aim: The aim of the study is to collect statistics of VPD in the Children's Clinical University hospital (CCUH) in Riga, Latvia from 2005 to 2016 year and to prove that VPD still quite often emerge among children in CCUH.
Results: Despite the NIP 883 cases of VPD conformed to selection criteria in CCUH in the time period from 2005 to 2016. During the period, there was 0 cases of tetanus or poliomyelitis, more detailed information was collected of patients with diphtheria and pertussis. All together 64 patients with diphtheria and 80 patients with pertussis were hospitalized in CCUH. From all the patients 39.64% were girls, 60.36% were boys. The mean age was 65.72 ± 65.01 months, with an interval from 1 to 215 months. Confidence interval (CI 95%) of age mean value is from 52.75 to 78.68 months. 10% patients with diphtheria and 8.2% patients with pertussis received treatment in ICU. Results show that diphtheria is observed on mean for older children, and the difference is significant. For all VPD average length of treatment in hospital was 12.45 ± 7.10 days, with an interval from 2 to 31 days. The study also included questionnaire that was sent to parents whose child was hospitalized in CCUH in 2014 with VPD. 52% answered that child was not vaccinated according to vaccination calendar.
Conclusions: VPD are important issue to deal with in Latvia because during 12 year period 883 patients received medical treatment in CCUH with average hospitalization almost two weeks.
Every hospitalization with VPD is painful, e.g.,full blood count was taken in 90%.
The results of our survey reveal that in 2014th more than a half of patients with VPD were not vaccinated according to vaccination calendar which means that the NIP cannot be as effective as it could be if every child was vaccinated.

Kopsavilkums

Vakcīnregulējamās slimības Bērnu Klīniskās Universitātes slimnīcā laika periodā no 2005. līdz 2016. gadam un galvenie nevakcinēšanās iemesli

Atslēgas vārdi: *Pediatrija, bērni, vakcīnas, vakcīnregulējamās slimības, vakcinācija*

Ievads: Nacionālā imunizācijas programma (NIP), ir veiksmīgs piemērs efektīvai profilaksei bērnu vecuma grupā. NIP palīdz mazināt saslimstību ar vakcīnregulējamām slimībām un mirstību no tām, bet vecāki arvien biežāk izvēlas izlaist vienu vai vairākas vakcīnas, kā arī veikt korekcijas laika periodā starp vakcīnām.
Mērķis: Pētījuma mērķis bija apkopot statistiku par vakcīnregulējamām slimībām Bērnu klīniskās universitātes slimnīcā (BKUS) Latvijā laika periodā no 2005. līdz 2016. gadam, lai pierādītu, ka vakcīnregulējamās slimības ir arvien biežāk sastopamas bērnu vecuma grupā.
Rezultāti: Neskatoties uz Nacionālo imunizācijas kalendāru laika periodā no 2005. līdz 2016. gadam 883 gadījumi atbilda atlases kritērijiem BKUS. Konkrētajā laika periodā nebija neviena stingumkrampju un poliomielīta gadījumu, detalizētāka informācija tika savākta par pacientiem, kuri bija hospitalizēti BKUS ar difteriju un garo klepu. No visiem pacientiem - 39,64% bija meitenes, 60,36% bija zēni. Pacientu vidējais vecums bija 65.72 ± 65,01 mēneši, ar intervālu no 1 līdz 215 mēnešiem. Ticamības intervāls (TI 95%) vecuma vidējai vērtībai ir no 52,75 līdz 78.68% mēnešiem.10% pacientu ar difteriju un 8.2% pacienti ar garo klepu tika stacionēti Intensīvās terapijas nodaļā. No rezultātiem var secināt, ka difterija tika diagnosticēta vecākiem bērniem nekā garais klepus un šī atšķirība ir statistiski nozīmīga. Visu pacientu ar vakcīnregulējamajām slimībām vidējais ārstēšanas ilgums slimnīcā bija 12.45 ± 10.7 dienas, ar intervālu no 2 līdz 31 dienai. Pētījuma otrās daļas ietvaros tika izsūtītas aptaujas anketas tiem vecākiem, kuri ārstējās BKUS ar vakcīnregulējamajām slimībām 2014.gadā. 52% no vecākiem atbildēja, ka bērns nav vakcinēts atbilstoši Latvijas vakcinācijas kalendāram.
Secinājumi: Vakcīnregulējamās slimības ir nozīmīga problēma bērnu vecuma grupā, jo 12 gadu laika periodā BKUS tika stacionēti 883 pacienti ar kādu no vakcīnregulējamajām slimībām un vidējas hospitalizācijas ilgums bija gandrīz 2

nedēļas. Katra hospitalizācijas epizode ar vakcīnregulējamajām slimībām ir sāpīga mazajiem pacientiem, jo, piemēram, pilna asinsaina tika ņemta 90% no visiem pacientiem, kaut arī šo hospitalizācijas skaitu būtu iespējams samazināt, ievērojot Latvijas Nacionālo vakcinācijas kalendāru.
Pētījuma rezultāti parāda, ka 2014. gadā vairāk kā puse no pacientiem BKUS ar vakcīnregulējamajām slimībām nebija vakcinēti saskaņā ar Latvijas Nacionālo vakcinācijas kalendāru, kas nozīmē, ka ir apdraudēta efektīva Nacionālās imunizācijas programmas darbība un vakcīnregulējamo slimību incidences mazināšana.

Introduction

Vaccination still is the most effective and the most used strategy for preventing the diseases that are called vaccine-preventable disease. Every year all over the World thousands of people suffer serious health problems, are hospitalized and even die because of vaccine-preventable diseases (CDC 2016). Most of those patients are previous totally healthy individuals. The prevalence of vaccine-preventable diseases worldwide is higher in adult age group than in children but still it is a threat for pediatric population (Tomczyk, Bennett, Stoecker et al. 2014).

In many countries, worldwide exactly the weak primary health care system is the main reason why a lot of children are left unimmunized. The other reason why a lot of children are left unimmunized is parental decision to refuse one or more vaccines or increase intervals between vaccinations (CDC 2012). Still the levels of total vaccine refusal are low but growing number of parents choose to refuse one or more vaccines or to vaccinate in an alternative schedule (Omer 2012). In Latvian National Immunization calendar are included 15 diseases that are totally covered from state and one vaccine, tick born encephalitis, that is partly covered by state (SPKC 2017). But still a lot of parents choose not to vaccinate their children just because of their decision. The main reason why parents refuse one or more vaccines is because they have concerns about safety and side effects of vaccination and this reason is 60 to 70% of all vaccine refusals (Salmon, Moulton, Omer, DeHar, Stokley, Halsey et al. 2005).

This study about **“Vaccine Preventable Diseases In Children's Clinical University Hospital In The Time Period From 2005 To 2016”** was done to prove that vaccine- preventable diseases are still an important threat in Latvian society. And to show that there is increasing numbers of parents who choose not to vaccinate their child or to vaccinate their child in an alternative schedule due to disinformation and popular trends among parents.

Material and Methods

Study consisted of two parts. The first part was retrospective study that took place in Children`s Clinical university hospital about 11 year time period from 2005 to 2016. The statistical data were collected in Children’s Clinical university hospital from patient medical charts and electronical data system “Andromeda”. Selection of the patients with vaccine-preventable disease was done only by the code of diagnosis. In the study were included all the vaccine-preventable diseases that are in National Immunization calendar in Latvia, except rotavirus and human papilloma virus. The second part of the study was prospective. The questionnaire was sent to those

parents who were in Children`s Clinical university hospital with their children with vaccine-preventable disease to find out about vaccination status of the patient. The questionnaire was sent only to those parents whose children were in Children`s Clinical University hospital with vaccine-preventable diseases in 2014.

Results

All together in the eleven year time period from 2005 to 2016 in Children`s Clinical university hospital were hospitalized 883 patients with vaccine-preventable disease. The analyzed diseases were acute poliomyelitis, tetanus, epidemic parotitis, measles, rubella, chicken-pox, diphtheria, pertussis, H.influenzae type B, pneumococcal infection, hepatitis B and all forms of tuberculosis. In the study were not included rotavirus and human papilloma virus, because those vaccines were introduced in Latvian National Immunization calendar only recently. The statistics were compared with information from Centre for Disease Prevention and Control. According to data from Centre for Disease Prevention and Control in the time period from 2005 to 2016 all together in Latvia were 51 356 patients with vaccine-preventable diseases, but at the same time in Children`s Clinical university hospital were only 883 cases, making it only 1.7% from all cases from all over Latvia treated in Children's Clinical university hospital.

During the time period from 2005 to 2016 altogether were acute poliomyelitis (n = 0), tetanus (n = 0), epidemic parotitis (n = 13), measles (n = 6), rubella (n = 49), chicken-pox (n = 564), diphtheria (n = 64), pertussis (n = 80), H.influenzae type B (n = 5), pneumococcal infection (n = 13), hepatitis B (n = 5) and all forms of tuberculosis (n = 28). During the selected time period, there were no cases of tetanus or poliomyelitis in Children's Clinical university hospital.

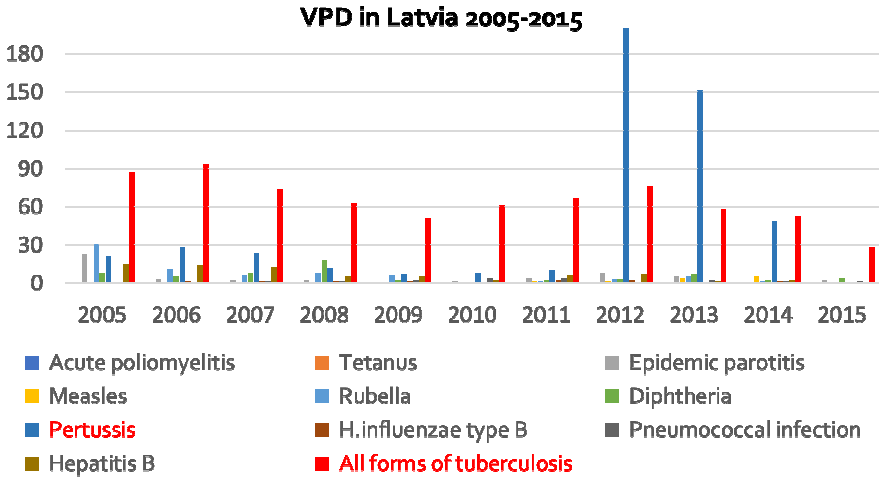

Figure 1.

It is well seen vaccine-preventable disease effect after vaccine introduction in National Immunization calendar. To see the effect of vaccine introduction the data about chickenpox were

analyzed (Figure 2). Chickenpox vaccine was introduced in Latvian National Immunization calendar in 2008 and it is seen in Figure 1 that after vaccine introduction there is rapid decrease in total numbers of chickenpox. There were 6717 cases in 2008 and in 2016 only 1587 cases with chickenpox in Latvia, that is seen that numbers from 2008 are decreased by 76%.

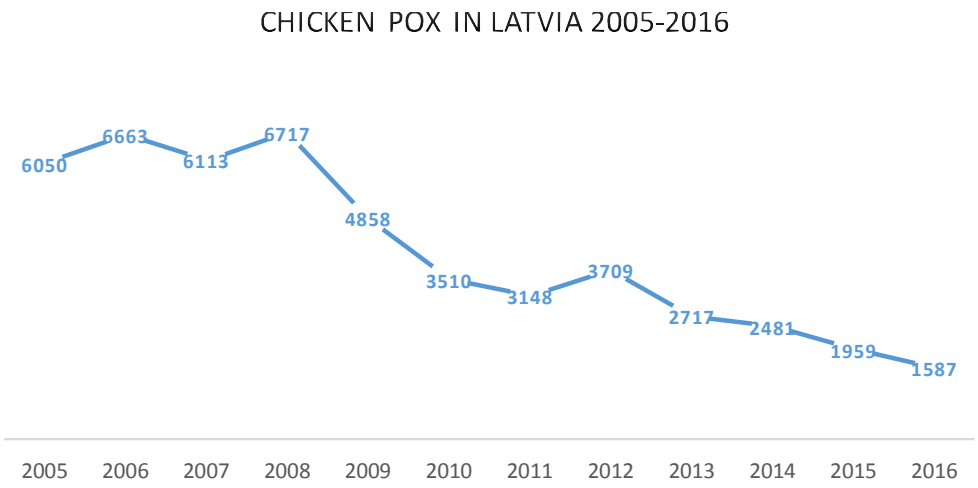

Figure 2. **The incidence of Chickenpox in Latvia in time period 2005-2016 (number of cases)**

In average children with vaccine-preventable diseases spent in the hospital 12.45 ± 7.10 days and in the interval from 2 to 31 days. From all the patients 40% were boys and 60% were girls. The mean age was 65.72 ± 65.01 months, with an interval from 1 to 215 months. Confidence interval (CI 95%) of age mean value is from 52.75 to 78.68 months.

While there were a lot of vaccine preventable disease cases and all together were 883 patients, more detailed information about diphtheria and pertussis were analyzed. In all the time period from 2005 to 2016 altogether 64 patients with diphtheria and 80 patients with pertussis were hospitalized and treated in Children`s Clinical university hospital in Riga. Results showed that diphtheria is observed on mean for older children than pertussis, and the difference is significant ($p < 0.05$). The mean value of hospitalization time in days for diphtheria were 15 days but for pertussis only 7 days. But for both diseases (diphtheria and pertussis) hospitalization interval were from 2 to 31 days. And the confidence interval (CI 95%) is from 11.04 to 13.87 days.

To prove that vaccine-preventable diseases can be really painful for little patients all invasive manipulations were analyzed from patient medical histories and documentations. 90% (108 from 120) received intravenous fluids or blood samples were taken. 10% from all patients with diphtheria and 8.2% from all pertussis case were admitted also in Intensive care unit that shows that vaccine-preventable diseases can be life-threating for the little patients. During time period from 2005 to 2016 there were no death cases because of vaccine-preventable diseases.

The second part of the study was prospective. Questionnaires were sent to those parents who were in Children`s Clinical university hospital with vaccine-preventable diseases in 2014. From those parents` answers that were received back it was analyzed that 52% from those patients were no vaccinated and 48% were vaccinated according to the National immunization calendar (*Figure 3*).

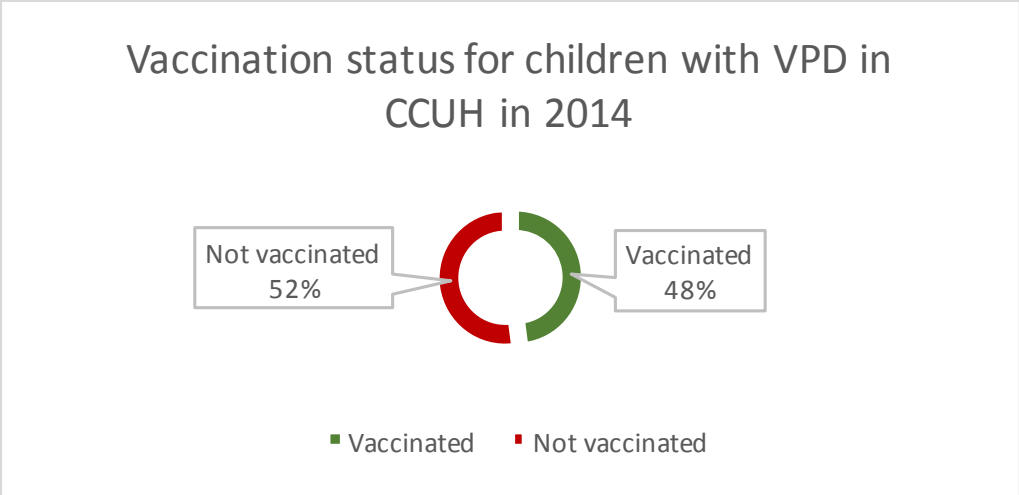

Figure 3. **Vaccination status for children with vaccine-preventable diseases in CCUH in 2014**

To find out the main reasons why parents choose not to vaccinate their children more data were analyzed. 33% decided not to vaccinate because of their own believes and thoughts, 25% of patients with vaccine-preventable disease had too small age to have the vaccination against exact disease, 25% of unvaccinated children had other chronic disease and 17% not to vaccinate their child because of vaccination complications to elder sibling.

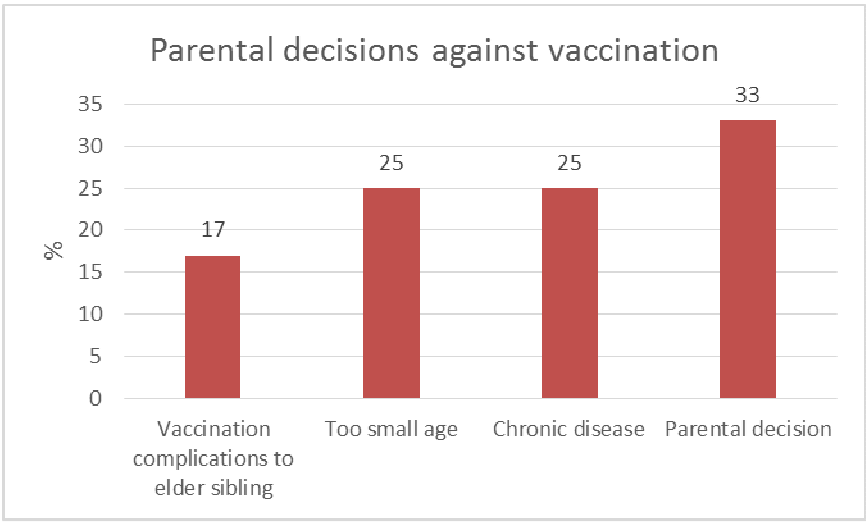

Figure 4. **Parental decisions against vaccination**

Discussion

Nowadays vaccine preventable diseases are again becoming more and more important discussion object. There are again problems with vaccine-preventable disease out-brakes, for example the measles in Europa in 2017. There is the feeling that we are back in the past and doctors need to discuss about the vaccine necessity again. Doctors must calmly and professionally explain vaccination positive effects and stress out importance not only for one individual, but investment and role in society, known “herd immunity” or “community immunity”. While there are some real contraindications for vaccines, more and more parents choose not to vaccinate their children without any reasonable excuse and giving popular misconceptions about vaccine side effects.

Patients with vaccine-preventable diseases are an important pressure to health care budget not only because manipulations and investigations that are needed to be done but also because of the long hospitalization time. According to the findings of these study, the mean hospitalization time with vaccine-preventable diseases were 12.45 ± 7.10 days.

One of the patients` parents are not working during the child hospitalization time. Having to take a leave from work, cause emotional stress for parents and dissatisfaction from administration and sometimes from colleges as well. It is also causing additional stress to family’s budget, since parents must take care of other children in the family and hiring nanny to be present with them until one of the parents are able to do that.

According to the literature the main reason why parents refuse one or more vaccines is because they have concerns about safety and side effects of vaccination and this reason is 60 to 70% of all vaccine refusals (Salmon 2005). Analyzing the data in CCUH it can be concluded that in Latvia the main reason, why child has not received all or part of vaccines that are included in The NIP, is parental decision (33%) – they have concerns about vaccine safety and side effects.

Conclusions

Vaccine preventable diseases are still an important issue to deal with in Latvia because during 11 year period (from 2005 to 2016) 883 patients received medical treatment in Children’s Clinical University Hospital with duration of hospitalization almost 2 weeks.

Every hospitalization with VPD is painful for little patients and emotionally stressful, since child is taken out from usual daily environment and put into hospital ward. Full blood count was taken in 90% of cases. A significant part of all diphtheria and pertussis patients were treated in Children’s Clinical University Hospital’s Intensive care unit.

In 2014 more than a half of patients with VPD were not vaccinated according to vaccination calendar and the most of them were not vaccinated because of parental decision, putting their children under risk for preventable illnesses and possible complications, because of common

misconceptions and considering that their opinion is more researched and more objective than doctor's.

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VACCUM EXTRACTION – MATERNAL AND NEONATAL COMPLICATIONS

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Abstract

Vacuum extractions – maternal and neonatal complications

Key words: *Vacuum extraction. Operative vaginal delivery. Maternity resolution*

Introduction: Vacuum extraction is in use as delivery instruments. Vacuum-extraction indications: fetal distress, dysfunction uteri, prolonged second stage of labor, maternal exhaustion. Use of vacuum extraction in the world is average 1.2-8.4% every year, in Riga Maternity Hospital in year 2014 it was made in 2.77% and in 2015 it was made 3.23%, but in 2016 fetal vacuum extractions was made in 4.18% of all deliveries.. Use of vacuum extraction is associated with higher risks for maternal complications like vaginal lacerations, and with neonatal complications like cephalohematoma, scalp abrasions.

Aim: The purpose of this research was to evaluate the complications for the mother and newborn, using vacuum extraction, and to compare them with spontaneous delivery.

Materials and methods: This study included group of vacuum-assisted deliveries in time period 2014-2016 (n=726) in Riga Maternity Hospital, and it was compared to the group of spontaneous vaginal deliveries (n=726). Data statistically processed in Microsoft Excel and SPSS Statistics 22.0.

Results: Results of the study are divided into two categories. The first category includes comparisons of the complications between two groups, and the differences are statistically significant ($p<0.05$): in vacuum-assisted deliveries vaginal lacerations was 13.8% more, cervical lacerations was 9.8% more than in group of spontaneous vaginal deliveries. Perineal lacerations were 25.6% less in group with vacuum extraction. In first category also is included neonatal cephalohematomas, which was 26.9% more, and clavicle factures was 3.3% more in vacuum-assisted deliveries. The second category includes comparisons of the complications between two groups, like subinvolutio uterus, superficial scalp wounds, retinal hemorrhage, facial nerve and brachial plexus damage, intraventricular haemorrhage, subgaleal hematoma and the differences are not statistically significant ($p>0.05$). Vacuum extraction was used for the first delivery in 86.9% of cases, for the second delivery 10.9% of cases.

Conclusion: Vacuum-assisted deliveries in comparison with spontaneous vaginal deliveries, are associated with higher risks for maternal soft tissue ruptures and neonatal cephalohematomas, clavicle factures. It is important to evaluate the indications for use of vacuum extractor. Staff skills, using vacuum extraction method, should be at a high level.

Kopsavilkums

Iespējamās komplikācijas dzemdētājai un jaundzimušajam, pielietojot augļa vakuumekstrakciju

Atslēgvārdi: *Vakuuma ekstrakcija. Operatīvās vaginālās dzemdības. Dzemdību atrisināšana*

Ievads: Augļa vakuumekstrakcija ir viens no vaginālo operatīvo dzemdību veidiem. Vakuumekstrakcijas indikācijas: augļa distress, dzemdes disfunkcijas, ieildzis dzemdību otrais periods, dzemdētājas spēku izsīkums. Pasaulē katru gadu vidēji tiek pielietos 1.2-8.4 % gadījumos, Rīgas Dzemdību namā 2014.gadā vakuuma ekstrakcija tika pielietota 2.77% gadījumu, 2015.gadā tas sastadīja 3.23% un 2016.gadā 4.18% gadījumos no visām šī gada dzemdībām. Augļa vakuuma ekstrakcijas kā biežākie sarežģījumi tiek minēti dzemdētājas maksts sienas plīsumi, jaundzimušajā – kefalohematomas, galvas ādas nobrāzumi.

Darba mērķis: Pētījuma mērķis bija izvērtēt sarežģījumus mātei un jaundzimušajām, dzemdībās lietojot augļa vakuuma ekstrakciju, un salīdzināt tos ar spontānām vaginālām dzemdībām.

Materiāli un metodes: Pētījumā grupā tika iekļautas dzemdības ar vakuumektrakcijas pielietošanu (n=726), kuras notikušas Rīgas Dzemdību namā laika posmā no 2014.-2016.gadam, tās tika salīdzinātas ar kontroles grupu (n=726). Dati statistiski apstrādāti ar Microsoft Excel un SPSS Statistics 22.0 programmu palīdzību.

Rezultāti: Pētījuma rezultātus iedala divās kategorijās. Pirmā kategorijā iekļauj sarežģījumu salīdzinājumus starp pētījuma un kontroles grupu, un to rezultāti ir statistiski nozīmīgi ($p<0.05$): pētījuma grupā maksts sienas plīsumi - par 13.8% vairāk, dzemdes kakla plīsumi - par 9.8% vairāk nekā kontroles grupai, starpenes plīsumi pētījuma grupā - par 25.6% mazāk nekā kontroles grupā. Pirmajā grupā ietilps arī jaundzimušā kefalohematomas - par 26.9% vairāk pētījuma grupai, atslēgas kaulu lūzumi - par 3.3% vairāk pētījuma grupai. Otrajā kategorijā iekļauj sarežģījumu salīdzinājumus starp pētījuma un kontroles grupu, dzemdētājai - dzemdes subinvolūcija, jaundzimušajām - virspusējās galvas ādas nobrāzumi, asinsizplūdumi tīklenē, *n.facialis* un *plexus brachialis* bojājumi, intraventrikulārie asinsizplūdumi, subgaleālās hematomas, un to rezultāti nav statistiski nozīmīgi ($p>0.05$): Augļa vakuumekstrakcija tika pielietota 86.9% pirmajās dzemdībās un 10.9% otrajās dzemdībās.

Secinājumi: Augļa vakuumekstrakcijas pielietošanas gadījumos biežāk novēro dzemdību ceļu traumatismu, ka arī jaundzimušā kefalohematomas un atslēgas kaulu lūzumus. Indikācijām vakuuma ekstrakcijas pielietošanā ir jābūt pamatotām. Personāla prasmēm, izmantojot vakuuma ekstrakcijas metodi, ir jābūt augstā līmenī.

Introduction

Fetal vacuum extractor is in use as delivery instruments. This is a method to assist delivery of a baby using a vacuum device. It is used in the second stage of labour if it has not progressed adequately. It may be an alternative to a forceps delivery and caesarean section. The use of fetal vacuum extractor is generally safe, but it can occasionally have negative effects on either the mother or the child. [7;8]

Vacuum extractor has a long history. The initial applications of vacuum techniques in deliveries began in the 18th century. While vacuum extractor became widely popular in Europe, the technique was little used in the United States until after the early 1980s, following the introduction of a series of new instruments, including disposable soft-cup extractors, new rigid cup designs, and handheld vacuum pumps. [2;7]

Use of vacuum extraction is variable in different countries. In the world it is average 1.2-8.4% every year, in Latvia 2014 2.2%, 2015 3.1 %, in Riga Maternity Hospital 2014 2.77%, 2015 3.23%, 2016 4.18%. [8] As we can see, use of these method is only increasing. In *Karolinska Institutet (Sweden*) (2014) study results - rates of vacuum extraction increased from 11.5% in 1992 to 14.8% in 2010. The risk of vacuum extraction increased with maternal age. The increased use of vacuum extraction over time was partly explained by increasing maternal age and increased use of epidural anesthesia. [5]

Vacuum device contain a cup, shaft, handle and vacuum generator. Vacuum cups may be metal, hard plastic or soft plastic and may also differ in their shape, size, and reusability. The soft cup is a pliable funnel- or bell-shaped dome, whereas the rigid type has a firm flattened mushroom-shaped cup and circular ridge around the cup rim. Several investigations have compared outcomes with various rigid and soft cups. Metal cups provide higher success rates, but greater rates of scalp injuries, including cephalohematomas. [2;7;8] In other study, Kuit et al., found that the only advantage of the soft cups was lower incidence of scalp injury. In a review, *Vacca,* concluded that there were fewer scalp lacerations with soft cup, but that the rate of cephalohematomas and subgaleal hemorrhage was similar between soft and rigid cups. [2;3;7;8]

Fetal vacuum-extraction most common indications are dysfunction uteri or fetal distress, prolonged second stage of labor, maternal exhaustion. [1;4;7]

It cannot be used when the baby is in the breech position or for premature births. [2]

As any other medical procedures, vacuum extraction also may have some complications. In literature and medical studies use of vacuum extraction is associated with higher risks for maternal complications like vaginal lacerations (due to entrapment of vaginal mucosa between suction cup and fetal head), and with neonatal complications like cephalohematoma, scalp abrasions, intracranial hemorrhage, subgaleal hematoma, retinal hemorrhage. [2;7;8;9]

Material and Methods

This study included group of vacuum-assisted deliveries in time period 2014-2016 (n=726) in Riga Maternity Hospital, and it was compared to the group of spontaneous vaginal deliveries (n=726) in time period 2014-2016 (n=726) in Riga Maternity Hospital. Data statistically processed in Microsoft Excel and SPSS Statistics 22.0. Retrospective case-control study.

Results

Results of the study are divided into two categories (Figure 1). The first category includes comparisons of the complications between two groups, and the differences are statistically significant ($p<0.05$): in vacuum-assisted deliveries episiotomy was made more than in control group. Also in vacuum-assisted deliveries vaginal lacerations and cervical lacerations was more than in group of spontaneous vaginal deliveries. In vacuum-assisted deliveries perineal lacerations were less than in control group.

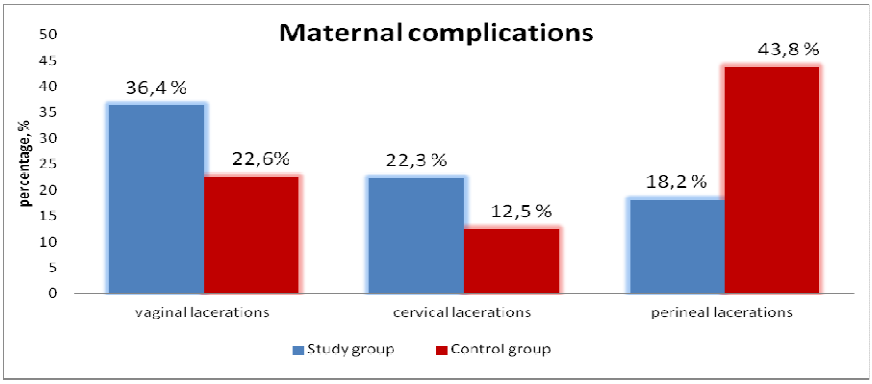

Figure 1. **Maternal comlications**

In statistically significant data category also is included neonatal complications like cephalohematomas and clavicle factures, which were more in vacuum-assisted deliveries (Figure 2).

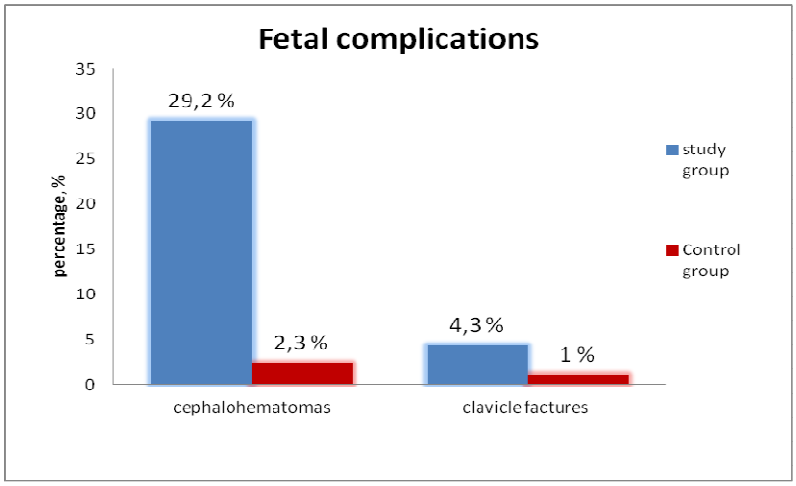

Figure 2. **Neonatal comlications**

The second category includes comparisons of the complications between two groups, and the differences are not statistically significant (p>0.05):

Maternal complications:

- in vacuum-assisted deliveries subinvolutio uterus was 0.3% more than in control group;

Neonatal complications:

- in study group superficial scalp wounds was 0.8% more than in control group;
- in study group retinal hemorrhage was 0.8%, in control group also – 0.8%;
- in study group facial nerve damage was 0.3% more than in control group;
- in study group brachial plexus damage was 0.3% more than in control group;
- in study group intraventricular haemorrhage was 1.8% more than in control group;
- in study group subgaleal hematoma was 0.3%, only in two cases, and in control group no subgaleal hematomas was detected.

Vacuum extraction was used for the first delivery in 86.9% of cases, for the second delivery 10.9% of cases and for the third delivery only in 2% of the cases (Figure 3).

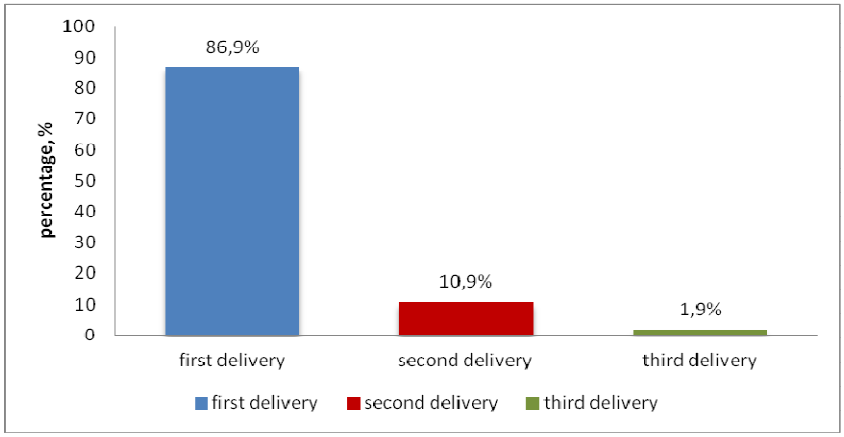

Figure 3. **The fetal vacuum extraction number in a row**

Discussion

This study showed, that episiotomy was made 63.4% more in vacuum-assisted deliveries in comparison with spontaneous vaginal deliveries. In literature is facts, that episiotomy during operative vaginal delivery also increases the incidence of postpartum hemorrhage and perineal infection, the need for stronger analgesia, and neonatal birth trauma. [1;6]

Taken together, it is important to evaluate the indications for use of the episiotomy in vacuum-assisted delivery.

Most common maternal complications, using vacuum extractor, are maternal soft tissue ruptures like vaginal vaginal lacerations and cervical lacerations. In opposite due to literature data [2;6;8] – this study shown that perineal lacerations in vaccum-assisted deliveries was significantly less

than in spontaneous vaginal deliveries. Which can be explained by the fact that the in this study was analyzed the first, second and third deliveries in a row, but in other medical studies was analyzed only first deliveries.

Most common neonatal complications in this study was shown – cephalohematomas and clavicle fractures. In literature and medical studies use of vacuum extraction is associated with higher risks for neonatal complications like cephalohematoma, scalp abrasions.[1;5;6] And there is no data about clavicle fractures, that was associated with fetal vacuum extraction. In literature clavicle fractures are the most common injury sustained by newborns during birth.[9]

Conclusions

Vacuum-assisted deliveries in comparison with spontaneous vaginal deliveries, are associated with higher risks for maternal soft tissue ruptures and neonatal cephalohematomas, clavicle factures.

It is important to evaluate the indications for use of vacuum extractor.

Acknowledgement

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REASONS FOR BLOOD DONOR DEFERRAL IN DAUGAVPILS REGIONAL HOSPITAL

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Abstract

Reasons for blood donor deferral in Daugavpils Regional Hospital

Key words: *blood donors, reasons of deferral, gender-related differences*

Blood donation involves many risks and striving for enlargement of number of donations is accompanied by means of maintaining blood safety. The procedure of blood donation becomes a complex process that includes evaluation of each individual donor according to strict selection criteria and involves screening of blood for transfusion-transmitted disease. Donors who do not meet the selection criteria are deferred on a temporary or permanent basis (WHO 2012; VADC 2013). The prevalence of transfusion-transmissible infections in blood donations in high-income countries is considerably lower than in low- and middle-income countries (WHO 2016). The blood donation rate in high-income countries is 33.1 donations per 1000 people, 11.7 donations in middle-income countries and 4.6 donations in low-income countries, respectively (WHO 2016). In Latvia, the number of donors per 1000 people is 17 (VADC 2016a). According to WHO (World Health Organization), the gender profile of blood donors shows that globally 28% of blood donations are given by women while this range varies widely. The aim of the current research is to summarize reasons for donor deferral during 2015 and 2016 in the city of Daugavpils and to search for the gender-related differences in reasons of donor deferral. The most common reasons for donor deferral in Daugavpils Regional Hospital's Blood Preparation Centre was low Hb level, poor veins, deferral for up to 6 months (tattoos, piercing, surgical procedures), positive anti-HCV test and chronic respiratory disorders. Women are more frequently deferred temporarily because of low Hb, poor veins and infectious or allergic skin disorders. Men are precluded from blood donation more often because of alcohol intake, hypertension, acute respiratory diseases, and deferred permanently because of positive anti-HCV test result.

Kopsavilkums

Atteikumu iemesli potenciālajiem asins donoriem Daugavpils reģionālajā slimnīcā

Atslēgvārdi: *asins donori, atteikumu iemesli, dzimumatšķirības*

Asins ziedošana ir saistīta ar daudziem riskiem, un tieksme pēc asins donoru skaita palielināšanas ir saistīta arī ar asins un to komponentu drošības ievērošanu. Asins ziedošana ir sarežģīts process, kas iekļauj katra asins donora novērtēšanu atbilstoši apstiprinātiem iekļaušanas kritērijiem un centralizētu asins komponentu kvalitātes kontroli: asins paraugu seroloģiskās, vīrusu molekulārās, imūnhematoloģiskās, kā arī asins komponentu mikrobioloģiskās pārbaudes. Donoriem, kuri neatbilst iekļaušanas kritērijiem, tiek atteikts asins ziedošanā uz kādu laiku vai uz mūžu (WHO 2012; VADC 2013). Ar asinīm pārnēsājamo slimību izplatība asins ziedošanas laikā ir ievērojami zemāka augsto ienākumu valstu grupā salīdzinājumā ar zemo un vidējo ienākumu valstīm (WHO 2016). Asins ziedošanas skaits augsto ienākumu grupas valstīs ir 33,1 ziedošana uz 1000 cilvēkiem, vidējo ienākumu valstīs – 11,7, zemo ienākumu valstīs – 4,6 (WHO 2016). Valsts asinsdonoru centrā un Daugavpils Reģionālās slimnīcas Asins sagatavošanas nodaļas apkopotie dati liecina, ka pagājušajā pārskata gadā Latvijā bija 17 donori uz 1000 cilvēkiem (VADC 2016a). Saskaņā ar Pasaules veselības organizācijas (WHO) datiem, 28% no asins ziedošanas reizēm ir veikušas sievietes, tomēr šis skaitlis ļoti variē starp pasaules valstīm. Šī pētījuma mērķis ir apkopot atteikumu iemeslus potenciālajiem asins donoriem Daugavpilī laika periodā no 2015. līdz 2016. gadam un atklāt iespējamās dzimumatšķirības atteikumu iemeslos. Biežākie atteikumu iemesli asins donācijai Daugavpils Reģionālās slimnīcas Asins sagatavošanas nodaļā bija zems hemoglobīna (Hb) līmenis, neatbilstošs vēnu stāvoklis, atteikums uz 6 mēnešiem sakarā ar tetovējumu, ausu caurduršanu, ķirurģiskām procedūrām, ka arī pozitīvs tests uz anti-HCV un hroniskās respiratorās saslimšanas. Sievietes visbiežāk saņem atteikumu uz laiku sakarā ar zemu Hb līmeni, neatbilstošo vēnu stāvokli un infekcijas vai alerģiskām ādas slimībām. Visbiežākie atteikumu iemesli vīriešiem ir alkohola uzņemšana, paaugstināts asinsspiediens, akūtas respiratorās slimības. Vīrieši biežāk saņem pastāvīgo atteikumu saistībā ar pozitīvu anti-HCV testa rezultātu.

Introduction

The number of first time donors in the State Blood Donor Centre (SBDC) (Valsts Asinsdonoru centrs (VADC)) increases annually. According to SBDC data it raised from 4375 (26.1%) in 2012 to 4755 (26.6%) in 2015. In the Latgale office, the situation is the opposite: the

number of first time donors has decreased in 4 years' time from 1207 (25.7%) to 866 (20.8%). In total in the country, the mean number of all donors in 5 years (2011-2015) was 33901.6 ± 1295.8 people. In 2015, the absolute number of blood donors was 34001 people (VADC 2016b).

In regard to blood donation rates, in high-income countries it is 33.1 donations per 1000 people, 11.7 donations in middle-income countries and 4.6 donations in low-income countries, respectively (WHO 2016). In Latvia in 2015, there were 17 donors per 1000 people (VADC 2016a). In total, in 2015 blood donation rate was 51440 people (VADC 2016b). The number of blood donor deferrals is also high and according to the statistical data, the donor deferral rates in 2011 was 7487 (17.8%), while in 2012 this number increased as high as 7950 (20%) deferrals (VADC 2013).

According to the Guidelines on Assessing Donor Suitability for Blood Donation published by WHO in 2012 "Blood transfusion services have the responsibility to collect blood only from donors who are at low risk for any infection that could be transmitted through transfusion and who are unlikely to jeopardize their own health by blood donation". This determines the necessity for maintaining blood safety by a rigorous process of prospective donors' assessment for suitability.

Blood donation involves many risks (WHO 2012; Khurram 2017) and striving for enlargement of number of donations is accompanied by the risks of impairment of blood safety. The procedure of blood donation becomes a complex process that includes evaluation of each individual donor according to strict selection criteria and involves screening of blood for transfusion-transmitted disease. Donors who do not to meet the selection criteria are deferred on a temporary or permanent basis (WHO 2012; VADC 2016b). Policy recommendations state that national donor selection guidelines and criteria should be based on epidemiological and/or scientific evidence or, where evidence is limited or lacking, on best practices (WHO 2012). Technical recommendations provide a summary of donor selection criteria that involves all starting from common health status at the moment of donation to common contraindications concerning age, body mass and sexual behavior.

There are different deferral rates in different countries and the number range from 8.7% to 25.6% (Abdelaal & Anwar 2016; Birjandi et al. 2013; Gonçalez et al. 2013; Khurram et al. 2017; Shrivastava et al. 2016). In Saudi Arabia the data were collected from January 2011 to December 2014 and 4035 (8.7%) of donor deferrals were reported out of 46370 blood donors (Abdelaal & Anwar 2016). Shrivastava and co-authors (2016) analyzed donor deferral rate over a period of 13 years from 2001 to 2013 and it was 11.5% of deferral rate in India (Shrivastava et al. 2016). Findings of Khurram and colleagues (2017) indicate that deferral occurred in 3156 (12.2%) of attempts and 280 (1.1%) were permanently deferred, while 2876 (11.1%) were temporarily deferred from January 2012 to December 2014 (Khurram et al. 2017). According to their data covering British population, the most common reasons for permanent deferral was a history of hepatitis B

infection (n = 147, 4.7% of all deferrals) (Khurram et al. 2017). Gonçales in 2013 report 216 866 (22.5%) of deferrals in Brazil for the period from August 2007 to December 2009 (Gonçalez et al. 2013). Almost the same period was taken to analysis in India – the years 2007 – 2008. The deferral rate reported by Birjandi was 25.6% (Birjandi et al. 2013).

Group of researchers from Ireland reported that a total of 613 men (2.4%) and 1624 women (8.4%) were deferred from donation because of a low hemoglobin (Hb) level (Baart et al. 2014). One of the major reasons for temporary donor deferral in Britain was also low Hb level (n = 971, 30.76%) (Khurram et al. 2017). In India, there were 19.4% of deferral because of low Hb (Shrivastava et al. 2016). In Brazil, low Hb levels were one of the main reasons for donor deferral and females were more likely to be deferred than males (30% vs. 18%, respectively) (Gonçales et al. 2013). In Iran, the deferral rate for females and males was 54.6% and 24.3%, respectively. Authors point on significant gender-differences in donor deferral rates ($p = 0.007$). The main reason for deferral in Isfahan Blood Transfusion Centers was abnormal blood pressure (Birjandi 2013).

Knowledge of the reasons for donor deferral can help in planning more efficient recruitment strategies and in evaluating donor selection criteria. This study aimed to summarize reasons for donor deferral during 2015 and 2016 in the city of Daugavpils and to search for the gender-related differences in reasons of donor deferral.

Materials and Methods

This retrospective study was conducted at Blood Preparation Department of Daugavpils Regional Hospital, Latvia, and comprised data of all blood donor deferrals reported from January 2015 to December 2016 in the hospital's blood bank, which is a Latgale office of the State Blood Donors Centre. The data was collected from the records maintained by the blood bank. Data collection was performed after receiving permission from Daugavpils University Biology and Medical Research Ethics Committee. 812 potential blood donors presenting themselves at Blood Preparation Department of Daugavpils Regional Hospital and deferred temporarily or permanently based on the donor deferral criteria were included in the study analysis. The reasons for donor deferral were analyzed after classification into the following categories: gender (male-female), year (2015-2016), the cause of deferral (temporary medical deferrals or permanent medical deferrals). Data was processed using IBM SPSS Statistics 20.0 version. The gender-based differences were assessed using Fisher's exact test and $p < 0.05$ was considered to be statistically significant.

Results

A total of 7088 prospective blood donors were registered for blood donation, while 3989 blood donors (56.28%) donated blood during the study period (Table 1). The number of donors that were precluded from blood donation was 812 (11.46%) between 2015 and 2016. In total, 3018 (42.58%) women and 4070 (57.42%) men were registered as prospective blood donors during the

all study period. The donor deferral rate was statistically significantly higher in women than men, being 452 (55.67%) deferrals in women and 360 (44.33%) in men (p = 0.0001) (Table 1).

Table 1. **Blood donation and deferral rates**

Donors	Women (n)	Men (n)	Total (n)
2015			
Blood donors	1542	1946	3488
Real donors	916	1043	1959
Donor deferrals	190	158	348
P-value	0.0002*		
2016			
Blood donors	1476	2124	3600
Real donors	909	1121	2030
Donor deferrals	262	202	464
P-value	0.0001*		
Total			
Blood donors	3018	4070	7088
Real donors	1825	2164	3989
Donor deferrals	452	360	812
P-value	0.0001*		

**P ≤ 0.05 indicates statistically significant differences between genders*

Analyzing the data by year, women were found to be less active donors both in 2015 and 2016 (Table 1). The proportion of donor deferrals in relation to the number of real donors in 2015 and 2016 differs significantly between genders (2015: p = 0.006; 2016: p = 0.0001). The number of deferrals were higher in women both in 2015 and 2016. Among the donors deferred in 2015, 158 (8.12%) were males, and 190 (12.32%) were females (p = 0.0002). In 2016, 202 (9.51%) males and 262 (17.75%) females were deferred (p = 0.0001).

Unclassified temporary reasons for donor deferral were the most frequent reasons for donor deferral in the both years. In total, 649 people (79.9% from all deferrals) were deferred temporarily because of the following reasons: low or high Hb, donor veins condition, alcohol intake, low body mass, immunization/vaccination etc. All reasons of this kind accounted for 159 deferrals (83.7%) in women and 116 (73.4%) in men in 2015 (p = 0.0243). In 2016, unclassified temporary reasons accounted for 233 women (88.9%) and 141 men (69.8%) (p = 0.0001).

The most frequent reason in this group of deferrals was low Hb, which was found in 421 people (51.9%). Low Hb was detected in 105 women (55.3%) and in 58 men (36.7%) during 2015 (p = 0.0006) and in 171 women (65.3%) and 87 men (43.1%) during 2016 (p = 0.0001). Women were deferred in the case of low Hb more often than men in both years, 61.0% and 40.3% respectively (p = 0.0001). The second most frequent reason for donors to be deferred was poor donor veins condition. In 111 people (13.6%) veins were not suitable for the blood donation procedure. Poor condition of veins was the reason for deferral of 30 women (15.8%) and 20 men (12.7%) in 2015 (p = 0.4454) and 43 women (16.4%) and 18 men (8.9%) in 2016 (p = 0.0187).

Accounting for both years simultaneously gender-related differences was present and women were more frequently deferred because of poor veins than men ($p = 0.0236$).

Other reasons from this group of deferrals accounted for less than 10%. Most frequent among them were: alcohol intake, medication, hypertension. For example, 23 people (2.8%) were deferred because of alcohol intake: 3 women (1.6%) and 11 men (7%) in 2015 ($p = 0.0132$) and 2 women (0.8%) and 7 men (3.5%) in 2016 ($p = 0.0451$). Men were deferred more often due to alcohol than women in both years ($p = 0.0011$). Hypertension was the reason for deferral in 1.8% (15 cases). Men were deferred because of hypertension more often: 6 times (3%) comparing with 1 (0.4%) in women during 2016 ($p = 0.0466$). In 2015, deferral rate was similar in both genders – 4 cases (2.1% in women, 2.5% in men) ($p = 1.000$). There were no gender-related differences in the deferral rate because of medication (antibiotics, antidepressants, etc.) in both years. In total, 6 women (1.32%) and 7 men (1.9%) were deferred during 2015-2016.

The most frequent reason of the deferrals lasting up to 6 months was because of recently made tattoos, piercing, acupuncture, diagnostic procedures, trauma etc. In 2015, 14 women (7.4% from all deferrals) and 15 men (9.5%) and in 2016, 7 women (2.7%) and 13 men (6.4%) were deferred for up to 6 months ($p = 0.5602$, $p = 0.1035$ respectively). Gender-related differences in the deferral rate for 6 moths were not found ($p = 0.10$).

The second most frequent temporary reason for deferral in blood donation was unsatisfactory results of blood analysis control from 23 people (2.8%). Five women (2.6%) and 4 men (2.5%) were deferred in 2015 because of this reason ($p = 1.000$). In 2016, no gender-differences were found ($p = 0.5728$). In two years, unsatisfactory results of blood analysis control was the reason for donor deferral in 11 women (2.4%) and 12 men (3.3%) ($p = 0.5247$).

Acute respiratory diseases (pneumonia, bronchitis, viral infections of upper respiratory tract etc.) were the third most frequent reason to defer 18 blood donors (2.2%). Two women (1.1%) and 8 men (5.1%) in 2015 ($p = 0.0498$) comparing with 1 (0.4%) and 7 (3.5%), respectively in 2016 ($p = 0.0239$) were deferred because of this reason. Men were deferred more often compared with women, 15 men (4.17%) and 3 women (0.66%), respectively ($p = 0.001$).

Five women (2.6%) and 4 men (2.5%) during 2015 ($p = 1.00$) and 1 women (0.4%) and 6 men (3%) during 2016 ($p = 0.0466$) were deferred due to infectious and allergic skin and nail diseases (psoriasis, dermatitis etc.). Deferral rate in case of infectious and allergic skin and nail diseases was statistically significantly higher in men comparing to women in 2016. No statistically significant differences between genders were found across the two-year period ($p = 0.2027$).

There were two most frequent permanent reasons for deferral: positive express test for anti-HCV (hepatitis C virus) and chronic respiratory disorders (bronchial asthma, chronic bronchitis

etc.). Both accounted for more than 2.0% of all deferrals. Other reasons were less frequent and accounted for less than 1.0% of all deferrals.

Eighteen donors (2.2%) were deferred because of positive express test for anti-HCV. In 2015, deferral rate was similar in both genders – 2 people (1.1% in women and 1.3% in men) (p = 1.000), but statistically significantly higher deferral rate due to positive anti-HCV test was in 2016 in men than in women, 13 (6.4%) and 1 (0.4%) respectively ($p = 0.0001$). Three women (0.6%) and 15 men (4.2%) were deferred in the two-year period ($p = 0.0011$).

Chronic respiratory disorders (bronchial asthma, chronic bronchitis etc.) were found in 17 blood donors (2.1%). We did not find statistically significant gender differences in the number of deferrals in 2015 ($p = 1.000$) and 2016 ($p = 0.3796$), and also across the study ($p = 0.4730$). Eight women (1.8%) and 9 men (2.5%) were deferred because of the presence of chronic respiratory disorders.

Discussion

In this study, the deferral rate was 11.46% while other countries have reported different numbers. Similar deferral rate was reported by Shrivastava et al. (2016) based on the data of the 13 years long study in India. Khurram et al. (2017) reported 12.2% deferral rate in England from January 2012 to December 2014. As reported by Birjandi et al. (2013) deferral rate in the American Red Cross Blood Services was 12.8%, Brazil – 21.6%, Singapore – 14.4%, India – 9% and Malaysia – 5.6% (Birjandi et al. 2013). According to Birjandi et al. 2013, deferral rate in the years 2007 – 2008 was 25.6% in Iran. Deferral rate in Daugavpils Regional Hospital's Blood Preparation department is similar to the data collected in England by Khurram et al. because the studied period was 2-3 years.

In this study, higher deferral rates were found in women. The same findings were reported in a study of Groot et al. (2015) which shows that women are deferred more often than men. Higher deferral rates in women than in men were also found in the studies by Birjandi et al. (2013), Gonçales et al. (2013), Agnihotri N. (2010), Khurram et al. (2017). Higher deferral rates in women can be explained by the higher rates of deferrals in case of low Hb which is more common for women. The same reason is mentioned in the study of Birjandi et al. (2013) and Gonçales et al. (2013). Additional attention should be payed to the iron deficiency problem by the government and Health care services.

In this study, the most frequent medical reasons for temporary donor deferral were low Hb and poor veins, accounting 51.9% and 13.6% respectively, which is similar to other studies done locally and internationally. Agnihotri N. (2010) reported low Hb (55.8%) as one of the most common reasons for deferral. Shrivastava et al. (2016) reported 19.4% of deferral because of low Hb in total. One of the major reasons for temporary donor deferral in Britain was low Hb level

(30.76%) (Khurram et al. 2017). According to Gonçales et al. (2013) low Hb level constituted 18.7% of all deferrals at three blood centers in Brazil.

This study reports some gender-differences in the reasons for donor deferral. In this study, women were deferred because of low Hb (61.0%) and poor veins (16.2%) more frequently than men in both years. Similar finding was also reported in other studies. Baart et al. (2014) showed that more women (8.4%) were deferred from donation because of a low hemoglobin level in Ireland compared to men (2.4%). Also in Brazil, deferrals for low hemoglobin/ hematocrit were much more likely to be females (Gonçales et al. 2013). According to Birjandi et al. (2013), the most common cause in female donors was low Hb level (42.3 %). However, Indian researchers report higher deferral rate because of low Hb in men (54%) compared with 46% were in females (Shrivastava et al. 2016). Abdelaal & Answar (2016) reported 17% of deferrals because of poor veins, that was the second most frequent reasons as in this study.

In this study, men were deferred more often because of hypertension, alcohol intake, acute respiratory disease and positive anti-HCV test. Also in study of Birjandi et al. (2013) the most common cause of deferred from blood donation within male donors was abnormal blood pressure (15.3 %). The same findings in regard to positive anti-HCV was also revealed in the study of Fu et al. (2013). Authors reported a higher frequency of HCV+ in men. As reported earlier in Klein (2012), the intensity and prevalence of viral infections is typically higher in males. Higher sex-specific vulnerability to many infections caused by viruses, bacteria, parasites, and fungi in men was mentioned also in studies of Giefing-Kröll C. et al. (2015), Lourenço *et al.* (2008), Klein and Roberts (2010). The evidence that men are more susceptible to hepatitis C virus (Klein, 2012), is supported by results of present study.

Conclusions

The most common temporary reasons for donor deferral in Daugavpils Regional Hospital's Blood Preparation Centre was low Hb level, poor veins and deferral for up to 6 months because of tattoos, piercing, surgical procedures etc. Positive anti-HCV test and chronic respiratory disorders (bronchial asthma, chronic bronchitis etc.) were the most frequent reasons for permanent donor deferral. Women are more frequently deferred temporarily because of low Hb, poor veins and infectious and allergic skin disorders. Men are precluded from blood donation more often because of alcohol intake, hypertension, acute respiratory diseases, and deferred permanently because of positive anti-HCV test result.

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USE OF URINE NITRITE TEST FOR DETECTING ASYMPTOMATIC BACTERIURIA DURING PREGNANCY

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Abstract

Use of urine nitrite test for detecting asymptomatic bacteriuria during pregnancy

Key words: *asymptomatic bacteriuria (ABU), nitrite test, antibacterial therapy, risk factors*

Introduction: Nitrite test is used as ABU screening method. It should be done every time urine analysis is performed. If test is positive, urine culture, antibacterial therapy course and control urine culture should be done. Guidelines recommend to do urine culture in 12-16 weeks of gestation, if woman has urinary tract infections risk factors.

Aim: Find out the use of nitrite test during pregnancy, analyze prenatal care tactics, ABU treatment, its conformity to guidelines, recommendations.

Materials and methods: For the retrospective research were randomly selected 180 women in puerperal period. Data was processed with SPSS22, Microsoft Excel 2013 and statistical calculator.

Results: The average age is 30,44 years. All women had antenatal care, urine analysis with nitrite test. Nitrite test was positive in 6,1% (n=11). Urine culture was made in 4 of these cases, and in 3 - it was positive. In this group therapy received 8 women (72.7%). Antibacterial therapy was prescribed to 5 women: in 2 cases, it was empiric, in 3 – depending on urine culture results. Urinary tract infections risk factors had 83.3% of women. None of them had had urine culture made because of them.

Conclusions: There is a need in improvement of antenatal care, as sometimes it might differ from the recommendations.

Kopsavilkums

Urīna nitrītu testa izmantošana lai atklātu asimptomātisko bakteriūriju grūtniecības laikā

Atslēgas vārdi: *Asimptomātiskā bakteriūrija (ABŪ), nitrītu tests, antibakteriālā terapija, riska faktori*

Ievads: Nitrītu tests tiek izmantots kā ABŪ skrīninga metode. To ir jālieto katru reizi veicot urīna analīzi. Ja nitŗītu tests ir pozitīvs, jāveic sekojošais urīna uzsējums, antibakteriālā terpija un kontroles uzsējums. Valdīnijas rekomendē veikt uzsējumu 12-16 grūtniecības nedēļās, ja sievietei ir urīnceļu infekcijas riska faktori.

Mērķis: Izvērtēt nitrītu testa izmantošanu grūtniecības laikā, prenatālās aprūpes taktiku, ABŪ ārstēšanu, tas atbilstību vadlīnijām, rekomendācijām.

Materiāli un metodes: Retrospektīvam pētījumam tika randomizēti izvēlētas 180 nedēļnieces. Dati tika apstrādāti ar SPSS22, Microsoft Excel 2013 un statistikas kalkulatoru.

Rezultāti: Vidējais vecums pētījuma grupā ir 30,44 gadi. Visām sievietēm bija antenatālā aprūpe, urīna analīzes ar nitrītu testu. Nitrītu tests bija pozitīvs 6,1% (n=11) . Urīna uzsējums tika veikts 4 gadījumos, un 3 tas bija pozitīvs. Pozitīvā testa grupā terapiju saņēma 8 sievietes (72,7%). Antibakteriālo terapiju saņēma 5 sievietēm: divos gadījumos – empīriskā terapija, trijos – atkarībā no uzsējuma rezultātiem. Urīnceļu infekcijas riska faktori bija 83,3% sievietēm. Nevienai sievietei netika veikts urīna uzsējums pamatojoties uz tiem.

Secinājumi: Ir nepieciešams uzlabot antenatālo aprūpi, jo tā bieži atšķirās no rekomendācijām.

Introduction

Asymptomatic bacteriuria.

Asymptomatic bacteriuria is bacteria concentration in urine higher than 10^5 CFU/ml in two urine samples without clinical symptoms. Incidence among pregnant women in literature does not differ: 2-7% (Rezeberga 2016: 645; Corton 2014: 2213), 1,9-9,5% (Yawetz), 5-10% (Reynars 2013: 642), 2-10% (Torres 2012), 2-15% (West 2014: 2). There is not united opinion about incidence difference in pregnant women group and non-pregnant women. *West and Moore, Yawetz et al* underline, that ABU incidence in pregnancy is two times higher than without pregnancy. (West 2014; Yawetz) In case in ABU it is high possibility that symptomatic urinary tract infections will develop: in 40% of cases acute cystitis develops, and in 20-40% - acute pyelonephritis. (SIGN

2012:16-18; Grade 2010: 21-22) Higher ABU incidence is associated with urinary tract anatomical and physiological changes during pregnancy. Most ABU cases develops in first pregnancy months because of higher urine concentration. (Rezeberga. 2016: 654)

Bacteria that causes ABU are following: *Escherihia coli* 70-90%; *Klebsiella pneumoniae* 5%; *Proteus mirabilis* 5%; *Enterobacter spp.* 3%; *Staphylococcus saprophyticus* 2%; *Proteus spp.* 2%, *Gardnerella vaginalis*, *Streptococcus agalactiae* 2-5% (Rezeberga 2016: 355)

Asymptomatic bacteriuria diagnose confirms only urine culture. (Grade 2010: 21-22)

The aim of antibacterial therapy is to destroy pathogenic microbes, decrease symptomatic urinary tract infection incidence and with it associated complications. (Torres 2012) While using antibiotics during pregnancy, should be careful with choice of drug because of its possible teratogenicity. (SIGN 2012:18) Choice of antibiotic should depend on urine culture results.

Following antibacterial medicaments are recommended in ABU therapy: nitrofurantoin, amoxicillin, amoxicillin in combination with clavulanic acid, cephalexin, phosphomycin.

(Rezeberga 2016: 655; Yawetz; Grade 2010: 21-22)

Comparing short term and long term therapy course, it is proven that short-term therapy is just as effective as long term therapy. (West 2014) In case of treated ABU the possibility that symptomatic urinary tract infections will develop is under 1%. (Corton 2014: 2213)

After therapy course (after 2-3 weeks) control urine culture should be made. (Rezeberga 2015: 9-10)

Asymptomatic bacteriuria complications are following: acute cystitis, acute pyelonephritis, low birth weight, increased perinatal mortality. (Rezeberga 2016: 645; Yawetz)

Antenatal care recommendations in Latvia.

In Latvia, standard antenatal care is determined by the Cabinet of Minister regulation Nr.611. Urine analysis is performed six times during pregnancy (at 10 week.; 16.-18 weeks; 25.-26 weeks; 29.-30 weeks; 34.-36 weeks; 38.-40 weeks). Every time urine nitrite test as ABU screening should be done. In case of positive nitrite test urine culture should be done to confirm ABU. Nitrite test in only screening method, only urine culture can confirm the diagnosis, if bacteria concentration in urine is higher than 10^5 CFU/ml. Antibacterial therapy is prescribed depending on culture results and bacteria sensitivity. After 2-3 weeks after therapy course control culture must be done. If it is negative, standard antenatal care is continued. If it is not – supportive antibacterial therapy can be prescribed (nitrofurantoin 50-100 mg daily) In this case single urine culture in the beginning of third trimester can be done. (Rezeberga 2015: 6, 9-10)

Guidelines in other European Union countries.

In United Kingdom, according to NICE *(National Institute for Health and Care Excellence)* recommendations, ABU screening using urine culture should be done in early pregnancy. (NICE. 2008)

Scottish guidelines (*Scottish Intercollegiate Guidelines Network*) underlines that urine nitrite or leucocyte esterase test is not sensitive enough to use it as screening method. Method of choice is urine culture. Guidelines offer following algorithm: to make urine culture at first antenatal visit, during second visit make repetitive culture, to exclude or confirm ABU diagnose. Necessary antibacterial therapy lasts 3-7 days, which is as effective as long term therapy. Guidelines recommends to choose antibacterial drug in conformity with local guidelines. (SIGN. 2012 - 16-18)

European Urology Association recommends to do ABU screening to all pregnant women in first trimester, prescribe antibacterial therapy and after treatment do control urine culture. As pregnancy is one of urinary tract infection risk factors, 3 days antibacterial therapy can be prescribed only using phosphomycin. (Grade 2010: 21-22)

Urine nitrite test and urine culture as ABU screening methods.

Nitrite test is made every time urine analysis is performed. This test is based on nitrate hydrolyzation to nitrite with nitrate reductase enzyme. (Wagenlehner 2017: 587) Positive nitrite test is associated with *Enterobacteriaceae spp.* bacteria existence in urine, which is most common urinary tract infection pathogen. Nitrite test is negative if there are Gram positive bacteria in urine. Nitrite test sensitivity is 41-57% and specificity 92-100%. Almost 2% of ABU cases cannot be detected with nitrite test, so urine culture is recommended. Using both nitrite and leucocyte esterase test sensitivity increases till 100%, but specificity decreases to 60-80%. Nitrite test using recommendation level is IIa, category B. (McAnnish 2013:200)

Urine culture is recommended as ABU screening method (recommendation level I, category A). Bacteria concentration higher than 10^6 CFU/ml evidence about clinically significant bacteriuria. It is recommended to do bacteriuria screening at 12-16 weeks of gestation to pregnant women without urinary tract infection risk factors. If woman has risk factors, consider repetitive urine culture. Despite the higher costs urine culture is “gold standard” for ABU diagnostics among pregnant women, because nitrite test and bacteria microscoping has worse positive and negative predictive values. Almost 80% of ABU during pregnancy are discovered at 12-16 weeks of gestation. (Rezeberga. 2016: 655)

In countries with lower ABU incidence it is not cost effective to use urine culture as screening method, therefore allow to use nitrite and leucocyte esterase test. (Corton 2014:2213)

Materials and methods

For this retrospective study 180 women in puerperal period were selected in Riga Maternity Hospital Mothers and child care unit in time period from 1.10.2016 till 31.01.2017. Inclusion criteria were antenatal case existence and singleton pregnancy (multiple pregnancy belongs to high risk pregnancies, perinatal morbidity and mortality is much higher than in singleton pregnancy).

During the survey data about anamnesis, sociodemographic data and urinary tract infection risk factors was collected. The information about antenatal care, pregnancy outcomes was collected form medical documentation (delivery histories and mother's passport).

Collected data was processed with IBM SPSSv22, Microsoft Excel 2013 and Diagnostic test evaluation calculator. Database was made in SPSSv22 program. To compare pregnancy outcomes in ABU and non-ABU groups *Two independent sample T-test* was used. To evaluate nitrite test as ABU screening method women who at one antenatal visit has both nitrite test and urine culture were selected. Diagnostic test evaluation calculator was used to find out urine nitrite test sensitivity and specificity, following *Receiver Operating Characteristic* (ROC) curve was analyzed.

The research was accepted by RSU Ethic Commission (29.09.2016).

Results

Study group characteristics

In study group 180 women in puerperal period were included. Average age of women is 30,44 years (SD = 5,49 years; min = 15; max = 43)

Level of education: 55% (n=99) women has higher education, 7,8% (n=14) has incompleted higher education, 11,7% (n=21) has secondary vocational, 17,2% (n=31) has general secondary and8,3% (n=15) – primary education. 45% of women (n=81) this delivery was first, 55% of women (n=99) had repeated delivery. Of these women 66 (36,7%) had second delivery, third – 23 (12,8%), 6 women had fourth (3.3%) and fifth – 2.2% (n=4).

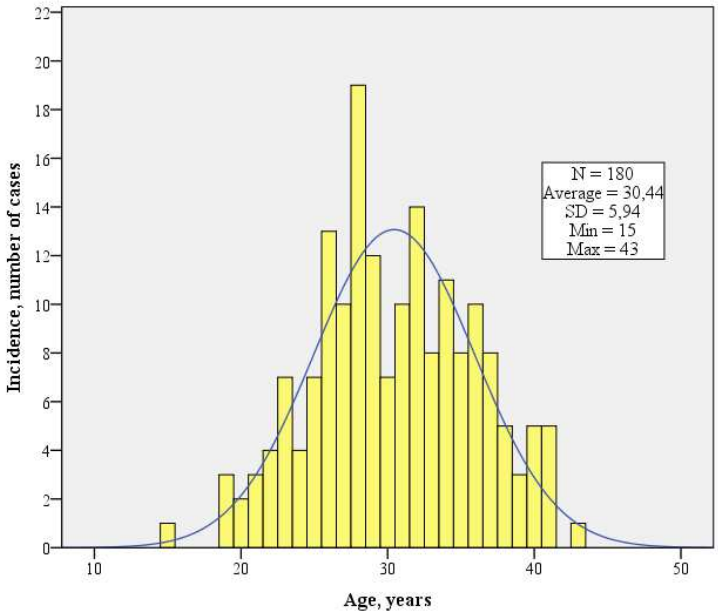

Figure 1. **Age distribution in study group**

Pregnancy outcomes

77,2% (n=139) of women had natural childbirth and in 22,8% (n=41) caesarian section was performed. Birth weight of newborn was divided into following groups: fetus macrosomy (n=38; 21,1%), normal weight (n=127; 70,6%), low (n=12; 6,67%), very low (n=1; 0,56%), especially low (n=2, 1,1%). Preterm delivery was observed in 21 cases (11,7%), term in 159 cases (88,3%).

Asymptomatic bacteriuria

The incidence of ABU in research group is 3,3% (n=6). In three cases was positive urine nitrite test, in other three cases urine culture was made because of leucocyturia and positive bacteria microscoping. Therapy in ABU group was prescribed to 5 women, all these women received antibacterial therapy. No one had made control urine culture after antibacterial therapy course, but standard antenatal care was continued.

The effect of ABU on pregnancy outcomes

Comparing pregnancy outcomes between ABU and non-ABU group (with *Two Independent Samples T-test*), there was no statistically significant correlation in following parameters: lower newborn weight (p=0,409), lower newborn height (p=0,645), preterm delivery (p=0,367). Comparing Apgare scales score, was found statistically significant correlation: in ABU group Aprape scale scores in first and fifth minute are lower (p=0,035; p=0,015).

Risk factors

Symptomatic urinary tract infections risk factors distribution in study group: multiparity 48,3% (n=87), urinary bladder catheterization 32,2% (n=58), urinary tract infection in anamnesis 30,6% (n=55), gestational diabetes 14,4% (n=26), urinary tract diseases 5,0% (n=9), ABU 3,3% (n=6), low socioeconomical status 2,2% (n=4), urological surgery in anamnesis 1,1% (n=2). As a whole risk factors are nonspecific and very widespread. 81,7% (n=147). No one had made urine culture because of risk factors.

Use of nitrite test and urine culture

Nitrite test was positive in 11 cases (6,1%). All pregnant women at least one time had urine nitrite test made. In case of positive nitrite test urine culture was made in 4 cases, and 3 of these 4 cases it was positive (bacteria concentration $\geq 10^5$ CFU/ml). In positive urine nitrite test group therapy was prescribed to 8 women (72,7%). Of these women, antibacterial therapy was prescribed to 5 women: in two cases empiric, and in three cases depending on culture results. Three women received homeopathic medicine. These women, who had positive urine culture after positive nitrite test received adequate specific antibacterial therapy.

Urine culture was made in 13 cases. Analyzing use of urine culture: in 4 cases, it was made after positive nitrite test, on 7 cases after bacteria and leucocytes microscoping and in 2 cases – when acute cystitis has developed. There was no urine culture made because of urinary tract infections risk factors. Positive urine culture was found in 8 cases.

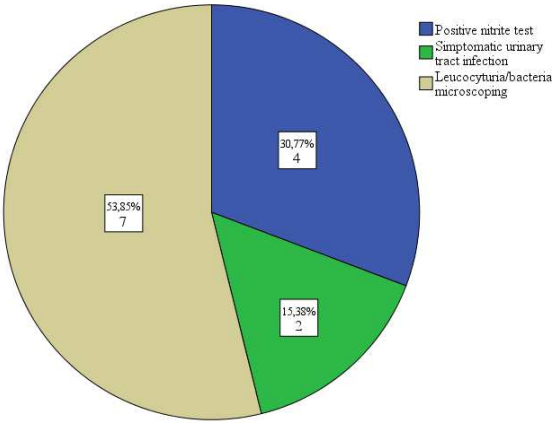

Figure 2. **Causes of urine culture performing**

To analyze urine nitrite test pregnant women, which had nitrite test and urine culture made at one antenatal visit, were selected. Based on the results of study nitrite test sensitivity is 37,5% (95% CI 8,52% - 75,51%) and specificity is 80% (95% CI 28,3% - 99,49%).

Table 1. **Urine nitrite test and urine culture evaluating table**

		Urine culture	
		Positive	**Negative**
Urine nitrite test	Positive	3	1
	Negative	5	4

Table 2. **Urine nitrite test evaluating table**

Statistics	**Value**	**95% CI**
Sensitivity	37,5%	8,52 – 75,51%
Specificity	80%	28,3 – 99,49%
Positive Likehood Ratio	1,88	0,26 – 13,42
Negative Likehood Ratio	0,78	0,39 – 1,56
Positive Predictive Value	75%	29,54 – 95,55%
Negative Predictive Value	44,44%	28,58 – 61,53%

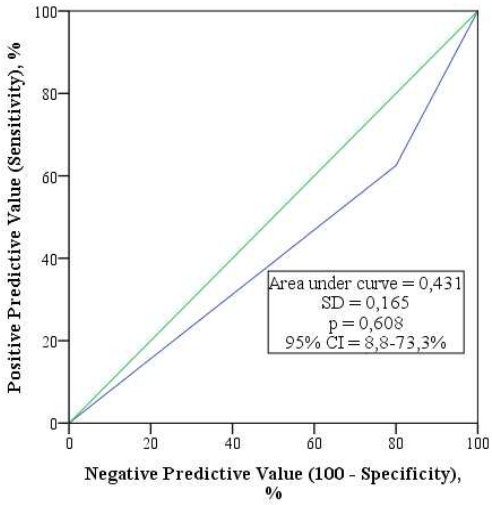

Figure 3. **Urine nitrite test ROC *(Receiver Operating Characteristics)* curve**

Analyzing nitrite test ROC curve, it is seen that area under the curve is 0,431, which means that urine nitrite test is not effective, but *p* value is 0,608, that is not statistically significant.

Leucocytes and bacteria microscoping

Leucocityria was observed in 37,8% (n=68), positive bacteria microscoping in 8,9% (n=16). Urine culture due to leucocyturia and bacteria microscoping was done in 3,89% (n=7).

Discussion

Researched problem is still very important, because often specialists does not follow recommendations. The incidence of ABU in high enough.

There still is not united opinion in academic literature about the most effective ABU screening method among pregnant women: is nitrite test still the most effective method or urine culture must be done. Several factors (ABU incidence, economic situation in country) should be taken in account.

As in the most cases ABU causes *E. Coli* (70-90%), there is a discussion, whether to wait results of urine culture or start empiric antibacterial therapy. It is necessary to examine all risks and benefits.

The incidence of ABU perhaps is much higher, but it can be analyzed only if all specialists will follow guidelines and recommendations, all pregnant women will have urine culture made after positive nitrite test or because of urinary tract infections risk factors. Nitrite test sensitivity and specificity perhaps is higher than in mentioned in academic literature due to previously mentioned reason.

Conclusions

There is a need in antenatal care improvement. Not all pregnant women had urine nitrite test made during every antenatal visit, what do not comply accepted recommendation in Latvia. Incorrect tactics in case of positive nitrite test was observed: only in 36,4% of cases following urine culture was made. Also in case of proved ABU, not in all cases antibacterial therapy was prescribed. In the case of adequate antibacterial therapy control urine culture was not made to ensure bacteria eradication. Incorrect antenatal care can lead to urinary tract infections complications.

About possible ABU can indicate not only urine nitrite test, but also leucocyturia and positive bacteria microscoping. Leucocyturia is quite widespread but not specific parameter. Bacteria microscoping should be taken in account, because nitrite test can’t detect Gram positive bacteria, but nitrite test is still the most effective ABU screening method. ABU diagnosis is confirmed only by urine culture.

Symptomatic urinary tract infections risk factors are not taken in account, but they are not specific and are widespread. Risk factors should be taken in account despite nitrite test results.

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TWIN TO TWIN TRANSFUSION SYNDROME (TTTS) MANAGEMENT – TWO COMPARATIVE CASE REPORTS

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Abstract
Key words: *Twin-to-twin transfusion syndrome (TTTS), monochorinic biamniotic (MCBA) pregnancy, fetoscopic laser photocoagulation, Quintero staging*
Introduction: TTTS is a serious condition that can complicate 8-10% of twin pregnancies with monochorionic biamniotic (MCBA) placentation. The diagnosis of TTTS requires 2 criteria: 1) the presence of a MCBA pregnancy; and 2) the presence of oligohydramnios (defined as a maximal vertical pocket of <2 cm) in one sac, and of polyhydramnios (a maximal vertical pocket of >8 cm) in the other sac. The Quintero staging system appears to be a useful tool for describing the severity of TTTS in a standardized fashion. Serial sonographic evaluation should be considered for all twins with MCBA placentation, usually beginning at around 16 weeks and continuing about every 2 weeks until delivery. Many patients with stage I TTTS may often be managed expectantly. The natural history of advanced (eg, stage ≥III) TTTS is bleak, with a reported perinatal loss rate of 70-100%, particularly when it presents <26 weeks. Fetoscopic laser photocoagulation of placental anastomoses is considered by most experts to be the best available approach for stages II, III, and IV TTTS in continuing pregnancies at <26 weeks. [Lynn 2013]
First case report description: Pregnant women K was 37 years old – her third pregnancy, she has had two deliveries. At that moment the patient was pregnant with MCBA twins. Several ultrasound scans were performed starting from week 17+6, all of them revealed growth discordance and gradually increasing poly- and oligohydroamnios. Only at 24th week fetal dopplerometry was performed, showing seriously abnormal a. umbilicalis flow and after that patient was sent for evaluation and treatment to fetal medicine department in Leuven Hospital in Belguim. There they revealed 54 % growth discordance and it has been decided to perform selective termination of severely affected twin. The procedure was performed – there were no complications afterwards, the patient was followed-up and the pregnancy progressed and a planned Caesarean section was performed on 40th gestational week.
Second case report description: A pregnant women E was 37 years old. She was having second pregnancy, has had one delivery. In this particular pregnancy she is having MCBA twins. While pregnancy is progressing, there are multiple ultrasonography's performed starting from 17+6 gestational week quite often. The conclusion of ultrasound on 20+0 gestational week was: F1 polyhydramnios and F2 oligohydramnios and growth discordance (28%). There was council arranged and a decision for further treatment in Belgium made – patient was going there for fetoscopic laser photocoagulation therapy. The diagnosis at that point: TTTS I stage, progressing (by Quintero classification). The procedure was done a couple of days later and the patient afterwards was closely followed-up. The pregnancy resulted in twin delivery at 35th gestational week.
Conclusion. Close monitoring in MCBA twin pregnancies is important. The right timing is crucial for better pregnancy outcomes. Also knowledge about the newest available procedures is needed for offering all the treatment possibilities in patients management.

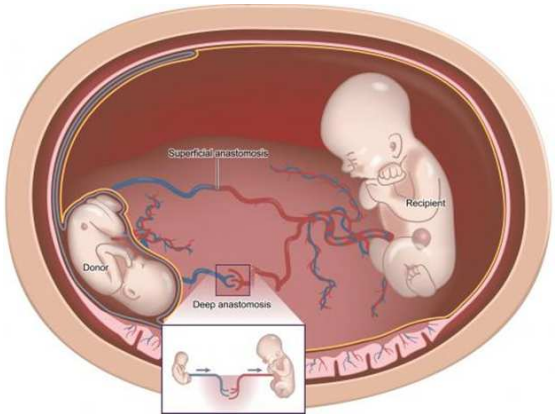
Kopsavilkums
Atslēgas vārdi.*: Dvīņu-dvīņu transfūzijas sindroms, monohoriotiska diamniotiska grūtniecība, MCBA, fetoskopiska lāzera fotokoagulācija, Kvintero klasifikācija*
Ievads: Dvīņu-dvīņu transfūzijas sindroms (DDTS) ir nopietns stāvoklis, kas komplicējas 8-10% monohoriotisku diamniotisku dvīņu grūtniecību gadījumā. DDTS diagnosticēšanai nepieciešams izpildīties 2 kritērijiem: 1) monohoriotiskai diamniotiskai dvīņu grūtniecībai un 2) oligohidroamniona (definēta kā dziļākās vertikālās kabatas lielums < 2cm) vienā amnija maisā un polihidroamnions (definēts kā vertikālās kabatas lielums > 8 cm) otrajā maisā. Kvintero klasifikācijas sistēma ir noderīgs rīks DDTS smaguma aprakstīšanai standartizēti. Multiplas, secīgas ultrasonogrāfiskas izmeklēšanas jāveic MCBA dvīņu grūtniecības gadījumā sākot no 16 gestācijas nedēļas atkārtojot to ik pēc 2 nedēļām līdz dzemdībām. Daudzus gadījumus ar DDTS I pakāpi iespējams atrisināt ar nogaidošu taktiku. Taču advancētas saslimšanas gadījumā (≥III pakāpi) tiek ziņots par perinatālu zaudējumu 70-100% gadījumu, it sevišķi, ja stāvoklis skāris pacienti, kas ir < 26 gestācijas nedēļā. Fetoskopiska lāzerkoagulācija placentas anastamozēm tiek uzskatīta par labāko pieejamo metodi II, III un IV pakāpes DDTS gadījumos, ja grūtniecības progresējusi < 26 gestācijas nedēļām. [Lynn 2013]
Pirmā klīniskā gadījuma apraksts: Grūtniece K ir 37 gadus veca – trešā grūtniecība, divas dzemdības anamnēzē. Pēdējā grūtniecība ar MCBA dvīņiem. Pacientei veikta ultrasonogrāfija 24+4 gestācijas nedēļu vecumā, kur slēdziens: Progresējoša grūtniecība ar MCBA dvīņiem. Fetus 1 (F1) atbilst 21+1 gestācijas vecam auglim, bet fetus 2 (F2) atblst 25+1 gestācijs vecam auglim. F1 diagnosticēta intrauterīna augšanas aizture, F2 – polihidroamnions. DDTS. Pēc konsīlija lēmuma paciente tiek transportēta uz Beļģiju ķirurģiskai ārstēšanai. Beļģijā tiek diagnosticēta 54% augšanas

diskonkordance un tiek lemts par selektīvas smagi cietušā augļa terminācijas nepieciešamību. Tika veikta selektīva augļa terminācija, kas noritēja bez komplikācijām. Paciente tiek pēc tam novērota līdz plānotai ķeizargrieziena operācijai 40. gestācijas nedēļā. Tālāk grūtniecība noritēja bez sarežģījumiem.
Otrā klīniskā gadījuma apraksts: Grūtniece E, kas arī 37 gadus veca. Otrā grūtniecība, bijušas 1 dzemdības. Patreizējā grūtniecība ar MCBA dvīņiem. Grūtniecībai progresējot, tiek veiktas atkārtotas ultrasonogrāfijas, sākot no 17+6 gestācijas nedēļas. Ultrasonogrāfijas slēdziens, kas veikta 20+0 gestācijas nedēļā: F1 polihidroamnions, F2 oligohidroamnions un augšanas diskordancec (28%). Tiek sasaukts konsīlijs, pēc kura tiek pieņemts lēmums par nepieciešamību sūtīt pacienti uz Beļģijas klīniku fetosopiskas lāzerkoagulāscijas placentas anastamozēm veikšanu. Tā brīža diagnoze – DDTS I pakāpe, progresējoša (pēc Kvintero klasifikācijas). Procedūra tika veikta Beļģijas klīnikā dažas dienas vēlāk. Pēc procedūras grūtniecība dēvējama par dihoriotisku monoamnotisku dvīņu grūtniecību – pēc tam paciente tiek novērota. 35 gestācijas nedēļā dvīņu dzemdības.
Secinājumi. Cieša MCBA dvīņu grūtniecības novērošana ir ļoti svarīga. Ir ļoti nozīmīgs pareizs plānojums ultrasonogrāfijas izmeklējumiem, nepieciešamības gadījumā, pieņemot lēmumu par iejaukšanos. Tāpat zināšanas par jaunākajām pieejamajām procedūrām ir svarīga, lai pacientiem varētu piedāvāt jaunākās ārstēšanas metodes.

Introduction

TTTS is the result of an intrauterine blood transfusion from one twin (donor) to another twin (recipient). TTTS only occurs in monozygotic (identical) twins with a monochorionic placenta. [Gussone 2015] Depending on the number, type and direction of the connecting vessels, blood can be transfused disproportionately from one twin (the donor) to the other twin (the recipient). [Gussone 2015] The diagnosis of TTTS requires 2 criteria:

1. the presence of a MCBA (monochoriotic biamniotic) pregnancy;
2. the presence of oligohydramnios (defined as a maximal vertical pocket of <2 cm) in one sac, and of polyhydramnios (a maximal vertical pocket of >8 cm) in the other sac. (Lynn 2013: 3)



Picture 1**. Placental anastamosis division in case of monochoriotic twin pregnancy**

Other causes for polyhydramnios should be excluded as fetal intestinal atresia, or stenosis, difficulty swallowing, neural tube defect, etc. And for oligohydramnios as well - rupture of the membranes, urinary tract atresia, renal agenesis, etc.

Serial sonographic evaluations usually beginning at around 16 weeks of gestation are performed and continuing about every 2 weeks until delivery. Screening for congenital heart disease is warranted in all monochorionic twins, in particular those complicated by TTTS. If left untreated, mortality rate is near 100%.

Quintero classification

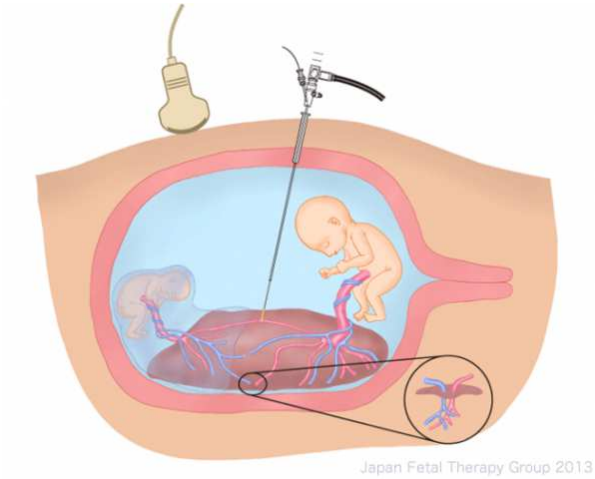
Table 1**. Quintero classification according to ultrasound findings in case of TTTS**

Stage	Ultrasound parameter	Categorical criteria
I	MVP of amniotic fluid	MVP <2 cm in donor sac; MVP >8 cm in recipient sac
II	Fetal bladder	Nonvisualization of fetal bladder in donor twin over 60 min of observation (Figure 2)
III	Umbilical artery, ductus venosus, and umbilical vein Doppler waveforms	Absent or reversed umbilical artery diastolic flow, reversed ductus venosus a-wave flow, pulsatile umbilical vein flow (Figure 3)
IV	Fetal hydrops	Hydrops in one or both twins
V	Absent fetal cardiac activity	Fetal demise in one or both twins

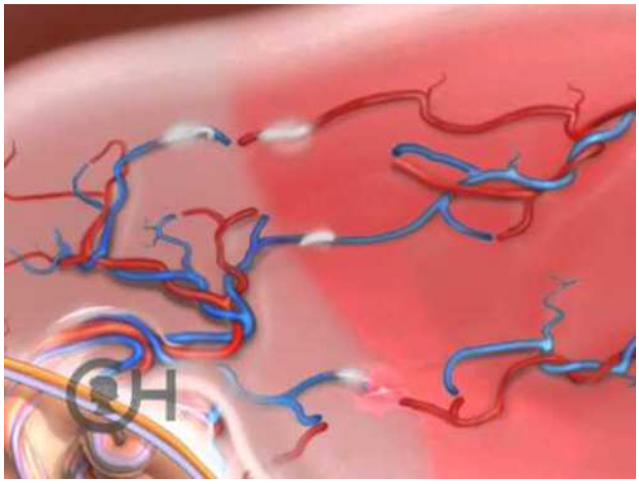
The most common procedure to treat TTTS is reduction amniocentesis. This procedure involves draining the amniotic fluid from around the recipient twin. This procedure may improve circulation in the donor twin especially if the anastomosis are superficial in the placenta and the TTTS is a lower stage. This procedure may need to be performed multiple times during the pregnancy. (Terence 2015)

Fetoscopic laser photocoagulation of chorionic plate vessels is a highly specialized procedure performed in a few centers around the world. This is mostly reserved for more severe cases, especially those that do not respond to amnioreduction. In pregnancies treated with fetoscopic procedures, the overall survival is 75% with 85% having at least 1 fetus survive. The fetal death rate for the donor is higher that the recipient following this procedure. (Terence 2015)

Fetoscopic laser photocoagulation of placental anastamoses is considered to be the best available approach for stages II, III, and IV TTTS in continuing pregnancies at <26 weeks. (Lynn 2013: 3) In the event of early TTTS, fetoscopic laser coagulation is technically feasible before 17 gestational weeks and obstetric and neonatal outcomes are comparable with those in cases of laser treatment performed after 17 weeks. (Lecointre 2014) In total, 34 studies reporting on 3,868 monochorionic twin pregnancies were included. The mean survival of both twins increased from 35 to 65% ($p = 0.012$) and for at least one twin from 70 to 88% ($p = 0.009$) over the past 25 years. Mean gestational age at birth remained stable over the years at 32 weeks gestation. Also, in the research there was significantly improved perinatal survival with the evolution of the laser technique from non-selective to selective, selective sequential and the Solomon technique ($p = 0.010$). (Akkermans 2015) Since the introduction of laser therapy for TTTS more than two decades ago, perinatal survival improved significantly. Improved outcome is probably associated with several factors, including evolution of the laser technique, learning curve effect, better referral and improved early neonatal care. (Akkermans 2015)



Picture 2. **Fetoscopic laser photocoagulation procedure. The coagulator is inserted into the womb under ultrasound control in operating theater and afterwards under visual control the coagulation of placental anastamoses is performed**



Picture 3. **The coagulation of anastamoses during fetoscopic laser photocoagulation procedure**

Timing of delivery depends on multiple factors. The ideal would be for delivery at term; however, evidence of lack of fetal growth or nonreassuring antepartum testing or preterm labor may result in a premature delivery. (Terence 2015)

First case report

A pregnant women K 37 years old – this is her 3rd pregnancy, she has had 2 deliveries before (both C-section because of breech presentation for the first child, with second child repeated C-section). The current pregnancy is MCBA twin pregnancy. The patient was having several ultrasound scans starting from 17th gestational week revealing growth discordance but on an ultrasound which was performed on 24th week of gestation plus 4 days there were significant changes in fetal Doppler noticed. The results of ultrasound can be seen further in the second table.

Table 2. **Results of ultrasound performed on gestational age of 24 weeks plus 4 days**

24 W + 4 days	Fetus 1	Fetus 2
Weight, g	406	811
Week of gestation	21^{+1}	25^{+1}
MVP, cm	3.87	15.55
A. umbilicalis PI	2.13	1.12
Urinary bladder	Seen	Seen

The conclusion according ultrasound: MCBA pregnancy. Fetus 1 is appropriate for gestational age of 24 weeks plus 4 days, fetus 2 – 25 weeks and 1 day. There is intrauterine growth retardation seen. Polyhydramnion of the second fetus. TTTS. On the next day at gestational age of

24 weeks and 5 days the council was organized and decision about patients sending to Leuven Clinics in Belgium for possible laser photocoagulation of placental anastamoses was made. On the same day fetal echocardiography was also performed. The conclusion: fetus 1 without cardiac pathology, but fetus 2 having unspecific secondary changes because of TTTS.

Table 3. **Results of ultrasound performed at gestational age of 24+6 in Leuven Clinic, Belgium**

	F1	F2
Weight, g	377	827
A. umbilicalis PI	3.58	0.89
ACM PSV	1.21	1.71

The patient was admitted in Leuven Clinic at gestational age of 24 weeks and 6 days – ultrasound was performed on gestational age of 25 weeks and following measures got (in the third table). The conclusion: 54% growth discordance. There was an advice for selective fetal termination of severely affected fetus given. The procedure took place on the same day as well another ultrasound after the procedure: fetus 2 – MVP (maximal vertical pocket) of 10 cm, cardiomegaly, congestion in liver, ACM PSV (arteria cerebri media peak systolic velocity) of 30 cm/s, arteria umbilicalis PI (pulsatility index) 0.98, ACM PI (arteria cerebri media pulsatility index) 1.49. Fetus 1 – MVP of 3 cm, asystole. The length of cervix: 41 mm. In the cervix there was hypoechogenic area visualized – polyp in cervix, which has been seen there before – patient's reply, although differential diagnosis of hematoma remains. The patient was discharged from Leuven Clinics in Belgium on gestational age of 25 weeks and 1 day. Afterwards the fetus is developing according to pregnancy. There was MRI for fetal head performed – no pathology revealed. The last ultrasound check-up took place on gestational age of 37 weeks and 6 days, when fetal weight was 3222 g, the size of fetus was as for 38 weeks of gestational age and the MVP was 8,65 cm and a date for planned C-section was set for gestational age of 39 weeks and 3 days.

Second case report

Gravida E 37 years old, this was her 2nd pregnancy, she has had 1 delivery. She was pregnant with MCBA twins. When performing ultrasound in frames of 2nd trimester screening program, the gestational age was 17 weeks and 6 days, the conclusion was – MCBA twin pregnancy. The first fetus was as for 17 gestational weeks old, the weight was 187 g, arteria umbilicalis PI was 1.33, MVP of 6.8 cm. The second fetus was as 17 weeks of gestational age old, the weight was 187 g, arteria umbilicalis PI 1.25 and MVP of 6.01 cm.

On repeated ultrasound at gestational age of 19 weeks the MVP of first fetus was 6.01 cm, but MVP of second fetus – 2.34 cm, measurements using Doppler were in normal range, urinary bladder was visualized. At gestational age of 19 weeks and 3 days fetal echocardiography was

performed and conclusion about no pathologies was made, but there was a suggestion to perform an echocardiography after the birth given.

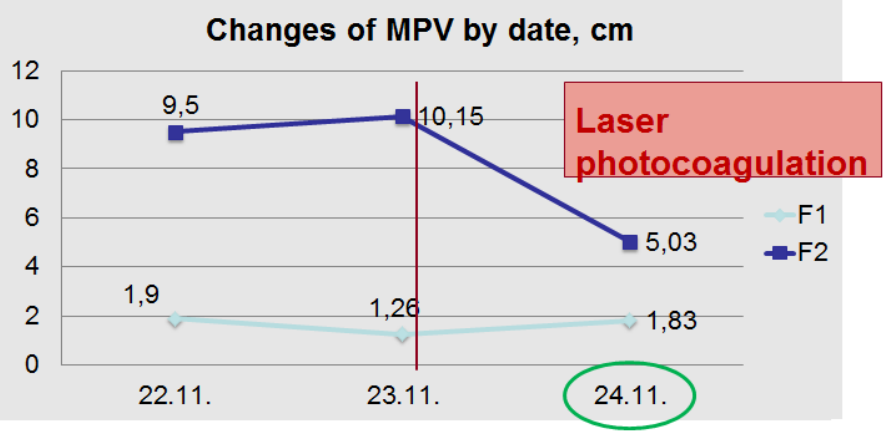
On the next ultrasound at gestational age of 19 weeks and 5 days the MVP of first fetus was 8.27 cm, but MVP of second fetus was 3.21 cm, measurements using Doppler were in normal range, urinary bladder visualized.

On the next ultrasound at gestational age of 20 weeks and 2 days the MVP of first fetus was 8.64 cm, for the second fetus could not been obtained. The weight for fetus 1 was 289 g, but for second fetus – 209 g (and it makes 28% difference). There was council organized and decision about possible treatment in Leuven Clinics of Belgium made. The patient was informed and agreed for that.

Table 4. **The results of ultrasound starting from gestational age of 17+6 until gestational age of 20+4**

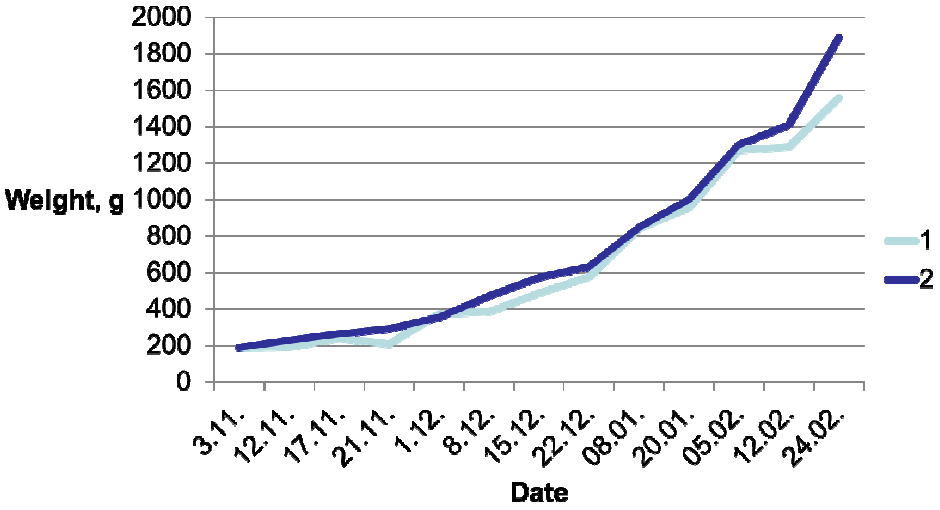
	3.11.		12.11.		17.11.		21.11.	
	17^{+6}		19^{+1}		20^{+0}		20^{+4}	
	F1	F2	F1	F2	F1	F2	F1	F2
GW according weight	17^{+0}	17^{+0}	17^{+2}	18^{+1}	18^{+2}	18^{+6}	17+5	19+2
Weight, g	187	187	192	229	238	263	209	289
MPV, cm	4	6.8	2.34	6.01	3.81	8.27		8.64
A. umbilicalis PI	1.25	1.33	1.54	1.41	1.54	1.77	1.51	1.7
Urinary bladder	"+"	"+"	"+"	"+"	"+"	"+"	"+"	"+"

At gestational age of 20 weeks and 5 days the patient was admitted in the Leuven Clinics and ultrasound performed there revealed MVP of first fetus 9.5 cm, for second fetus 1.9 cm. Ultrasound at gestational age of 20 weeks and 6 days – MVP of first fetus was 10.15 cm and for second fetus of 1.26 cm. The conclusion was MCBA twin pregnancy. TTTS, I stage by Quintero classification but progressing. It was an indication for laser photocoagulation therapy of placental anastamoses. The procedure was performed on the same day. Follow-up ultrasound was performed one day after the photocoagulation at gestational age of 21 weeks of gestation, revealing MVP of first fetus – 5.03 cm, of the second fetus – 1.83 cm. The Doppler measures of the second fetus were in normal ranges but of the first fetus there was reverse flow in ductus venosus (which is a common appearance after this procedure). The length of cervix was 41 mm. The patient was discharged on the same day.



Picture 4**. Mean vertical pocket (MVP) changes for both fetuses in Leuven Clinic, Belgium before and after performing laser photocoagulation for placental anastamoses**

During the next month patient was having ultrasound evaluation once per week – all measurements were in normal ranges.



Picture 5. **Weight gain for both fetuses after the procedure during further pregnancy according to ultrasound measurements**

Conclusion

There are two comparative case reports with the same pathology only different management, when in the first case the diagnosis was delayed and that is why the chosen treatment modality was even more severe, but in the second case, using rather new technique, it resulted in successful pregnancy resolution. These two cases show how important is diagnostics and right timing as well the knowledge about newest available treatment methods and quick decision making when dealing with TTTS. As recommended there should be several sonographies performed starting from gestational age of 16 weeks including Doppler measurements.

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DIPHTHERIA VACCINATION COVERAGE AMONG ADULTS IN GENERAL PRACTICE

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Abstract

Diphtheria vaccination coverage among adults in general practice

Key words: *Diphtheria vaccination coverage (DVC), adult vaccination, revaccination, vaccination failure*

Introduction: Diphtheria is a vaccine preventable infectious disease with serious potential consequences up to disability and death. DVC among adults in Latvia (56%; 2015) doesn't reach recommended level – 80%.

Aim: To analyze DVC among adults in General Practice (GP) and identify reasons for avoiding vaccination.

Materials and methods: The longitudinal research was done by analyzing medical documentation of 620 adult patients in a GP practice. Patients with no revaccination filled in a questionnaire, containing questions regarding participant's gender, age, education level and reasons for avoiding vaccination. Data was statistically processed in SPSS Statistics 22.0.

Results: 44% (n=271) haven't received diphtheria revaccination. The results of questionnaire were as follows: respondents in age group from 25 to 40 (81.1%; p = 0.001) and people with high school education level (89.7%; p = 0.013) received vaccines during their childhood more frequently than people older than 65 years (69.2%; p = 0,001) and elementary school level educated participants(54,5%; p = 0.013).The main reasons for vaccination avoidance among elementary education level responders were high price (33.3%; p=0,003) and unavailability of vaccination facilities among high school education responders(47.6%; p=0,003). People with professional education level claimed to have receive too little information regarding effectiveness of vaccination procedure (57.9%; p=0,003). Respondents in age group from 25 to 40 (69.8%; p=0,034) and people who do not have children of their own (73.2%; p = 0.01) – were unfamiliar with manifestation of diphtheria infection. The respondents with secondary professional school education level had no information regarding free availability of diphtheria vaccine (61.9%; p=0,01). Male patients were more uninformed regarding revaccination possibilities than female patients (65.2%; p = 0.024). The responders in age group from 25 to 40 years lacked knowledge regarding tetanus transmission route (52.8%; p = 0,008), but it was well known fact to the respondents with children (69.5%; p = 0.037).

Conclusion: DVC among adults in GP practice doesn't reach the recommended population protective level. Communication strategies focused on education of patients may result in increase of vaccination coverage.

Kopsavilkums

Pieaugušo vakcinācijas aptvere pret difteriju ģimenes ārsta praksē

Atslēgvārdi: *difterijas vakcinācijas aptvere (DVA), pieaugušo vakcinācija, revakcinācija, nevakcinēšanās iemesli*

Ievads: Difterija ir vakcīnatkarīga slimība, kam var būt smagas sekas līdz pat nespējai un nāvei. 2015.gadā DVA ir 56%, kas nesasniedz rekomendēto līmeni – 80%.

Mērķis: Analizēt DVA pieaugušajiem ģimenes ārsta praksē un identificēt cēloņus, kāpēc vakcinācija netiek veikta.

Materiāli un metodes: Analizējot 620 pacientu medicīnisko dokumentāciju ģimenes ārsta praksē, tika veikts šķērsgriezuma pētījums. Pacientiem, kuriem nebija veikta revakcinācija, tika izsniegta anketa, kurā bija jautājumi par pacienta dzimumu, vecumu, izglītības līmeni un nevakcinēšanās iemesliem. Dati tika statistiski apstrādāti, izmantojot SPSS Statistics 22.0.

Rezultāti: 44% (n=271) nav saņēmuši revakcināciju pret difteriju. Anketēšanas rezultāti: respondenti vecuma grupā no 25 līdz 40 gadiem (81.1%; p = 0.001) un respondenti ar augstāko izglītību (89.7%; p = 0.013) ir biežāk saņēmuši vakcīnas bērnībā nekā tie, kuri ir vecāki par 65 gadiem (69.2%; p = 0,001) un ar pamatskolas izglītību (54,5%; p = 0.013). Nevakcinēšanās iemesli respondentiem ar pamatskolas izglītību visbiežāk bija augsta cena (33.3%; p=0,003), bet ar vidusskolas izglītību – grūti sasniedzami vakcinācijas punkti (47.6%; p=0,003). Savukārt pacienti ar profesionālo izglītību atzīmēja, ka ir saņēmuši nepietiekamu informāciju par vakcinācijas efektivitāti (57.9%; p=0,003). Respondenti vecuma grupā no 25 līdz 40 gadiem (69.8%; p=0,034) un tie, kuriem nav bērnu (73.2%; p = 0.01) bija vismazāk zinoši par difterijas izpausmēm. Vīriešu dzimtas respondent bija mazāk informēti par revakcinācijas iespējām, salīdzinot ar sievietēm (65.2%; p = 0.024). Respondenti vecuma grupā no 25 līdz 40 gadiem bija vismazāk informēti par stingumkrampju ierosinātāju pārneses (52.8%; p = 0,008), bet tas bija labi zināms respondentiem, kuriem ir bērni (69.5%; p = 0.037).

Secinājumi: DVA pieaugušajiem ģimenes ārsta praksē nesasniedz rekomendējamo līmeni. Nepieciešama pacientu izglītošana, lai sasniegtu lielāku DVA.

Introduction

Immunization prevents illness, disability and death from vaccine-preventable diseases including cervical cancer, diphtheria, hepatitis B, measles, mumps, pertussis (whooping cough), pneumonia, polio, rotavirus diarrhoea, rubella and tetanus.

Diphtheria once was a major cause of illness and death among children. Starting in the 1920s, diphtheria rates dropped quickly with the widespread use of vaccines (cdc.gov).

The recommended level of diphtheria vaccination coverage (DVC) among adults is 80% to protect population from disease. Global coverage with diphtheria-tetanus vaccine is estimated at 86% (WHO). Global vaccination coverage is generally holding steady (WHO). DVC among adults in Latvia doesn't reach the recommended level and is estimated at 56% (2015) with tendency to decrease. (Imunizācijas valsts padomes darba sēdes protokols 2016. gada 8. novembrī).

Many factors contribute to low adult vaccination rates, including limited public awareness about adult vaccinations, misinformation about vaccines, lack of vaccine requirements for adults, gaps in incorporation of routine vaccine needs assessment and recommendations for adults during health care visits, and acute medical care taking precedence over preventive services (Williams 2016).

It is important to highlight that since 2006 there have been 133 cases of diphtheria registered in Latvia. The lethality rate is 7.8% (number of lethal cases: 13). Furthermore none of them had received diphtheria vaccination. The highest incidence is among children and adults >60 years old. (Imunizācijas valsts padomes darba sēdes protokols 2016. gada 8. novembrī).

As mentioned diphtheria is a vaccine-preventable infectious disease. Diphtheria usually involves the respiratory system and more commonly the tonsillopharyngeal area. Symptoms start progressively and include: sore throat, weakness, dysphagia, nausea, headache, pain (lesions of cutaneous diphtheria are often, but not always, painful), shortness of breath, weakness of pharyngeal muscles, difficulty swallowing. After progression of the infection, patients develop systemic toxicity (Bruce M Lo 2015).

Signs include:

- Gray membrane covering pharynx and dislodging the membrane usually causes bleeding;
- Fever (usually mild);
- Neck edema;
- Cutaneous diphtheria is often forming a deep 'crater-like' ulcer;
- Tachycardia, pulmonary congestion, and signs of heart failure can develop if diphtheria toxin enters the circulation and affects the heart;
- A demyelinating peripheral and cranial sensory/motor neuropathy may occur, leading to pharyngeal and even diaphragmatic paralysis (Foster et al 2011).

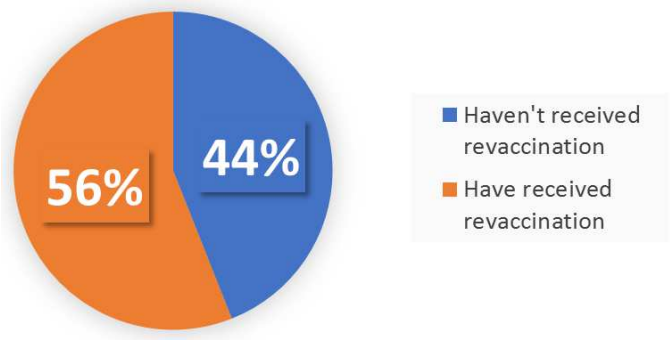
It is important to diagnose diphtheria early because if diagnosis is delayed diphtheria can lead to serious consequences up to disability and death (Foster et al 2011).

Materials and methods

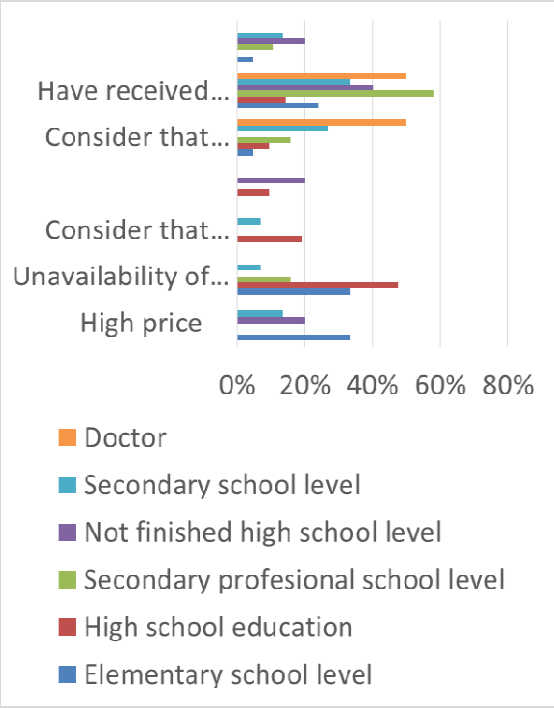
The longitudinal research was done by analyzing medical documentation of 620 adult patients in a GP practice. Patients with no revaccination filled in a questionnaire, containing questions regarding participant's gender, age, education level and reasons for avoiding vaccination. Data was statistically processed in SPSS Statistics 22.0.

Results

44% (n=271) of adult patients haven't received diphtheria revaccination.

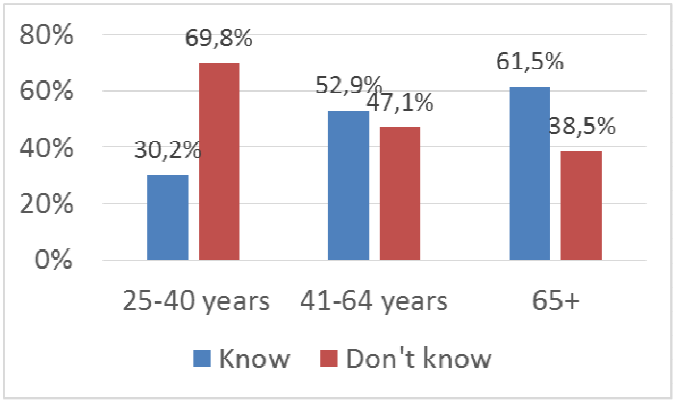


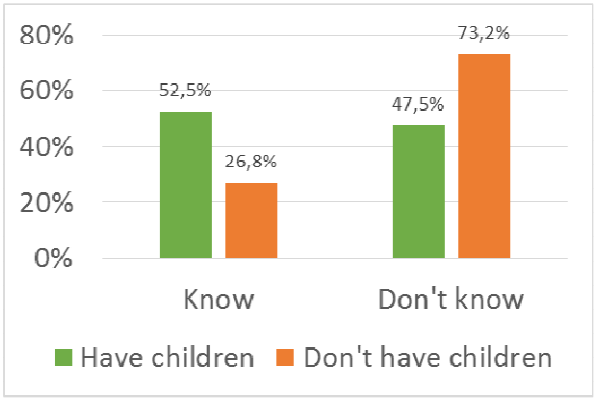
The results of questionnaire were as follows: respondents in age group of 25 to 40 (81.1%; p = 0.001) and people with high school education level (89.7%; p = 0.013) received vaccines during their childhood more frequently than people older than 65 years (69.2%; p = 0,001) and elementary school level educated participants(54,5%; p = 0.013).



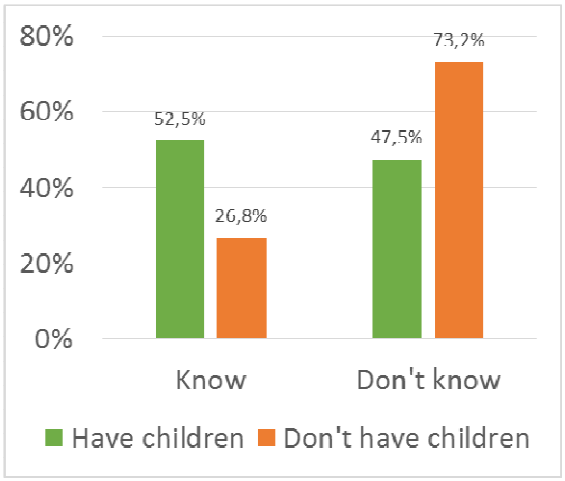
The main reasons for vaccination avoidance among elementary education level responders were high price (33.3%; p=0,003) and unavailability of vaccination facilities among high school education responders(47.6%; p=0,003). People with professional education level claimed to have receive too little information regarding effectiveness of vaccination procedure (57.9%; p=0,003).

Respondents in age group from 25 to 40 (69.8%; p=0,034) and people who do not have children of their own (73.2%; p = 0.01) – were unfamiliar with manifestation of diphtheria infection.

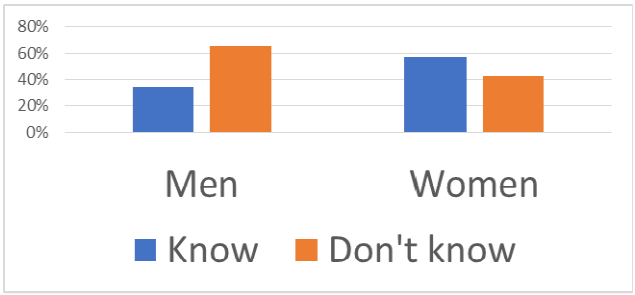




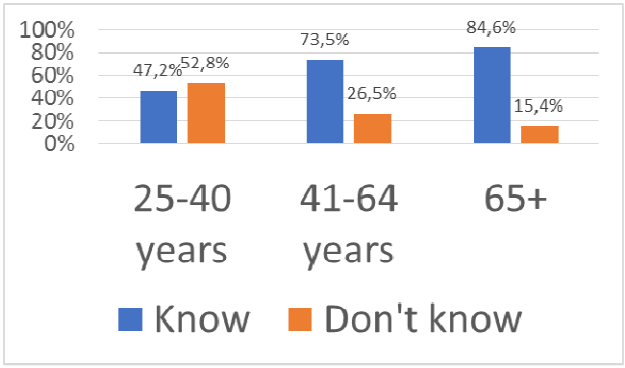
The respondents with secondary professional school education level had no information regarding free availability of diphtheria vaccine (61.9%; p=0,01).

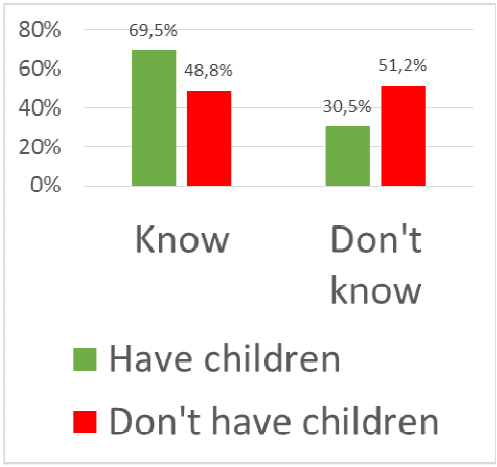


Male patients were more uninformed regarding revaccination possibilities than female patients (65.2%; p = 0.024).



The responders in age group from 25 to 40 years lacked knowledge regarding tetanus transmission route (52.8%; p = 0,008), but it was well known fact to the respondents with children (69.5%; p = 0.037).





Discussion

To control and prevent diphtheria epidemics, it is necessary to achieve and maintain high vaccination coverage with three or more doses of diphtheria toxoid among adults and children (Bisgard 2000). It is important to understand disease management too. In our study the less informed responders was in age group from 25 to 40 years, responders without children and men group. Thus, general practitioners need to draw special attention to educate these persons about diphtheria and immunization.

The actual problem is also vaccination centres availability. The procedure of vaccination is not time consuming and do not require a lot of space, therefore, for example, mobile vaccination points would be considered (cdc.gov).

The introduction of immunization educational materials in general practice would be large support to healthcare providers to increase patients' awareness about disease management and immunization (Foster 2011).

Conclusion

- DVC among adults in GP practice doesn't reach the recommended population protective level.
- Communication strategies focused on education of patients may result in increase of vaccination coverage.
- Respondents in age group from 25 to 40 and people who do not have children of their own were unfamiliar with manifestation of diphtheria infection and tetanus transmission route.
- Most common reasons for avoiding vaccination were unavailability of vaccination facilities, consideration that vaccine is not effective and too little information available regarding effectiveness of vaccination.

Acknowledgement

We would like to express our gratitude to our supervisor Professor Jānis Zaļkalns for research support.

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DIFFERENTIAL DIAGNOSIS IN PATIENT WITH EARLY ONSET DEMENTIA AND EXTRAPYRAMIDAL SYSTEM DISORDERS: A CASE REPORT

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Abstract

Differential diagnosis in patient with early onset dementia and extrapyramidal system disorders: a case report

Key words: *neurodegenerative disease, dementia, Alzheimer's disease, Lewy Body disease, magnetic resonance*

Introduction: Dementia is a progressive, chronic, and incurable neurodegenerative disorder, with a prevalence that increases with age (Kapo *et al*. 2011).

Case report presentation: 34 years old man has been suffering several years from sleep disorder of unknown origin, later movement disorders, uncontrolled arms, legs jerking, which was followed by memory impairment, which in one-year period rapidly progressed. Magnetic resonance imaging of brain points to neurodegenerative disorder and Alzheimer disease (AD) is quite possible. Laboratory examination is not specific to AD and, thus, the diagnosis of AD couldn't be based on biomarkers. The patient's clinical presentation could comply with Dementia with Lewy body and Parkinson's disease dementia but with a high probability any of these diagnoses cannot be held. Laboratory testing ruled out Creutzfeldt-Jakob disease, neuromuscular disease and autoimmune encephalitis. Huntington's chorea and Wilson's disease were excluded through genetic testing. The diagnosis of early sporadic Alzheimer's dementia had been established according to NINDCA-ARDA criteria.

Conclusions: In the presence of dementia, clinical overlap poses significant challenges in differential diagnosis and, brain biopsy is essential to obtain a definitive diagnosis.

Kopsavilkums

Diferenciāla diagnoze pacientam ar agrīnu demenci un ekstrapiramidālas sistēmas traucējumiem: klīniskais gadījums

Atslēgvārdi: *neirodeģeneratīva slimība, demence, Alcheimera slimība, Levi ķermenīšu slimība, magnētiska rezonanse*

Ievads: Demence ir progresīva, hroniska un neārstējama neirodeģeneratīva slimība, tās sastopamība palielinās ar vecumu (Kapo *et al*. 2011).

Gadījuma apraksts: 34 gadus vecs vīrietis vairākus gadus cieta no miega traucējiem bez zināma iemesla, vēlāk sākušies kustību traucējumi, nekontrolēta roku, kāju raustīšanās, īsi pēc tam parādījās atmiņas traucējumi, kuri gada laikā strauji progresējuši. Magnētiska rezonanse raksturīga neirodeģeneratīvai saslimšanai, radioloģiskā aina varētu atbilst Alcheimera slimībai. Alcheimera slimībai specifiskie laboratoro izmeklējumu izmaiņas netika konstatētas un līdz ar to Alcheimera slimības diagnoze nevar balstīties uz biomarķeriem. Pacienta klīniskā aina atbilst Levi ķermenīšu demencei un Parkinsona slimības demencei, bet ar lielu varbūtību nevienu no šim diagnozēm nevar uzlikt. Ar laboratoriskām analīzēm tika izslēgta Kreicfelda-Jakoba slimība, neiromuskulārā saslimšana, autoimūns encefalīts. Veicot ģēnētiskos testus, tika izslēgta Hantingtona horeja un Vilsona slimība. Balstoties uz NINDCA-ARDA kritērijiem, tika uzstādīta agrīna, sporadiska Alcheimera demence.

Secinājumi: Demences klīniskās ainas pārklāšanās rada ievērojamas problēmas diferenciāldiagnostikā, un smadzeņu biopsija ir būtiska, lai uzzinātu galīgo diagnozi.

Introduction

Dementia is a progressive, chronic, and incurable neurodegenerative disorder (Kapo et al. 2011). Neurodegenerative diseases are characterized by the progressive loss of neurons in the brain or spinal cord. Acute neurodegeneration may result from stroke or trauma, cause a localized loss of neurons at the site of injury. Processes of chronic neurodegeneration may develop during a long period and come out with the loss of a particular neuronal subtype or generalized loss of neuronal populations (Lunn et al. 2011).

Neurodegenerative disease can be classified according to underlying pathological process: synucleinopathies, tauopathies, cerebral amyloidosis spinocerebellar ataxia, Huntington's disease, hereditary spastic paraplegia, amyotrophic lateral sclerosis, clinically unclassifiable parkinsonism, Unverricht-Lundborg disease, prion diseases. Synucleinopathies are Parkinson's disease, Lewy Body disease, multiple systemic atrophy. Tauopathies includes: Alzheimer's disease, chronic traumatic encephalopathy, corticobasal degeneration, frontotemporal lobar degeneration, Pick disease, progressive supranuclear palsy. Cerebral amyloidosis: cerebral amyloid angiopathy, transthyretine-associated cerebral amyloidosis, neuronal intranuclear hyaline inclusion disease (Gaillard et al.).

Dementia is characterized by the decline in memory and gradual loss of patient's language, behavior, and executive functions (Kapo et al. 2011). Dementia may be classified as either primary degenerative dementia or secondary dementia. Primary degenerative dementia includes cortical dementias such as Alzheimer's disease (AD), frontotemporal dementia (FTD) and subcortical dementias such as Huntington's chorea, Parkinson's disease, progressive supranuclear palsy. Secondary dementia category includes cerebrovascular disease, drug or toxin induced, metabolic or electrolyte disturbance, endocrinopathies, encephalitis, neurosyphilis, HIV infection, HSV-1 infection, nutritional, head trauma, mass effect, hydrocephalus, psychiatric and others (Smith et al.).

Dementia incidence increases exponentially with age from 1% in the group age 60-65 years, to approximately 40% in the group aged 85 years (Kapo et al. 2011). It is a very common disease, the number of people living with dementia worldwide in 2015 was 46.8 million, and will likely reach 74.7 million in 2030 and 131.5 million in 2050 (World Alzheimer's report 2015).

The most common cause of dementia in an aging population is AD (50-70%), followed by vascular disease (20-30%), frontotemporal dementia (5-10%) and Lewy Body disease (5%) (Johnstone 2016) other common causes include Parkinson's disease and Huntington's disease. FTD is less well-known cause, but it with AD actually represents the most common cause of dementia in persons younger than age 65 (Miller et al. 2013).

Dementia treatment depends on its cause. Progressive dementia, such as AD, is incurable, there is no treatment that stops its progression. However, there is medical treatment that may temporarily improve symptoms in cases of AD or other cases of dementia. For instance, medication for memory loss (cholinesterase inhibitors, NMDA receptor antagonist), medication for behavior and personality changes (antidepressants, antipsychotic). FTD like AD does not have specific treatment. There are medications that can reduce agitation, irritability and/or depression and benefit medication is SSRIs. It is very important to educate family about the disease and visit caregiver support groups can be helpful (Peterson et al. 2016).

Case report description

34 years old man has been suffering several years from sleep disorder of unknown origin, later movement disorders, uncontrolled arms, legs jerking, which was followed by memory impairment, which in one-year period rapidly progressed. Patient was admitted to Pauls Stradins Clinical University Hospital with objectively expressed cognitive defects (MOCA score -12 points). A rigid gait, *marche à petits pas*, myoclonic jerks, ataxia in both legs and positive Romberg's sign was also of notice. Magnetic resonance imaging of the brain revealed diffuse cortical and hippocampal atrophy that points to neurodegenerative disorder and AD is quite possible taking into consideration the predominant temporal lobe atrophy (Figure 1 and 2).

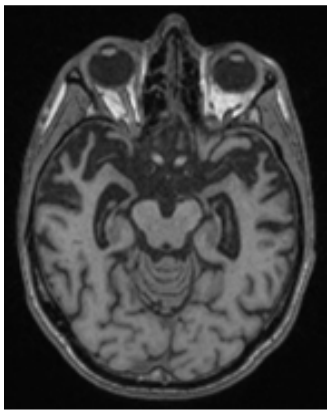

Figure 1. **Cortical and hippocampal atrophy T1-weighted image**

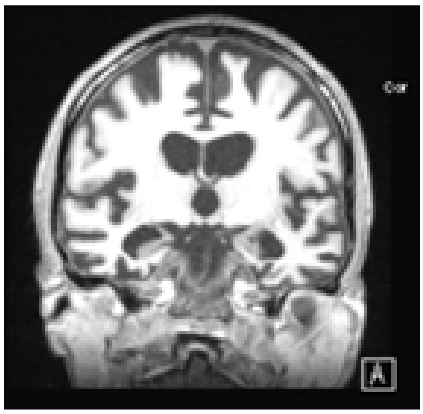

Figure 2. **Cortical and hippocampal atrophy**

AD specific laboratory examination showed a slightly reduced B42 amyloid level, but the Tau-protein was within normal range (Table 1), which generally is not specific to AD and, thus, the diagnosis of AD couldn't be based on biomarkers.

Table 1. **Laboratory test**

Examination	Result	Normal value
T-tau	207 pg/ml	(<296.50pg/ml)
P-tau 181p	<20 pg/ml	(<56.50 pg/ml)
Aβ 1-42	456 pg/ml	(>538.50 pg/ml)

The patient's clinical presentation could comply with Dementia with Lewy body and Parkinson's disease dementia which causes the patient memory impairment, executive function impairment, parkinsonism (rigid gait, bradykinesia), depression, anxiety and apathy, but it is not enough for with a high probability any of these diagnoses cannot be held. Patient did not show any improvement from anti-parkinsonian therapy and L-dopa test was negative.

Huntington's chorea and Wilson's disease were excluded through genetic testing. Laboratory testing also ruled out Creutzfeldt-Jakob disease, neuromuscular disease, autoimmune encephalitis, syphilis and HIV infection (Table 2). Cerebrospinal fluid was within normal range.

Table 2. **Laboratory test**

Examination	Result
14-3-3 protein	Negative
VGCCs	Negative
NMDA receptor antibodies	Negative
Syphilis TP IgM, IgG	Negative
HIV1/2	Negative
HIV 1 Antigen	Negative

Alzheimer's disease was diagnosed according to NINDCA-ARDA criteria (McKhann et al. 2011) − the patient correspond to all criteria: interfere with the ability to function at work or at usual activities; represents a decline from previous levels of functioning and performing; condition are not explained by delirium or major psychiatric disorder; cognitive impairment is detected and diagnosed through a combination of history-taking from the patient and a knowledgeable informant as well as objective cognitive assessment; has the cognitive or behavioral impairment (impaired ability to acquire and remember new information; impaired reasoning and handling of complex tasks, poor judgment; changes in personality, behavior, or comportment − impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy).

Probable AD dementia according to McKhann et al. (2011) is diagnosed when disease has insidious onset, symptoms have a gradual onset over months to years, not sudden over hours or days, clear-cut history of worsening of cognition by report or observation, should be amnestic presentation and patient has impairment in learning and recall of recently learned information, or should be nonamnestic presentation, patient has executive dysfunction. Should be excluded substantial concomitant cerebrovascular disease, core features of Dementia with Lewy bodies other than dementia itself, prominent features of behavioral variant frontotemporal dementia, prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia, evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity (McKhann et al. 2011). As described patient corresponds to these criteria and after the council, the diagnosis of early sporadic Alzheimer's dementia had been established according to NINDCA-ARDA criteria. Myoclonus diminished significantly with Clonazepam. He is clinically observed.

Discussion

This research shows the difficulties of diagnosis definitive disease in patient with early onset dementia, because patient symptoms have clinical overlap of many others disease symptoms and laboratory findings does not fit the disease that clinically is more possible.

Zhu *et al.* writes that early-onset Alzheimer's disease (EOAD), with onset of symptoms before 65 years of age, is rare and generally accepted that EOAD accounts for 1% to 2% of AD cases. While Cacace *et al.* writes that late onset dementia (LOAD) mostly represent with typical memory phenotype, but atypical presentation is more frequently reported in EOAD patients. Atypical clinical presentation consists of visual dysfunction, apraxia, dyscalculia, fluent and non-fluent aphasia, executive dysfunction. In this case patient has apraxia and executive dysfunction.

Cacace *et al.* writes that between 35% to 60% of EOAD patients have at least one affected first-degree relative and by 10% to 15% of those familial EOAD patients, the mode of inheritance is autosomal dominant transmission. Bird has described that most individuals with early onset familial Alzheimer's disease (EOFAD) generally have one parent diagnosed with the disease or a second-degree relative (e.g., an uncle, aunt, and/or grandparent) who has or had EOFAD. It affects people younger than age 65 and often onset age of 55 years. In this case nobody in patient family has not dementia, therefore patient have early sporadic Alzheimer's dementia not early onset familial Alzheimer's disease.

Major AD biomarkers according to McKhann *et al.* may be divided into two classes based on the biology which they measure. The first, concentration of amyloid-beta (Aβ) protein in cerebrospinal fluid (CSF) is low because of it deposition in brain. Anoop *et.al* has described that the amount of total Aβ in CSF is not well correlated with AD. Many studies have demonstrated a decrease of CSF Aβ42, however, in few studies was found unchanged or increased CSF Aβ42 in AD. In our case patient has slightly decreased Aβ42. McKhann *et al.* writes that the second category relate to biomarkers of downstream neuronal degeneration or injury, which elevated CSF tau protein, both total tau (t-tau) and phosphorylated tau (p-tau) and decreased ^{18}fluorodeoxyglucose (FDG) uptake on positron emission tomography in temporo-parietal cortex. Anoop *et al.* in the researches described that, that tau protein can present in normal individual CSF, but only in low concentration. T-tau is very sensitive biomarker for detecting AD, but it has limited ability to discriminate AD from other forms of dementia because t-tau also increased in CSF of others form of dementia including vascular dementia and FTD. P-tau is more sensitive and specific than t-tau and Aβ42 in discrimination AD from normal aging and other dementia. But patient tau-protein was within normal range.

In this case patient has specific clinical manifestation and radiological image corresponds to AD guideline criteria that has described by McKhann *et al.*: disproportionate atrophy on structural

magnetic resonance imaging in medial, basal, and lateral temporal lobe, as well as medial parietal cortex.

Patient has hippocampal atrophy, and Ho *et al.* writes that it is typical to AD but in Lewy body disease, the hippocampus remain normal in size and it is helping to distinguish these diseases.

Conclusion

In this case, patient should be followed-up. In the presence of dementia, clinical overlap poses significant challenges in differential diagnosis and, study the patient clinical, laboratory and radiological examination in detail is essential to obtain a definitive diagnosis.

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SMALL BOWEL BLEEDING - RADIOLOGICAL FEATURES, ENDOVASCULAR EMBOLIZATION EFFICIENCY AND EARLY COMPLICATIONS

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Abstract

Small bowel bleeding - radiological features, endovascular embolization efficiency and early complications

Key words: *Bleeding, angiography, endoscopy, interventional radiology, embolization*

Aim: To evaluate the most common causes of small intestine bleeding in patients who underwent the procedure of visceral angiography in the Department of Interventional Radiology, Rīga East University Hospital, compare endoscopic and radiological findings, to assess treatment and early complications after endovascular embolization.

Materials and methods: Retrospective study included evaluation of medical history of patients with small bowel bleeding who underwent angiographic examination in three-year period between January 2014 and December 2016. Angiographic, endoscopic and radiological findings were evaluated and compared. Data analysed by SPSS, Microsoft Office Excel.

Results: A total of 32 patients were included. 59,4 % men (n=19) and 40,6% women (n=13). The age of patients ranged from 33 to 91 years with mean age 65,9. The most common site of haemorrhage was duodenum, in 75% (n=24) of cases, followed by jejunum in 15,6% (n=5) and ileum 6,3% (n=2). In one case (3,1%) precise source of bleeding hasn't been diagnosed after endoscopic, radiological and angiographic evaluation.

In majority of cases bleeding occurred because of ulcers (in 62,5%), all of them found in duodenum. In 12,5% AVM were diagnosed (n=4). Dieulafoy lesion was the source of bleeding in 6,3% (n=2). Postoperative bleeding occured in 6,3% (n=2). Tumor found in 1 case (3,1%). One case of diffuse angiopathy and coagulopathy in patient with lymphoma was found during the study. In two cases the exact cause of bleeding has not been documented.

In 84% of cases the endoscopic and angiographic findings were similar: detected presence of bleeding and it's location. In other 16% of cases the results of endoscopy were different from angiography. Endoscopy showed negative results in 22.6% of all cases, but more often when bleeding was located in jejunum (66%) and ileum (33%), but all of duodenum lesions were seen during endoscopy. Angiography was non-informative in 2 patients (6.3%)

Conclusions: Recognizing small bowel bleeding remains a diagnostic challenge, especially if it is present in distal parts of intestine. Most common source of bleeding were duodenum ulcers, which were diagnosed by endoscopy. But it is less useful in visualising processes in ileum and jejunum. Angiography in these cases is more useful for diagnosis. Endovascular embolization is relatively safe and effective treatment method. Vascular pathology is relatively frequent cause of mid-gastrointestinal bleeding.

Kopsavilkums

Tievo zarnu asiņošana – radioloģiskā aina, endovaskulārās embolizācijas efektivitāte un agrīnas komplikācijas

Atslēgvārdi: *Asiņošana, angiogrāfija, endoskopija, invazīva radioloģija, embolizācija*

Darba mērķi: Noskaidrot galvenos tievo zarnu asiņošanas iemeslus pacientiem, kam veikta viscerālā angiogrāfija RAKUS Invazīvas radioloģijas nodaļā. Salīdzināt radiolololoģisko, angiogrāfisko un endoskopisko atradni. Izvērtēt pielietoto terapiju un tās efektivitāti, agrīnas komplikācijas pēc endovaskulārās embolizācijas.

Materiāli un metodes: Retrospektīvs pētījums, kas balstās uz pacientu medicīniskās dokumentācijas analīzi, kam tika veikta viscerālā angiogrāfija sakarā ar tievo zarnu asiņošanu Rīgas Austrumu klīniskās universitātes slimnīcā Invazīvas radioloģijas nodaļā. Tika analizēti un salīdzināti angiogrāfijas, endoskopijas un radioloģisko izmeklējumu rezultāti. Izmantotas SPSS, Microsoft Office Excel.

Rezultāti: Pētījumā analizēti 32 pacientu dati. 59,4 % vīrieši (n=19) un 40,6% sievietes (n=13). Pacienti bija vecumā no 33 līdz 91, vidējais vecums 65,9 gadi. Biežāka asinošanas lokalizācija -divpadsmitpirkstu zarna - 75% gadījumu (n=24). *Jejunum* asiņošanu novēroja 15,6% gadījumu (n=5), *ileum* - 6,3% (n=2). Vienā gadījumā (3,1%) precīza asiņošanas vieta nav noteikta pēc endoskopiskās, radioloģiskās un angiogrāfiskās izmeklēšanas. Biežākais asiņošanas iemesls ir čūlas (62,5%), visas lokalizējas *duodenum.* 12,5% gadījumu tika diagnosticētas AVM (n=4). *Dieulafoy* bojājums - 6,3% (n=2). Pēcoperācijas asiņošana diagnosticēta 6,3% (n=2). Vienā gadījuma atrasts audzējs (3,1%). Vienam pacientam konstatēta difūza angiopātija un koagulopātija sakarā ar limfomu. Divos gadījumos asiņošanas precīzs iemesls netika dokumentēts. 84% gadījumu endoskopiskā atradne neatšķirās no angiogrāfiskās un norādīja uz asiņošanas esamību un tās lokalizāciju. Pārējos 16% gadījumu endoskopijas rezultāti atšķirās no angiogrāfijas datiem.

Endoskopijas negatīvi rezultāti tika iegūti 22.6%, visbiežāk pie *jejunum* (66%) un *ileum* (33%) lokalizētas asiņošanas. Visus *duodenum* bojājumus redzēja endoskopiski. Angiogrāfija bija neinformatīva divos gadījumos (6,3%).
Secinājumi: Tievo zarnu asiņošana saistīta ar diagnostikas grūtībām, īpaši ja asiņo distālās zarnas daļas. Biežākais asiņošanas avots, divpadsmitpirkstu zarnas čūlas, diagnosticējamas endoskopiski. Bet šī metode ir mazāk informatīva pie *ileum* un *jejunum* bojājumiem. Angiogrāfija šajos gadījumos ir vairāk noderīga. Endovaskulārā embolizācija ir relatīvi droša un efektīva ārstēšanas metode. Vaskulārās patoloģijas ir biežs vidēja kuņģa zarnu trakta asiņošanas iemesls.

Introduction

Despite the fact that small bowel is less common source of gastrointestinal bleeding than stomach and large bowel, it is more often associated with diagnostic and treatment problems, leading to anaemia. Approximately 5% of gastrointestinal bleeding occurs from the small bowel (Gunjan 2014; Gerson 2015). Treatment options and outcomes are dependent on diagnostic modalities, which can reveal the source of haemorrhage. Multidisciplinary team is required in small bowel bleeding management, including emergency medicine, gastroenterology, intensive care, surgery and interventional radiology specialists.

Small bowel traditionally is divided in three parts. Duodenum, the proximal part of small bowel, is included in the upper digestive tract, that is located above the lig. Treitz. The symptoms include haematemesis and/or melena. Most common aetiology of bleeding are peptic ulcers. Upper endoscopy is the diagnostic test of choice, that allows to visualize pathology in duodenum and to provide haemostasis (Vipul 2011). If the source of bleeding is not identified after upper and lower endoscopy, it is defined as obscure bleeding. In this case jejunum or ileum (mid-gastrointestinal) bleeding is suspected. Further examinations are necessary to indicate the underlying pathology. More detailed methods include video capsule endoscopy (VCE), push-entoroscopy, balloon-assisted enteroscopy (SBE and DBE), CTA, CT and MR enterography and digital subtraction angiography (DSA).

The commonest lesions responsible for small bowel bleeding are vascular, especially in elderly patients. Other described causes include tumours, inflammatory lesions and medications (NSAIDs) (Gunjan 2014). The various small bowel vascular anomalies described include angiodysplasia, telangiectasia, phlebectasia, arteriovenous malformation (AVM), Dieulafoy's lesion and varices.

DSA (digital subtraction angiography) is an imaging technique, that allows to visualize vascular pathologies, using endovascular radio-opaque contrast agent administration directly into blood vessels. Active bleeding is present if DSA shows contrast extravasation into bowel lumen. Bleeding can be suspected if one of following is present: contrast filling of spaces outside the bowel lumen (diverticula), arterial spasm, vascular tufts and early draining veins (angiodisplasia), hyperaemia (inflammation), neovascularity (tumour), pseudoaneurisms or arteriovenous fistulas. The main advantage of DSA is the ability to perform endovascular therapeutic interventions.

Endovascular embolization is a minimally invasive technique, that allows to achieve haemostasis and to close pathological vessels using special glue, microspheres or coils. Femoral artery is most common approach. Complications after endovascular embolization include bowel infarction, bleeding recurrence, punction site complications.

The aim of our study was to evaluate the most common causes of small intestine bleeding in patients who underwent the procedure of visceral angiography in the Department of Interventional Radiology, Rīga East University Hospital, compare endoscopic and radiological findings, to assess treatment and early complications after endovascular embolization.

Materials and methods

Retrospective study included evaluation of medical history of patients with small bowel bleeding who underwent angiographic examination in three-year period between January 2014 and December 2016. Small bowel defined as duodenum, jejunum and ileum. Examined vessels included *a. mesenterica* superior and *a. gastroduodenalis* branches. Angiographic, endoscopic and radiological findings were evaluated and compared. Data analysed by SPSS, Microsoft Office Excel. Descriptive statistics function and Pearson Chi square test used to compare data.

Results

A total of 32 patients were included. 59,4% men (n=19) and 40,6% women (n=13). Age ranged from 33 to 91 years, mean age 65,9 years (SD ±16.8).

The most common site of haemorrhage was duodenum, in 75% (n=24) of cases, followed by jejunum in 15,6% (n=5) and ileum 6,3% (n=2). In one case (3,1%) precise source of bleeding hasn't been diagnosed after endoscopic, radiological and angiographic evaluation. *See Fig. 1.*

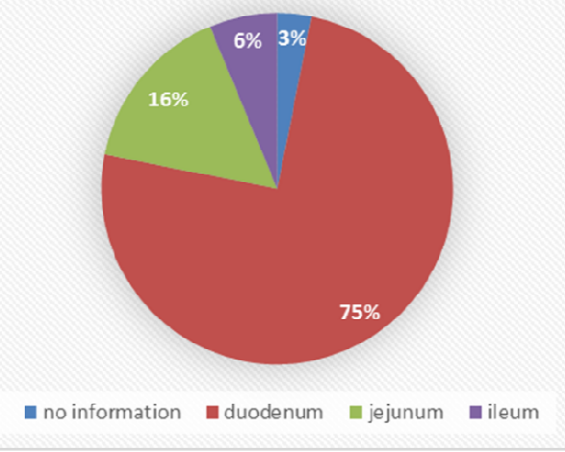


Figure 1. **Bleeding location**

In majority of cases bleeding occurred because of ulcers (in 62,5%), all of them found in duodenum and diagnosed by endoscopy. Vascular anomalies were quite frequent: AVM diagnosed in 4 patients (13%), 2 of them found in jejunum, 1 - in ileum, 1 – in duodenum. *Dieulafoy's* lesion

found in 2 patients (6%) (all in duodenum). Other diagnosed pathologies: postoperative bleeding occurred in 6,3% (n=2), tumour found in 1 case (3,1%). One case of diffuse angiopathy and coagulopathy in patient with lymphoma. In two cases exact cause of bleeding was not documented. *See Fig. 2.*

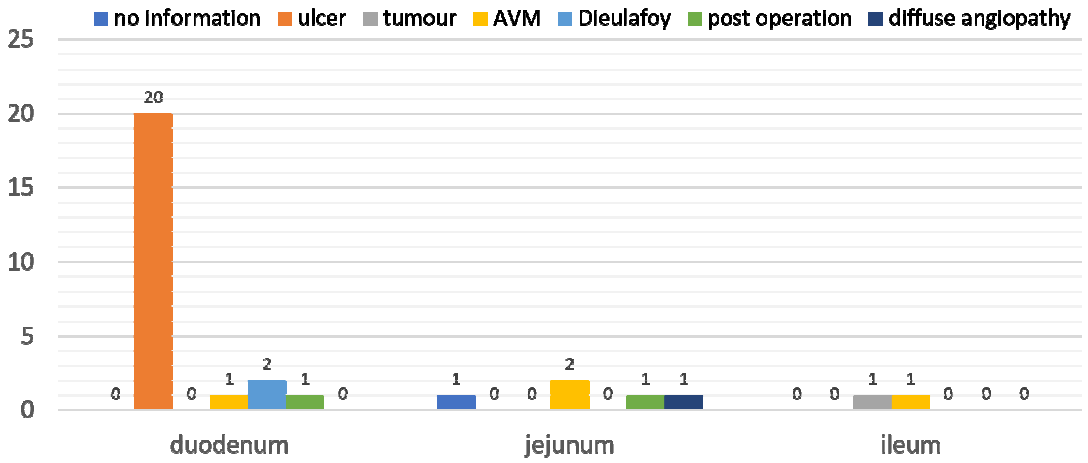


Figure 2. **Cause of bleeding in different small bowel parts**

In 84% of cases endoscopic findings did not differ from DSA and indicated the presence of bleeding and its location. In other 16% endoscopic findings were different from angiography. Endoscopy was negative in 22.6%, more often in jejunum (66%) and ileum (33%) bleeding. All duodenum lesions seen during endoscopy.

DSA showed active bleeding in 25% of patients. In 6% indirect signs of bleeding were present. DSA was negative in 7% of cases (n=2). Three AVM were visualized, one of them with signs of active bleeding. Tumour and capillary malformation were also seen in angiography. In 47% the purpose of DSA was preventive embolization after endoscopic haemostasis in patients with high re-bleeding risk, the presence of bleeding was not described in these cases. *See Fig.3*

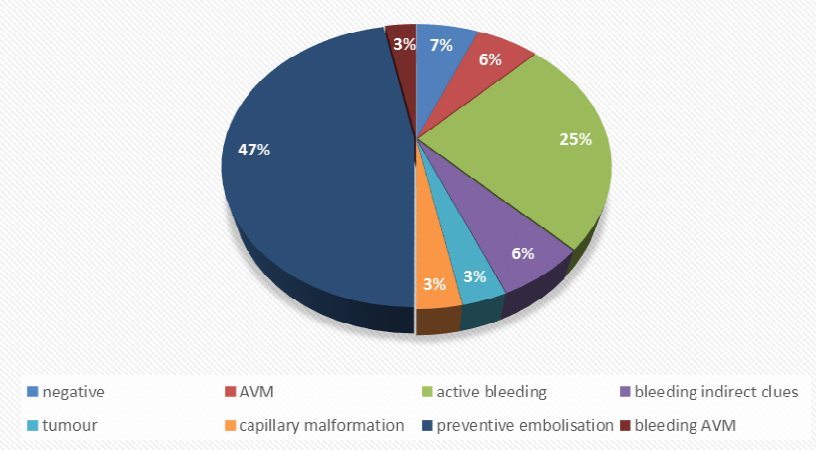
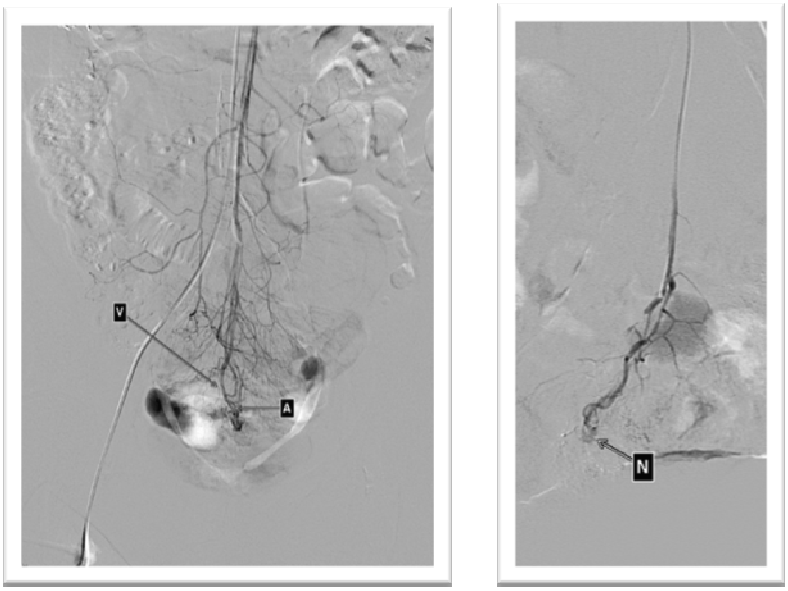


Figure 3. **DSA findings (%)**



A B

Figure 4. **AVM in digital subtraction angiography images: picture A – contrast enhanced artery (A) and vein (V) connect bypassing the capillary system and form AVM nidus (N) in the picture B**

CT was performed in 9 patients. In 34% of cases it was negative. In 3 cases (33%) active bleeding was visualized. Other findings are AVM, tumour and diffuse angiopathy. *See Fig. 4.*

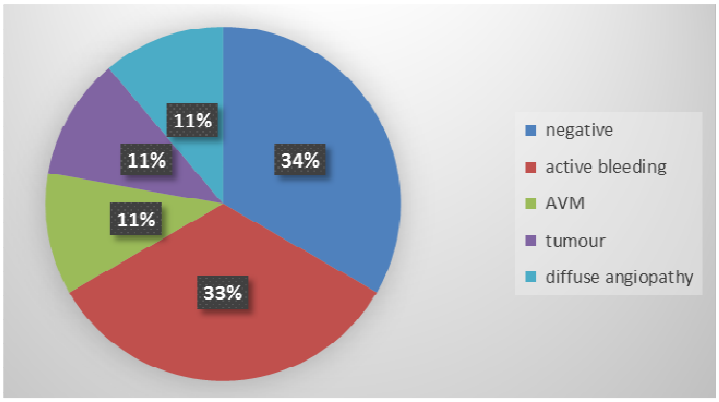


Figure 5. **CT findings (%)**

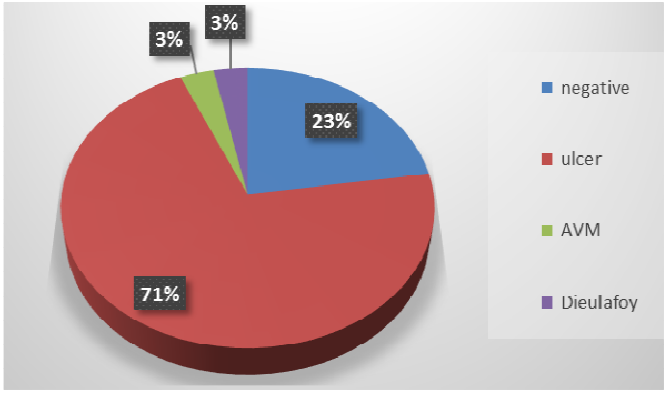


Figure 6. **Endoscopic findings (%)**

Endoscopy was negative in 23% of cases, all of them represented bleeding from distal parts of small intestine. Most common endoscopic finding was duodenum ulcers. *See Fig. 5*

The majority of patients (91%) required blood transfusion to correct anaemia. Endoscopic haemostasis was performed in 24 patients (75% of all patients), endovascular embolization was used in 97% (n=31). 25% (n=8) of patients required surgical intervention. *See Fig. 6.*

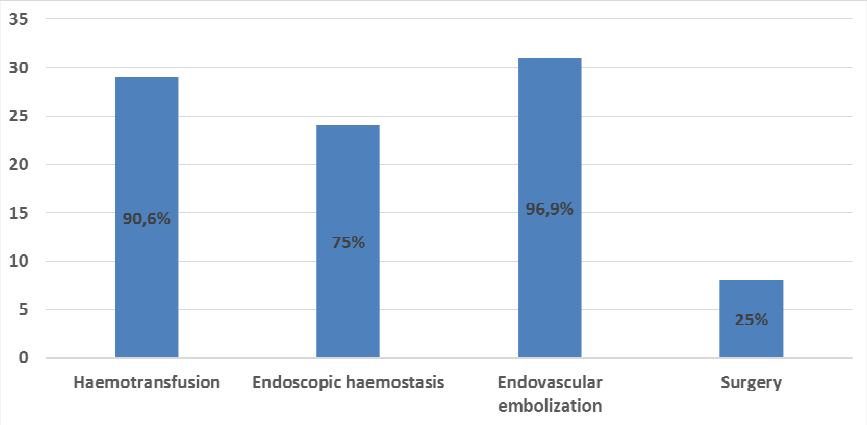


Figure 7. **Therapy: Percent of patients received different types of treatment**

Endovascular embolization was effective in 84% of cases, but in 16% (n=5) rebleeding occurred. In 90% of cases there were no early complications. Complications occurred in 10%, when bowel ischemia was present (required bowel resection). In 2 cases *exitus letalis* despite the treatment (Diagnosis: lymphoma; chronic pancreatitis and complications after pancreas resection surgery).

Discussion

Duodenum bleeding differs from jejunum and ileum in incidence, aetiology and management. More often bleeding occurs because of ulcers, is diagnosed and treated endoscopically. Jejunum and ileum is beyond the reach of conventional upper and lower endoscopy. Balloon assisted enteroscopy (DBE or SBE) use is limited. In few cases push-enteroscopy with paediatric colonoscope was performed. Intraoperative endoscopy used in few patients. Video capsule endoscopy is an option in case of chronic bleeding in stable patients. Patients who are admitted to Department of Interventional Radiology more often have acute bleeding that require immediate haemostasis.

Most common causes of mid-gastrointestinal bleeding are vascular, as it is mentioned in literature. (Gunjan 2014) Other findings include tumours, post-operation bleeding, diffuse angiopathy.

All Dielafoy's lesions were diagnosed in duodenum. This pathology is very rare in jejunum and ileum, accounting for approximately 1%, but more often it is described in stomach (71%) and duodenum (15%). (Baxter 2010) No diverticulosis cases found during the study. This pathology is

more frequent in younger patients. Mainly elderly patients included in the study. To achieve statistically significant data, it is necessary to continue study including more patients.

Endovascular embolization allows to achieve haemostasis when lesion can't be managed endoscopically. Complication rate is higher, then described in literature, but it is difficult to compare because of small number of cases analysed. (Weldon 2008) The result of treatment depends on patient's diagnosis, comorbidities, bleeding localization.

Conclusion

- Recognizing small bowel bleeding remains a diagnostic challenge, especially if it is present in distal parts of intestine.
- Most common source of bleeding, duodenum ulcers, are diagnosed by endoscopy.
- Endoscopy was less useful in visualising processes in ileum and jejunum.
- Angiography in these cases was more useful for diagnosis and treatment.
- Mostly endoscopic and DSA findings did not differ and showed presence of bleeding and its location.
- Vascular pathology is relatively frequent cause of mid-gastrointestinal bleeding.
- Small bowel bleeding in most cases require blood transfusion due to anaemia.
- Endoscopy is widely used to treat duodenal bleeding, while in distal bowel lesions mainly endovascular treatment is more helpful.
- Endovascular embolization is relatively safe and effective treatment method.
- The most serious complication after endovascular embolization is bowel ischemia.

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DELIRIUM AFTER CARDIAC SURGERY INCIDENCE AND RISK FACTORS

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Abstract

Delirium after cardiac surgery incidence and risk factors

Key words: *Delirium, cardiac surgery, risk factors*

Due to increase of average age of population old people have become specific social group creating the need to pay more attention to health care problems.
The aim of our study – to identify reasons of cognitive dysfunction in patients after heart surgery. The research was carried out in Pauls Stradins Clinical University Hospital in Cardiac surgery anaesthesia and intensive care unit. Research included all patients for whom the cardiac surgery was planned and performed during time period from 4 January to 1 February 2016.
The Paper proved that postoperative period after cardiac surgery in patients is associated with cognitive disorders. After heart surgery delirium was developed in four patients (8,5%), hyperactive delirium was found in three patients (6,4%), hypoactive delirium was found in one patient (2,1%).
By analysing impact of pre-operative diseases and adjacent diseases on cognitive function after cardiac surgery it was concluded that age (p - 0,042), strokes/transient ischemic attack (p - 0,05) and history of sleep disorders (p - 0,013) have statistically credible impact on development of post-operative delirium.
There are no evidences that drug therapy applied during perioperative period has impact on development of post-operative delirium in patients after heart surgery.
By analysing post-operative outcomes in patients after cardiac surgeries it was concluded that the following factors have statistically credible impact on development of post-operative delirium: duration of artificial lung ventilation (p -0,009) and re-surgery (p – 0,016).

Kopsavilkums

Delīrija incidence un riska faktori pacientiem pēc sirds operācijām

Atslēgvārdi: *Delīrijs, sirds operācijas, riska fakroti*

Sakarā ar to, ka ir pieaudzis iedzīvotāju vidējais vecums, veci cilvēki ir kļuvuši par noteiktu sociālu grupu, kas rada nepieciešamību pievērst lielāku uzmanību veselības aprūpes problēmām.
Darba mērķis - identificēt kognitīvās disfunkcijas iemeslus pacientiem pēc sirds operācijām. Pētījums tika veikts Paula Stradiņa Klīniskās universitātes slimnīcas sirds ķirurģijas anesteziolоģijas un intensīvās terapijas nodaļā. Pētījumā tika iekļauti visi pacienti, kuriem plānota un veikta sirds operācija laika periodā no 2016. gada 4. janvāra līdz 1. februārim.
Darbā ir pierādīts, ka pacientiem pēc sirds operācijām pēcoperācijas periods ir saistīts ar kognitīviem traucējumiem. Četriem pacientiem pēc sirds operācijas (8,5%) attīstījās delīrijs, trīs pacientiem tika konstatēts hiperaktīvs delīrijs (6,4%), vienam – hipoaktīvs delīrijs (2,1%).
Analizējot pirmsoperācijas slimības un blakusslimību ietekmi uz kognitīvo funkciju pēc sirds operācijas statistiski ticama ietekme uz pēcoperācijas delīrija attīstību ir vecumam (p - 0,042), insultiem/ tranzitora išēmiska lēkme (p -0,05) un miega traucējumiem anamnēzē (p - 0,013).
Pētījuma populācijai nav pierādījumu, ka perioperatīvā periodā pielietotai medikamentozai terapijai ir ietekme uz pēcoperācijas delīrijas attīstību pacientiem pēc sirds operācijām.
Analizējot pēcopēracijas rezultātus pacientiem pēc sirds operācijām statistiski ticama ietekme uz pēcoperācijas delīrija attīstību ir mākslīgās plaušu ventilācijas ilgumam (p - 0,009) un bijušai reoperācijai (p – 0,016).

Indroduction

In recent decades in the world, including Latvia, there are observed significant demographic changes associated with aging of society – proportion of old people and thereby also average age of population increases. Due to increase of average age of population old people have become specific social group creating the need to pay more attention to health care problems.

Such anatomical and physiological changes as function deterioration of different organ system, deterioration of compensatory and adaptation reactions in elderly people body, significantly increase pathology risk of central nervous system. As a result, develops acute mental health disorders such as delirium in postoperative period (Корячкин 2013).

Postoperative delirium is recognized as the most common surgical complication in older adults, occurring in 5% to 50% of older patients after an operation (Ибрагимов 2009). Furthermore, all-cause mortality increases by at least 10–20% for every 48 hours of delirium (Whitlock et al. 2011). In Latvia within last three years the number of cardiovascular surgeries has increased. Thus, the number of patients in intensive care units is increasing with every year.

Delirium is serious complication in older people because delirium episode can cause a range of adverse events including serious postoperative complications, prolonged sedation, hospitalisation in intensive care unit and in hospital, loss of functional independence, decreased cognitive function and death, as well as to increase costs of medical care.

The risk of developing delirium after surgery is best described as a relationship between a physiologic stressor and predisposing patient risk factors. Risk factors for postoperative delirium are well established.

The National Institute for Health and Care Excellence issued a delirium clinical guideline that highlighted 5 major risk factors for delirium: age greater than 65 years, chronic cognitive decline or dementia, poor vision or hearing, severe illness, and the presence of infection. Another systematic review focusing on delirium after operations identified the following risk factors for development of postoperative delirium: increased age, cognitive impairment, visual or sensory impairment, functional dependence, self-reported excess alcohol use, and specific laboratory or electrolyte abnormalities.

Operation-specific risk factors for the development of postoperative delirium are based on the degree of operative stress. For example, low operative stress procedures such as cataract surgery result in delirium in 4% of cases (Milstein et al 2002) in comprarison to high surgical risk procedures such as vascular operations which result delirium in 36% of cases (Marcantonio el al 2002). Vascular and cardiac surgeries are associated with a high incidence of delirium, possibly because cerebral complications of atherosclerosis may also reduce brain reserve (Whitlock et al. 2011).

Delirium diagnosis and treatment are essential components of optimal surgical care of older adults. To date, health care professionals are familiar with managing organ dysfunction in organs such as the kidneys and lungs in the perioperative setting, but are less familiar with caring for brain dysfunction despite its increasing clinical impact (Whitlock et al. 2011).

Postoperative delirium is not preventable in all patients, but it may be prevented in some, and its severity and duration may be limited in others, especially if promptly recognized and managed (Whitlock et al. 2011).

Material and methods

The research was carried out in Pauls Stradins Clinical University Hospital in Cardiac surgery anaesthesia and intensive care unit. Research included all patients for whom the cardiac surgery was planned and performed during time period from 4 January to 1 February 2016. There was created research protocol where in the course of research pre-operative indicators, data fixed during surgery, and post-operative indicators were recorded and analysed.

Patient exclusion criteria:

- Cognitive impairment before surgery (mini mental state examination (MMSE) < 24);
- Cardiopulmonary reanimation during surgery or in intensive care unit (ICU).

Cognitive function of patients is measured with MMSE scale. MMSE test to a patients was made before/after heart and carotid surgery in the following stages: after extubation and after dicharge from the ICU.

All patients surgery was done under general anesthesia by sevoflurane with endotracheal intubation.

There was created research protocol where in the course of research pre-operative indicators, data fixed during surgery, and post-operative indicators were recorded and analysed:

- Demographics parameters (age, gender);
- Preoperative variables:
  - The medical history of a patient, active tobacco use, active alcohol use,
  - hemodynamics parameters (arterial pressure, pulse rate, ejection fraction),
  - Potassium, sodium and hemoglobin concentration in blood.
- Operative variables:
  - Operation time and mechanical lung ventilation time,
  - Lowest partial pressure of arterial oxygen (PaO_2), lowest oxygen saturation, blood transfusion,
  - Lowest hemoglobin concentration in blood
  - Hemodynamics parameters (the average blood pressure before and after artificial circulation, frequence of heart rate before surgery and after it),
  - Vasoactive medication applicable during the surgery (norepinephrine, korotrop, dobutamine).

- Postoperative variables:
  - Mechanical lung ventilation time, number of days in ICU and in stationary,
  - Blood electrolytes, hemoglobin concentration in the blood after extubation, and leaving ICU,
  - Fixed data about central nervous system affecting drugs which was used after surgery,
  - Fixed data about vasoactive drugs which was used after surgery,

Study data obtained and analyzed with statistical processing program SPSS 23.0 for Windows and MS Excel. With Mann – Whitney U test was examined whether the results of control group patients and delirium patients are statistically different. Corelation of two independent groups wasa considered to be statististically signifacnt if the p-value in the results was less than 0,05. This statistical method was chosen by Riga Stradins University specialists.

Results

The study involved 47 patients after heart surgery (Figure 1.1.).

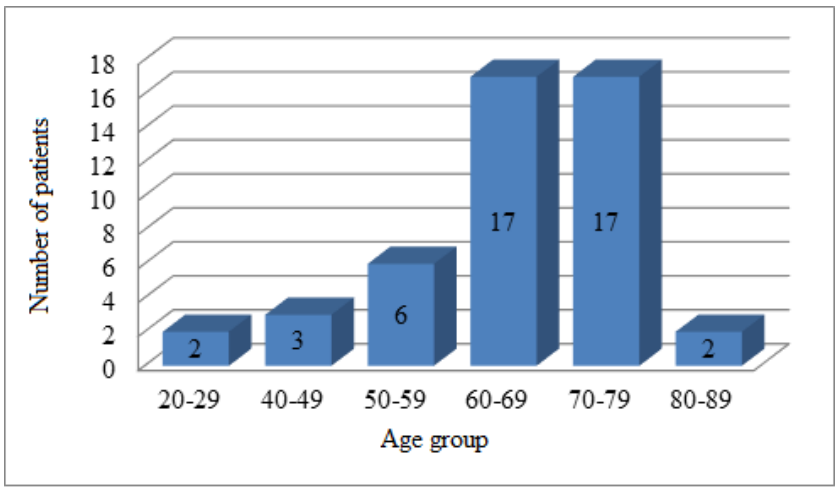

Figure 1.1. **The Age groups of patients included in study**

After heart surgery delirium was developed in four patients (8,5%), hyperactive delirium was found in three patients (6,4%), hypoactive delirium was found in one patient (2,1%) (Figure 1.2.).

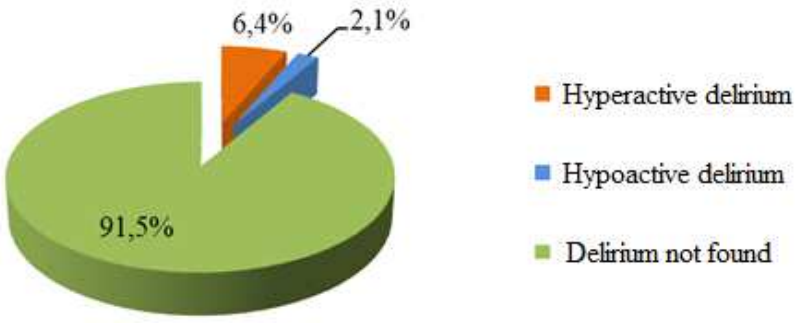

Figure 1.2. **Incidence of postoperative delirium**

For patients with delirium found in postoperative period ICU stay was longer - 3,5 ± 1,29 days, while for a control group 1,58 ± 0,9 days (p=0,0049). For patients with postoperative delirium found the hospital stay was longer - 18,25 ± 2,25 days, while for a control group 13,41 ± 4 days (p=0,006).

By analysing impact of pre-operative diseases and adjacent diseases on cognitive function after cardiac surgery it was concluded that strokes/transient ischemic attack (TIA) and history of sleep disorders have statistically credible impact on development of post-operative delirium (Table 1.1.).

Table 1.1. **Preoperative variables**

Parameter	Control (n=43)	Delirium (n=4)	Univariate P-value
Age (years)	64,26 ± 12,58	76 ± 7,5	0,042*
Gender (female)	46,5%	25%	0,617
Tobacco use (active)	16,3%	0%	1
Alcohol Use (active)	4,7%	0%	1
Hypertension (yes)	79,1%	100%	0,574
Myocardial infarction (previous)	27,9%	0%	0,56
Cerebrovascular history (yes)	7%	50%	0,05*
Sleeping disorder (yes)	30,2%	100%	0,013*
Pulmonary disease (yes)	23,3%	25%	1
Diabetes (yes)	16,3%	25%	0,539
Renal disease (yes)	16,3%	25%	0,539
Gastritis/peptic ulcer (yes)	9,3%	50%	0,074
Infectious disease (yes)	2,3%	0%	1
Sleep apnea (yes)	48,8%	75%	0,609
Sodium concentration (mmol/l)	142 (141 – 144)	141,5 (133,5 – 142)	0,196
Potassium concentration (mmol/l)	4,45 ± 0,43	4,68 ± 0,4	0,364
Haemoglobin (g/l)	136 (128 – 143)	140 (131 - 146,75)	0,594
CRO (mg/l)	1,3 (0,3 – 3,78)	3,4 (0,88 – 13,43)	0,292
Pulse rate (beats/min)	70 (70 – 80)	85 (63 – 99,5)	0,326
SAP (mmHg)	130 (130 – 140)	130 (122,5 – 137,5)	0,519
DAP (mmHg)	80 (79 - 80)	80 (76,25 – 80)	0,783
Ejection fraction (%)	58 (50 – 60)	55 (48,25 – 58,75)	0,495

There are no evidences that operative outcomes have impact on development of post-operative delirium in patients after cardiac surgery (Table 1.2.).

Table 1.2. **Operative variables**

Parameter	Control (n=43)	Delirium (n=4)	Univariate P-value
Operation time (min)	196,51 ± 43,32	226,25 ± 26,89	0,09
Ventilator time (min)	94 (80 – 108)	90,5 (84,25 – 139,5)	0,755
Lowest oxygen saturation (%)	98 (80 – 100)	99 (93,5 – 100)	0,898
Volume load, blood excluded (ml)	643,95 ± 1129,72	758,5 ± 722,07	0,699
Lowest partial pressure of arterial oxygen (mmHg)	152,21 ± 56,78	185 ± 66,98	0,472
Haemoglobin lowest recorded (g/l)	7,3 (6,3 – 8,3)	6,5 (6,08 – 7,38)	0,21
Blood products required (yes)	23,3%	25%	1
Midazolam required (yes)	2,3%	0	1
Norepinephrine required (yes)	14%	50%	0,129
Korotrop required (yes)	0%	25%	0,085

Dobutamine required (yes)	16,3%	0%	1
Average blood pressure before artificial circulatory (mmHg)	108,44 ± 11,33	120 ± 10,6	0,183
Average blood pressure after artificial circulatory (mmHg)	85,23 ± 8,27	84,75 ± 10,4	0,543
Heart rate frequency before surgery (beats/min)	70 (60 – 80)	75 (70 – 80)	0,364
Heart rate frequency after surgery (beats/min)	80 (74 – 80)	80 (72,5 -95)	0,619

By analysing post-operative outcomes in patients after cardiac surgeries it was concluded that the following factors have statistically credible impact on development of post-operative delirium: duration of artificial lung ventilation and re-surgery (Table 1.3.).

Table 1.3. **Postoperative variables**

Parameter	Control (n=43)	Delirium (n=4)	Univariate P-value
Ventilator time (min) (min)	205,93 ± 89,2	351,25 ± 108,96	0,009*
Potassium, sodium and hemoglobin concentration in blood after extubation			
Sodium concentration (mmol/l)	138 (136 - 139)	139 (136 – 142)	0,519
Potassium concentration (mmol/l (mmol/l)	4,3 (4,2 – 4,7)	4,65 (4,45 – 5,15)	0,116
Haemoglobin (g/l)	109 (99 – 117)	88,5 (73,25 – 118,75)	0,17
Potassium, sodium and hemoglobin concentration in blood leaving ICU			
Sodium concentration (mmol/l)	137 (135 – 140)	140,5 (138,25 – 145)	0,047
Potassium concentration (mmol/l (mmol/l)	4,3 (4,2 – 4,6)	4,5 (4,08 – 4,78)	0,727
Haemoglobin (g/l)	104,34 ± 13,84	101,5 ± 14,43	0,783
CRO (mg/l)	93,53 ± 57,72	131,08 ± 28,62	0,115
Re-surgery (yes)	2,3%	50%	0,016*
Benzodiazepine required (yes)	18,6%	0%	1
Fentanyl required (yes)	90,7%	50%	0,074
Norepinephrine required (yes)	25,6%	75%	0,073
Korotrop required (yes)	9,3%	0%	1
Dobutamine required (yes)	18,6%	0%	1

Discussion

The study involved 47 patients after heart surgery. The Paper proved that postoperative period after cardiac surgery in patients is associated with cognitive disorders. After heart surgery delirium was developed in four patients (8,5%), hyperactive delirium was found in three patients (6,4%), hypoactive delirium was found in one patient (2,1%). For patients with delirium found in postoperative period ICU stay was longer - 3,5 ± 1,29 days, while for a control group 1,58 ± 0,9 days (p=0,0049). For patients with postoperative delirium found the hospital stay was longer - 18,25 ± 2,25 days, while for a control group 13,41 ± 4 days (p=0,006).

In our study it is proved that age is a risk factor of postoperative delirium. The National Health and Care Excellence Institute in the US has developed a postoperative delirium clinical guidelines and identified one of the risk factor – age over 65 years. Age is associated with atherosclerosis of greater sleep and aortic artery and increase brain stroke and TIA risk. Studies of stroke/TIA was demonstrated as a predisposing factor for the development of postoperative

delirium (American Geriatrics Society Expert Panel 2015, Vidan MT *et al.* 2009, Ибрагимов 2009). Also this study showed statistically significant stroke/TIA history effect on postoperative delirium development.

Sedative and analgesic medications are routinely administered to patients receiving mechanical ventilation to reduce pain and anxiety. These medications, however, are not without detrimental effects. Continuous intravenous sedation is associated with prolonged mechanical ventilation. Prolonged mechanical ventilation was another strong risk factor associated with in-hospital delirium in cardiac surgery population (Arenson BG *et al.* 2013). By analysing post-operative outcomes in patients after cardiac surgeries it was concluded that the following factors have statistically credible impact on development of post-operative delirium: duration of artificial lung ventilation and re-surgery.

Statistically significant effect on development of postoperative delirium also noted for reoperation ($p > 0,05$). This is due to the fact that the patients after repeated surgery have prolonged the average duration of artificial lung ventilation and hypotension.

There are no evidences that drug therapy applied during perioperative period has impact on development of post-operative delirium in patients after cardiac surgery.

Conclusions

1. Delirium was found for patients after heart surgery during the postoperative period. After heart surgery delirium was developed in four patients (8,5%), hyperactive delirium was found in three patients (6,4%), hypoactive delirium was found in one patient (2,1%).
2. By analysing impact of pre-operative diseases and adjacent diseases on cognitive function after cardiac surgery it was concluded that age (p - 0,042), strokes/TIA (p - 0,05) and history of sleep disorders (p - 0,013) have statistically credible impact on development of post-operative delirium.
3. There are no evidences that drug therapy applied during perioperative period has impact on development of post-operative delirium in patients after heart surgery.
4. By analysing post-operative outcomes in patients after cardiac surgeries it was concluded that the following factors have statistically credible impact on development of post-operative delirium: duration of artificial lung ventilation (0,009) and re-surgery (p – 0,016).

Acknowledgement

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THE ESTIMATION OF THE PROGNOSTIC VALUE OF INTRA-ABDOMINAL PRESSURE AND ABDOMINAL CIRCUMFERENCE IN NEONATES WITH NECROTIZING ENTEROCOLITIS

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Abstract

The estimation of the prognostic value of intra-abdominal pressure and abdominal circumference in neonates with necrotizing enterocolitis

Key words: *Necrotizing enterocolitis, intra-abdominal pressure (IAP), abdominal circumference (AC), abdominal distention, clinical monitoring*

Introduction: Necrotizing enterocolitis (NEC) remains a major cause of morbidity and death in neonates. Fast diagnosis of NEC is essential for successful management and is mostly based on ultrasonography and radiography findings.

Aim: To determine whether there is a significant difference in intra-abdominal pressure and abdominal circumference in neonates with a different stage of the disease using Bells staging system.

Materials and methods: Retrospective data analysis was performed on 24 neonates with diagnosed or suspected NEC (Bell stage 1-3) and measured intra-abdominal pressure and abdominal circumference acquired data was compared to dr.Ilze Meldere et.al developed a specific formula for estimating normal abdominal circumference. Statistical analysis was carried out with IBM SPSS 22.0.

Results: Data of 24 neonates was collected and analysed. The average time of birth in neonates was 29 gestational weeks. Mean difference from normal values in AC depending on baby's weight was +1,87 cm (min-3,6; max+9,4cm). One way ANOVA with Post Hoc analysis showed statistically significant difference in Bell stage groups (p=0,046), specifically of abdominal circumference difference (ACD) in Bell stages I and III (P=0,039) and tendency between stages II and III (P=0,138).

IAP was elevated in all measurements. Median IAP was 8mm/Hg (min2; max14 mm/Hg), intra-abdominal hypertension (IAP>10mm/Hg) was observed in 14 measurements (20%). Positive pressure ventilation, that can change IAP in healthy babies up to 8mm/Hg and was used during treatment was taken into account, and in 67,6% of cases, IAP still was elevated. Kruskal-Wallis analysis showed that distribution of IAP is not the same across Bell stages (p=0,044), specifically between stage I and III (p=0,038)

Conclusion: IAP and AC are statistically higher in the severe stage of NEC.

Kopsavilkums

Intra-abdominālā spiediena un vēdera apkārtmēra prognostikās vērtības izvērtēšana jaundzimušajiem ar nekrotizējošo enterokolītu

Atslēgas vārdi: *Nekrotizējošs enterokolīts (NEK), Intra-abdominālais spiediens (IAS), Vēdera apkārtmērs (VA)*

Ievads: Nekrotizējošais enterokolīts ir vadošais saslimstības un nāves cēlonis jaundzimušajiem. Ātra NEK diagnostika ir ārkārtīgi svarīga NEK veiksmīgai ārstēšanai un pamatojas galvenokārt uz ultrasonogrāfijas un rentgenattēlu atradni.

Mērķis: Noteikt, vai ir nozīmīga IAS un VA saistība ar dažādām slimības stadijām, izvērtējot slimības pakāpi pēc Bella slimības stadiju klasifikācijas.

Materiāli un metodes: Retrospektīva datu analīze tikai veikata 24 jaundzimušajiem ar aizdomām vai diagnosticētu NEK (Bella stadijas 1-3). IAS un VA dati tika salīdzināti ar Meldere et al. izveidoto formulu jaundzimušo sagaidāmā vēdera apkārtmēra izvērtēšanai. Statistiskā analīze tika veikta ar programmu IBM SPSS statistics 22.versiju.

Rezultāti: Retrospektīvi tika ievākti un analizēti dati par 24 jaundzimušajiem. Dati par 24 jaundzimušajiem tika ievākti un analizēti. Vidējais dzimšanas laiks bija 29 gestācijas nedēļas. Vidējā atšķirība no sagaidāmā vēdera apkārtmēra bija +1,87 cm. One way ANOVA statistiska analīze uzrādīja nozīmīgu sakarību starp VA un dažādām slimības stadijām (p=0,046), īpaši 1.un 3.stadiju (p=0,039). Starp 2. un 3.stadiju tika novērota saistība, kas nebija statiski nozīmīga. (P=0,138).

IAS bija paaugstināts visos mērījumos. Mediānā vērtība bija 8 mm/Hg. Intra-abdominālu hipertensiju novēroja 20% gadījumu. Pozitīvā spiediena ventilācija, kas var izmainīt IAS līdz 8 mm/Hg zīdaiņiem bez vēdera dobuma pataloģijas un ko izmanto NEK terapijā, tika ņemta vērā. 67,6% IAS joprojām varēja uzskatīt par paaugstinātu. Statistiskā analīze uzrādīja, ka IAS sadalījums dažādās Bell stadijās statistiski ticami atšķiras (0,044), īpaši starp 1.un 3.slimības stadiju (p=0,038)

Secinājumi: Augstākam IAS un VA ir ticama saistība ar smagāku NEK stadiju.

Introduction

Necrotizing enterocolitis (NEC) remains a major cause of morbidity and death in neonates. The incidence of NEC varies from 1 to 3 per 1000 live births depending on intensive care unit (Yigit 2008) Mortality can reach 30% in neonates without perforation and 50% with intestinal perforation. The mortality rate has not significantly diminished for the last two decades (Marion 2008). Therefore, fast diagnosis of NEC is essential for the successful management, which is based on ultrasonography and radiography results, combined with clinical presentation. Controversies regarding different treatment options and indications for surgery prevent clear standardised evidence-based guidelines. Clinicians must base decisions on their understanding of the disease and on the best available evidence (Gibbins 2008).

Disease typically is characterised by abdominal distension, bloody stools and pneumatosis intestinalis. Clinically disease can have a wide spectrum of signs from mild such as feeding intolerance to severe, such as intestinal necrosis and perforation leading to septic shock. In fulminant cases worsening from minimal symptoms to peritonitis and death can be observed within 12 hours of the disease. Usually, terminal ileum and proximal colon are affected, but in severe cases, entire bowel and stomach can be involved (Tooley 2003, Kliegman 2016).

Necrotizing enterocolitis, called the disease of prematurity (Khong 2015), is strongly associated with early gestational age and very low birth weight. Over 90% of affected infants are born before 36 weeks of gestation (Marion 2008) yet precise etiology remains unknown and is probably multifactorial. Suggested etiologies include immature intestinal mucosa with an insufficient immune response, intestinal ischemia, infection and endogenous production of inflammatory mediators (e.g., PAF, TNF, cytokines) that precipitate intestinal injury (Tooley 2003).

The disease usually develops in the second or third week of life. Presentation of the disease include non – specific signs, such as unstable body temperature, glucose levels, hypotension, lethargy, bradycardia; gastrointestinal signs such as feeding intolerance, gastric residuals, that often contain bile, vomiting, abdominal distention, occult or gross blood in stool, diarrhea, absent bowel sounds, tenderness, redness or bluish discoloration of the abdominal wall. Radiological signs include bowel dilatation and wall thickening, fixed, dilated loop, intestinal pneumatosis, gas in *v. portae*, free gas in the peritoneal cavity in cases where intestinal perforation has developed. Laboratory findings can include elevated or decreased count of leukocytes, with or without left shift, thrombocytopenia, neutropenia, metabolic and/or respiratory acidosis and evidential parameters of disseminated intravascular coagulation (DIK syndrome) (Tooley 2003, Kliegman 2016).Most of the characteristic findings are summarized in Bells classification of the disease, dividing it into three main stages – suspected, proven or severe NEC, widely used in clinical practice.

Proven or hypothesized risk factors for NEC are prematurity (>95% of cases), aggressive advance in enteral feeding, hyperosmolar formulas, feeding of cow milk, hypoxia, bacterial colonization, congenital heart disease, especially patent ductus arteriosus, polycythemia, steroid and indomethacin use, catheterization of umbilical vessels, respiratory distress syndrome, cocaine use during pregnancy, perinatal hypotension, sepsis, and many others, depending on the research. (Tooley 2003, Cunningham 2014).In term infants, the disease is thought to be secondary to birth asphyxia, Down syndrome, congenital heart disease, rotavirus infection and Hirschsprung disease. (Kliegman 2016). Necrotizing enterocolitis remains one of the most common reasons for emergency surgery in neonates (Yigit 2008).

Aim

The goal of the study was to determine whether there is a significant difference in intra-abdominal pressure and abdominal circumference in neonates with different stages of the disease based on widely used Bell's staging system.

Materials and methods

Retrospective data analysis was performed on 24 neonates with diagnosed or suspected NEC (Bell stage 1-3). Intra-abdominal pressure (IAP) and abdominal circumference (AC) was measured and Bell's stage was determined each day for 2-3 days. Acquired data was split in 71 independent cases.

As there are no accepted normal values of the AC in newborns, the analysis of the acquired data was performed using the specific formula, developed by dr.Ilze Meldere et.al. The purpose of the formula was to estimate normal abdominal circumference in healthy neonates 30 minutes after birth without feeding depending on their body weight. In the overall population, abdominal circumference, as well as birth weight, does not differ between girls and boys. AC can be influenced by the timing of feeding, a resistance of the anterior abdominal wall, phase of breathing and amount of fat, what can be the reason for the lack of accepted reference values (Meldere 2015).

The linear regression equation for estimating and predicting normal abdominal circumference in unfed preterm infants is as follows: $y = 0.0053x + 14.83$ (y = abdominal circumference in cm; x = body weight in g; 0.0053 = regression coefficient; 14.83 = regression constant) (Meldere 2015).

Statistical analysis was carried out using IBM SPSS statistics version 22.0.

Results

During the study, data of 24 neonates were gathered and thoroughly analysed. The average time of birth of neonates was 29 gestational weeks. 13 neonates were boys and 11 were girls. In 32% of cases, neonates had NEC Bell's stage I (suspected NEC), in 39% Bell's stage II and in 25% Bell's stage III.

The average difference from normal values in AC depending on baby's weight was +1.87 cm (min-3.6cm; max+9.4cm). In 10 measurements AC was lower than expected (17%). In 12 measurements the difference was within +1 cm (20%), and in 32 measurements (53%) the difference was greater than +3cm (figure 1).

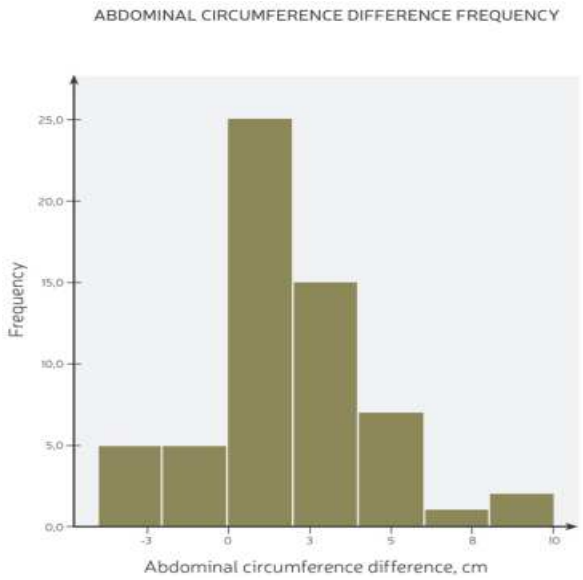

Figure 1. **Abdominal circumference difference frequency**

One way ANOVA with Post Hoc analysis showed a statistically significant difference in different Bell stage groups (p =.046), specifically in Bell stages I and III (p =.039). Moreover, the tendency between stages II and III was identified (p =.138) (figure 2).

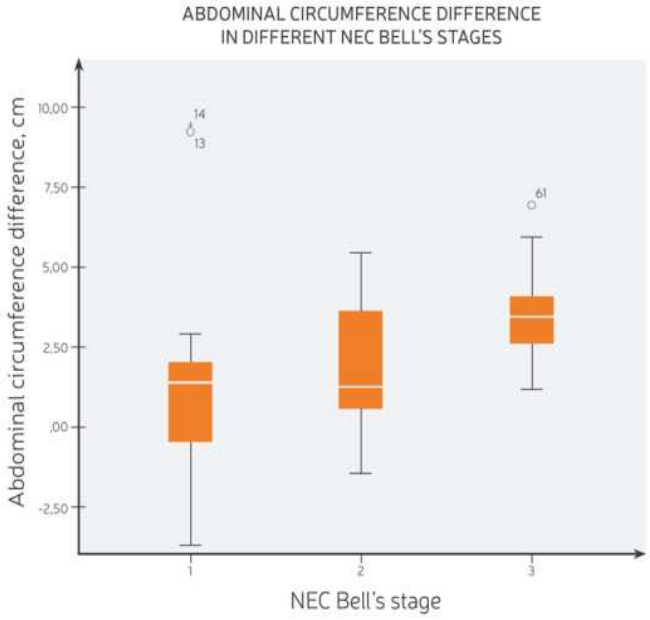

Figure 2. **Abdominal circumference difference in different NEC Bell's stages**

IAP was elevated in all measurements. Median IAP was 8mm/Hg (min2mm/Hg; max14mm/Hg). Positive pressure ventilation, which can change IAP in healthy babies up to 8mm/Hg and was used during the treatment, was taken into account. However, in 67.6% of cases, IAP still was elevated (figure 3).

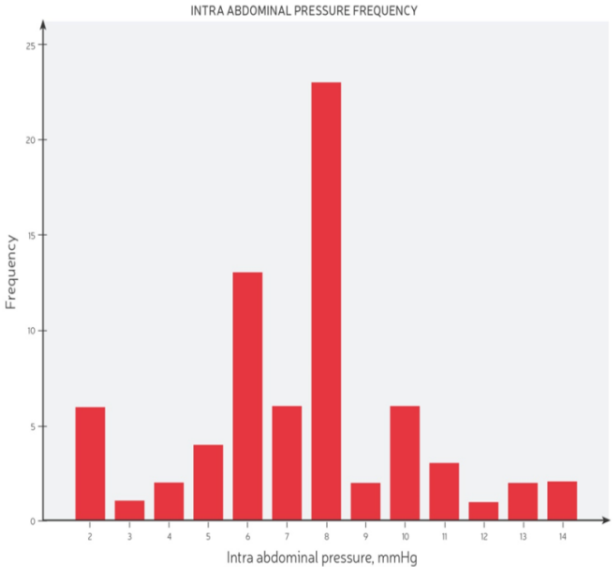

Figure 3. **Intra-abdominal pressure frequency**

In Bell stage I the ratio between observed IAP and normal IAP was 1:1.3; in stage II it was 1:2.1; and in stage III to 1:3.5. There was no significant difference between abdominal hypertension and different Bell stages. Kruskal-Wallis analysis showed that the distribution of IAP is not the same across Bell stages (p =.044), especially between stage I and III (p =.038) (figure 4).

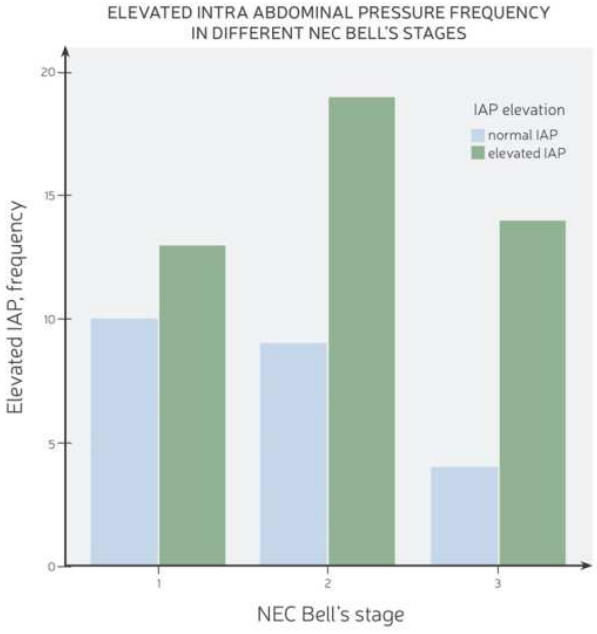

Figure 4. **Elevated intra-abdominal pressure frequency in different NEC Bell's stages**

Intra-abdominal hypertension (IAP>10mm/Hg) was observed in 14 measurements (20%). There was not found a statistically significant correlation between Intra-abdominal hypertension and higher Bell stage (figure 5).

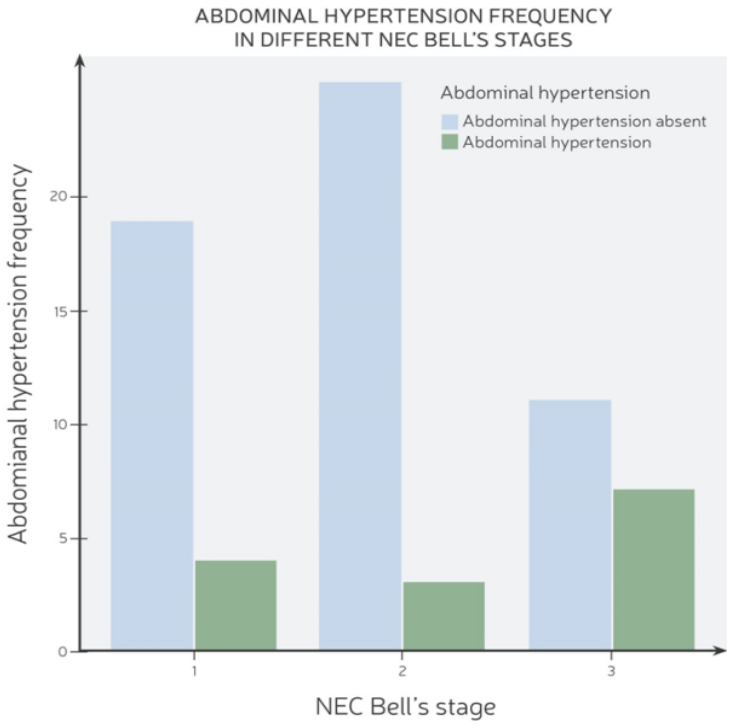

Figure 5. **Abdominal hypertension frequency in different NEC Bell's stages**

Discussion

Necrotizing enterocolitis typically is characterised by abdominal distension, bloody stools and pneumatosis intestinalis. Clinically disease can have a wide spectrum of signs from mild such as feeding intolerance to severe, such as intestinal necrosis and perforation leading to septic shock (Tooley 2003, Kliegman 2016).

Abdominal distention usually occurs in the early stage of the disease (Creasy 2014). In healthy newborns, abdominal circumference (AC) measurement is necessary to ascertain the size of the abdominal viscera. Before the presentation of definite NEC, most common described clinical signs are bloody stool (32%), gastric residuals (48%) and increased abdominal girth (66%) (Christensen 2010). In infants who developed Stage IIIA NEC, 100% presented with abdominal distention (Gregory 2011). These nursing assessments, which are part of a thorough abdominal exam, are not to be overlooked, as changes from baseline are highly likely to be associated with patients who develop advanced stages of NEC (Gregory 2011). Therefore detected increased abdominal girth should raise a strong suspicion about NEC and put a child under the active monitoring.

Increased abdominal circumference has diagnostic importance. In newborns with NEC or another disease of the abdominal cavity, it is necessary to evaluate abdominal distention via abdominal circumference to evaluate the possibility of the disease. In those with proven NEC abdominal girth should be measured frequently as a monitoring of clinical worsening, because each clinical stage of NEC is associated with higher abdominal circumference (Meldere 2015, Yigit 2008), and a sudden increase in abdominal girth warrants an immediate abdominal radiograph to assess for a pneumoperitoneum (Sharma 2013).

In our study, average AC difference from expected calculated value was elevated in 83% of cases. In 63% it was greater than 1 cm, and in 53% it exceeded 3 cm value. In the group that had lower AC than calculated, no one had severe NEC – suspected and proven NEC was 50 % and 50% accordingly. In those 3 cases where AC was more than 3cm lower than expected, all had only suspected NEC. In those who had expected AC value above 3 cm or more only 10% (n=2) had suspected NEC. 45% (n=9) had proven NEC and 45% (n=9) had severe NEC.

Statistically significant difference in different Bell stage groups (p =.046) was found, especially in Bell stages I and III. Results found in our study correspond with those found in the literature that elevated AC in most cases is associated with probability and severity of NEC.

Sukhtonic et al study showed that neonates with NEC, compared to Control patients, demonstrated a significant increase in IAP, which increased progressively with exacerbation of NEC and reached a peak value before the operation (Sukhotnik 2009).

World society of abdominal hypertension and compartment syndrome defines normal IAP 0 mm/Hg in a well child and 1-8 mm/Hg in a child on positive pressure ventilation (PPV). (WSACS 2017). In our study IAP exceeded 0 mm/Hg in all measurements. Median IAP was 8mm/Hg (min2mm/Hg; max14mm/Hg). In 67.6% of cases, IAP was elevated despite positive pressure ventilation.

In Sukhtonic et al. research, mean IAP in NEC group was 9 mm/Hg, but in control group 4.8 mm/Hg. The study did not analyse the reason of IAP in control group, but NEC definitely is not the only reason. In our study median IAP was 8 mm/Hg. In those infants having IAP 8 mm/Hg, 52% had suspected NEC, 22% proven NEC and 26% severe NEC. In study mean peak value 13.3 mm/Hg was associated with clinical exacerbation of NEC and need for surgery. In our study IAP value 9mm/Hg or above in 75% was associated with proven or severe NEC 31% and 44% respectively (Sukhotnik 2009).

In our study statistical analysis showed that the distribution of IAP is not the same across Bell stages (p =.044), especially between stage I and III (p =.038). In Bell stage I the ratio between observed IAP and normal IAP was 1:1.3; in stage II it was 1:2.1; and in stage III to 1:3.5.

Intra-abdominal hypertension can cause significant morbidity and mortality due to altered respiratory mechanics, reduced venous return and cardiac output. Elevated intra-abdominal pressure can result in renal failure, organ dysfunction and hemodynamic instability (WSACS 2017).

In or study intra-abdominal hypertension (IAP>10mm/Hg) was observed in 14 measurements (20%). There was not found a statistically significant correlation between Intra-abdominal hypertension and higher Bell stage.

The study showed promising results. Higher AC, as well as IAP, correlates with more severe stage of the NEC. Regular measurements of these parameters could help in patient monitoring to help notice when child's clinical situation is worsening and active measures should be taken.

Authors carried out a retrospective study. All measurements were made and Bells stage determined by dr.I.Meldere, a neonatologist in Riga Children's hospital. All data was registered in medical histories. As IAP and AC are not routinely measured in children with NEC in hospital practice, other NEC cases during the period were excluded from the study due to the lack of needed data.

For future research of the subject authors would like to conduct a prospective study including more patients, measuring IAP and AC more frequently and with closer association with clinical and radiological findings, as well therapy used during treatment. It also would be a great success to gather data of normal AC values depending on child's anthropometric parameters not only 30 minutes after birth, bet through all the neonatal period and to get a better understanding in interpreting these values in the context of potential value changing factors. Authors would like to gather data about AC and IAP values in children staying in NICU with or without abdominal pathology as well as to create a control group consisting of well children.

Conclusion

In most of the cases neonates had greater abdominal circumference than it would be expected.

All patients had elevated intra-abdominal pressure. In approximately 1/3 of cases it could be explained with positive pressure ventilation use during treatment.

High abdominal circumference is associated with more severe stage of the disease.

Elevated intra-abdominal pressure can be associated with clinical worsening and higher Bell's stage.

Despite the fact that IAP and ACD are not routinely measured, they can be potentially developed into an effective tool for fast initial diagnosis of NEC and for prediction of clinical worsening. They are easy, safe and available measurements. However, more data has to be collected for deeper evaluation of their possible significance.

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SAFETY OF AMIODARONE IN PRE-TREATMENT IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION UNDERGOING ELECTRICAL CARDIOVERSION

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Abstract
Key words: *Atrial fibrillation, electrical cardioversion, amiodarone, Qtc interval*
Electrical cardioversion (ECV) is an effective and widely used treatment method for the restoration of sinus rhythm in patients with persistent atrial fibrillation (AF). Literature data has shown that only 23% of patients remain in sinus rhythm one year after ECV. To reduce recurrence of arrhythmia pre-treatment with amiodarone can be used. Amiodarone is the most effective agent at preventing relapse of AF after ECV. The use of amiodarone is related with serious changes in electrocardiogram (ECG) and increasing risk of life-threatening arrhythmias. The given study aim was to clarify amiodarone pre-treatment safety before ECV. We have enrolled 150 patients with persistent AF undergoing ECV in this study. 101 patients (66.9%) used oral amiodarone at least two weeks before procedure. ECG data were analyzed before and after ECV. Considering sexual differences in ECG male and female data were analyzed separately. In women group (n=45) minimal QTc before ECV (300 ms, maximal – 466 ms (mean 376 ms). After ECV minimal QTc was 366 ms, maximal 549 ms (mean 448 ms). In man group (n=56) maximal QTc before ECV was 309 ms, maximal 535 (mean 349 ms). Minimal QTc after ECV in man group was 367 ms, maximal 557 ms (mean 454 ms). The use of amiodarone in pre- treatment in patients with persistent AF is a safe method to increase efficiency of ECV and reduce recurrence of arrhythmia. There was not found any significant changes in QT interval before and after ECV.

Kopsavilkums
Elektriska kardioversija (EKV) ir efektīva un plaši lietota ārstēšanas metode sinusa ritma atjaunošanai pacientiem ar persistējošo ātriju fibrilāciju (Āfib). Pēc literatūras datiem tikai 23% pacientu saglabājas sinusa ritms gadu pēc EKV. Aritmijas recidīvu mazināšanai pirms sinusa ritma atjaunošanas tiek lietoti dažādi antiaritmiskie līdzekļi, no kuriem vislielāka efektivitāte piemīt amiodaronam. To lietošana ir saistīta ar nozīmīgam izmaiņām elektrokardiogramā (EKG) un palielinātu dzīvību apdraudošo aritmiju rašanās risku. Šī pētījuma mērķis bija noteikt amiodarona īslaicīgas lietošanas drošumu pirms EKV. Pētījumā tika iekļauti 150 pacienti ar persitējošo ātriju fibrilāciju, kam sinusa ritma atjaunošanai tika veikta EKV. 101 (66.9%) pacients lietoja amiodarona tabletes vismaz divas nedēļās pirms EKV. EKG tika veiktas pirms un pēc EKV. Ņēmot vērā dzimuma raksturīgas atšķirības elektrokardiogrāfijā, dati tika analizēti atsevišķi sievietēm un vīriešiem. Sieviešu grupā (n=45) minimālais QTc pirms EKV bija 300 msek, maksimāla – 466 msek. (vidēji 376 msek.). Pēc sinusa ritma atjaunošanas minimālais QTc 366 msek., maksimāla –549 (vidēji 448 msek). Vīriešu grupā (n=56) QTc intervāls pirm EKV bijis robežās no 309 msek. līdz 535 msek. (vidēji 349 msek.), pēc EKV no 367 msek. līdz 557 msek. (vidēji 445 msek.). Vīriešiem (n=105) minimāla SR pirms EKV bija 51xmin, maksimāla 141xmin. Amiodarona lietošana pacientiem ar persitējošo Āfib pirms EKV ir droša metode EKV efektivitātes uzlabošanai un Āfib recidīvu riska mazināšanai. Pirms un pēc EKV nozīmīgas izmaiņas Qtc intervālā netika konstatētas.

Introduction

Atrial fibrillation is the most common type of arrhythmia and is associated with a wide range of potential complications and a significant increase in morbidity and mortality. (Waktare 2002:

14) The major complications of atrial fibrillation are thromboembolic events ranging from stroke to mesenteric ischemia and acute limb ischemia. (Menke 20102) In order to avoid these life threatening complications, the restoration of sinus rhythm is recommended. Cardioversion is performed as a part of rhythm control treatment strategy, and it successfully restores sinus rhythm. There are two types of cardioversion: electrical cardioversion and pharmacological cardioversion.

From current clinical experience, pharmacological cardioversion is the preferred strategy in patients presenting with recent onset atrial fibrillation (within 48 h). Electrical cardioversion is the recommended strategy in case of prolonged atrial fibrillation. (Sulke 2007: 29)

Direct current cardioversion is one of the most effective methods of converting atrial fibrillation into sinus rhythm. However, not all attempts of cardioversion are successful, and 1 year after cardioversion approximately 50% of patients present with a relapse of atrial fibrillation. (Sulke 2007: 149).

Complete shock failure and immediate recurrence are estimated to occur in approximately 25% of patients undergoing electrical cardioversion, and sub-acute or early recurrences occurring within 2 weeks appear in another 25%. (Van Gelder 1999: 276) Additional administration of antiarrhythmic drugs shows an improvement of conversion rate and an increase in successful maintenance of sinus rhythm after cardioversion. Drugs such as amiodarone and sotalol generally increased the likelihood of a successful cardioversion in comparison with the control drug. (Braham 2005: 1862) However, amiodarone has serious systemic adverse effects. It has been suggested to be associated with an increase in mortality as a result of long QT syndrome which is characterized by prolongation of the QT interval and by the occurrence of life threatening tachyarrhythmias. (Nkomo 2001: 246) (Tores 1986: 145)

Aim of the article

To detect the usage of different antiarrhythmic drugs including amiodarone in patients with long acting atrial fibrillation undergoing electrical cardioversion in Latvian Cardiology Center, and to determine the influence of amiodarone on electrocardiogram changes and to compare the results to control group.

Material and methods

This prospective study enrolled 150 patients with long-standing atrial fibrillation undergoing electrical cardioversion in Paul Stradins Clinical University Hospital, Department of Arrhythmology in 2016. Anamnestic data was based on interviews and medical records. Data obtained by the questionnaire included atrial fibrillation paroxysm duration, co-morbidities such as arterial hypertension, diabetes mellitus, heart failure, stroke and chronic kidney disease, previously used medications including antiarrhythmic drugs and anticoagulants.

Electrocardiographic data was collected from electrocardiograms before and after electrical cardioversion for each patient. Electrocardiograms were analyzed separately in man and woman due to electrocardiographic differences among genders.

Following electrocardiographic parameters were used: heart rate, QRS duration, QTc interval before and after electrical cardioversion.

Statistical analysis was conducted using SPSS 20.0 software.

Results

Participants were predominantly men (105 of 150; 70%) with a mean age of 64 years (min.-33, max.-83); 45 participants were woman (30%). Average age in women group was 67 years (min.- 37, max.-84). Mean body mass index in female group 31,42 kg/ m^2 (minimum 22,5 kg/ m^2, maximum 48.6 kg/ m^2, SD 6), in male group 29,6 kg/ m^2 (minimum 21,3 kg/ m^2, maximum 42,4 kg/ m^2, SD 4,4). 76 (50%) patients (6 women, 70 men) were smokers.

The most common co-morbidities in this study were arterial hypertension (98.6%) and heart failure (91%). Diabetes was founded in 17% of all patients. In 8% COPD was present in anamnesis, 7.6 % suffered from obstructive sleep apnea. Myocardial infarction was detected in 14%, 6% had a stroke in previous medical history.

All enrolled patients before electrical cardioversion used anticoagulants. The usage duration was at least three weeks for all anticoagulants except fraxiparine.

Most commonly used anticoagulant was rivaroxaban (40.4%). Dabigatran and warfarin usage was equally - 43 (28.5%) patients used warfarin and 43 (28.5%) dabigatran. Four patients (2.7%) received low molecular weight heparins (fraxiparine). Patients using fraxiparine underwent electrical cardioversion after unsuccessful sinus rhythm restoration with pharmacological cardioversion. These patients were admitted to hospital within 48 hours form atrial fibrillation paroxysm onset. Fraxiparine was administered only during hospitalization.

Before electrical cardioversion 101 (67.3%) patients used amiodarone, 11 (7.3%) used aethacizine, and 6 (4.0%) patients used propafenone. In 32 cases (21.3%) antiarrhythmic drugs were not used.

Study participants presented different durations of atrial fibrillation. In 17 patients (11.3%) the time of onset was less than 30 days, duration of 30-90 days was present in 50 participants (33,3%), and in 17 patients (11,3%) the duration was longer than 90 days. Atrial fibrillation paroxysm longer than 180 days was detected in 64 patients (47.7%). There were enrolled two patients (1.3%) with unknown duration of atrial fibrillation in this study.

All enrolled patients underwent electrical cardioversion. In all cases, anterior - posterior electrode positioning was used. Sinus rhythm was restored in 43 (95%) women and in 102 men (97%). The success rate after a single discharge was 87.3 %. 2 electrical shocks were required for 9.3% of patients and 3.3% of patients benefited from a third shock. Initial discharge was 150 J in 10% of all patients. In 76.7% of patients 200 J were used, 300 J were used for 6% of patients, and 360 J for 3.3% of patients.

In man group average heart rate before electrical cardioversion was 83 bpm (minimal 51; maximal 141 bpm), after mean heart rate was 61 bpm. (table 1)

Average QRS duration was the same before and after procedure, 117 ms. Differences were found in maximal and minimal ranges. Before electrical cardioversion minimal QRS complex was 84 ms, maximal 222 ms, after minimal 78 ms and maximal 209 ms.

Mean QTc interval before electrical cardioversion was 399 ms (minimal 309 ms, maximal 535 ms), after procedure average QTc interval was 454 ms (minimal 367 ms, maximal 557 ms).

Table 1. **Electrocardiographic parameters in man used amiodaron**

	Mean	Standart deviation	Minimal	Maximal
Heart rate before ECV, bpm	82	18	51	141
Heart rate after ECV, bpm	61	11	44	97
PQ interval, ms	199	38	140	360
QRS complex before ECV, ms	117	31	84	222
QRS complex after ECV, ms	117	28	78	209
QTc interval before ECV, ms	399	48	309	535
QTc interval after ECV, ms	454	41	367	557

Bpm- beats per minute; ECV – electrical cardioversion; ms-milliseconds

In women group average heart rate was 89 bpm (minimal 59 bpm, maximal 134 bpm) before procedure and after electrical cardioversion heart rate decreased till 60 bpm (minimal 36 bpm, maximal 83 bpm).

Average QRS complex duration before and after was the same 103 ms. There were differences in maximal and minimal values before and after procedure. (Table 2)

Table 2. **Electrocardiographic parameters in woman used amiodaron**

	Mean	Standart deviation	Minimal	Maximal
Heart rate before ECV, bpm	89	18	59	134
Heart rate after ECV, bpm	60	8	36	83
PQ interval, ms	190	36	83	270
QRS complex before ECV, ms	103	21	85	186
QRS complex after ECV, ms	103	20	80	170
QTc interval before ECV, ms	376	44	300	466
QTc interval after ECV, ms	448	44	366	549

Bpm- beats per minute; ECV – electrical cardioversion; ms-milliseconds

Mean QTc interval before procedure was 376 ms (minimal 300 ms, maximal 466 ms), after cardioversion mean QTc interval increased (minimal 366 ms, maximal 549 ms).

In order to compare data in patients who previously used amiodarone to patients who did not use amiodarone we used a control group of patients who did not use any antiarrhythmic drugs before electrical cardioversion.

Average heart rate before electrical cardioversion was 85 bpm (minimal 56 bpm, maximal 124 bpm) in man (n=18) without previous usage of antiarrhythmic drugs, after procedure it was 63 bpm (minimal 47 bpm, maximal 125 bpm). (Table 3)

Mean QRS complex before and after procedure was the same, 111 ms. Minimal QRS complex before ECV was 86 ms, maximal – 153 ms. After procedure minimal QRS complex duration was 93 ms, maximal 156 ms.

Average QTc interval before electrical cardioversion was 383 ms (minimal 290 ms, maximal 443 ms), after it was 436 ms (minimal 360 ms, maximal 494 ms).

Table 3. **Electrocardiographic parameters in man without usage of oral antiarrhythmics**

	Mean	Standart deviation	Minimal	Maximal
Heart rate before ECV, bpm	85	19	56	124
Heart rate after ECV, bpm	63	17	47	125
PQ interval, ms	206	36	150	280
QRS complex before ECV, ms	111	18	86	153
QRS complex after ECV, ms	111	16	93	156
QTc interval before ECV, ms	383	44	290	443
QTc interval after ECV, ms	436	33	360	494

Bpm- beats per minute; ECV – electrical cardioversion; ms-milliseconds

In woman group without previous usage of oral antiarrhythmic drugs (n=14) mean heart rate before procedure was 91 bpm (minimal 60 bpm, maximal 124 bpm), after 64 bpm (minimal 45 bpm, maximal 106 bpm). (Table 4)

Mean QRS complex was 117 ms (minimal 78 ms, maximal 197 ms) before and 113 ms (minimal 80 ms, maximal 169 ms) after electrical cardioversion.

Average QTc interval before cardioversion was 382 ms (minimal 253 ms, maximal 477 ms), after it was 437 ms (minimal 328 ms, maximal 524 ms).

Table 4. **Electrocardiographic parameters in woman without usage of oral antiarrhythmics**

	Mean	Standart deviation	Minimal	Maximal
Heart rate before ECV, bpm	91	20	60	124
Heart rate after ECV, bpm	64	13	45	106
PQ interval, ms	208	57	115	354
QRS complex before ECV, ms	117	38	78	197
QRS complex after ECV, ms	113	30	80	169
QTc interval before ECV, ms	382	65	253	477
QTc interval after ECV, ms	437	52	328	524

Bpm- beats per minute; ECV – electrical cardioversion; ms-milliseconds

Discussion

In the group of male participants with previous usage of amiodarone heart rate before and after electrical cardioversion was lower than in control group (82 bpm vs. 85 bpm, 61 bpm vs. 63 bpm). Mean QRS complex duration before and after procedure was the same in both groups. In amiodarone group QRS complex duration was longer (117 ms vs. 111 ms). Mean QTc interval in amiodarone group before cardioversion was 399 ms, in control group 383 ms. After procedure QTc interval was 454 ms in amiodarone group and 436 ms in control group. Only prolongation in QTc interval was detected in amiodarone group after electrical cardioversion. However, this prolongation is not significant. Due to definition of prolonged QTc interval it should be > 450 ms in men.

In woman group heart rate before electrical cardioversion was lower in amiodarone users (89 bpm vs. 91 bpm), the same tendency was after procedure (60 bpm vs. 64 bpm).

Average QRS complex duration before and after cardioversion was the same 103 ms, in control group before it was 117 ms, after – 113 ms.

Mean QTc in amiodarone users before electrical cardioversion was shorter than in control group (376 ms vs. 382 ms), after procedure shorter QTc was in control group (448 ms vs. 437 ms). There was no significant prolongation of QTc in all groups. Prolonged QTc interval is considered when it is more than 470 ms for woman.

There were no significant changes in electrocardiogram before and after electrical cardioversion in both group. Mean QTc interval was longer in amiodarone users group than in control group. It confirms that amiodarone prolongs QTc interval despite the short usage of this antiarrhythmic drug.

Conclusion

Amiodarone usage before electrical cardioversion is a safe and effective method to improve electrical cardioversion outcome in patients with long-standing atrial fibrillation. In this study, no significant changes in electrocardiogram in both groups were detected. Amiodarone usage prior to electrical cardioversion in patients with long lasting atrial fibrillation is safe without risk of life threatening arrhythmias.

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COMORBIDITIES IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION UNDERGOING ELECTRICAL CARDIOVERSION IN LATVIAN CARDIOLOGY CENTER

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Abstract
Key words: *Atrial fibrillation, electrical cardioversion, comorbidity, complication*
Atrial fibrillation is the most common sustained cardiac arrhytmia and it is associated with various comorbidities. This study aims to investigate the prevalence of comorbidities among patients with persistent atrial fibrillation undergoing electrical cardioversion in Latvian Cardiology Centre and compare to literature data.The study enroled 150 patients with persistent atrial fibrillation undergoing electrical cardioversion. Anamnestic data were based on interview and medical records. 45 woman and 105 man were enrolled. Average age in man group was 64 years (min.-33, max.-83), in woman – 67 years (min.-37, max.- 84). 76 (51,4%) out of enrolled patienst were smoker or with smoking in anamnesis. The most common comorbidity was found to be arterial hypertension (98.6%), grade 1 in 29,1%, grade 2 in 66.2%, grade 3 in 2.6%, heart failure 91 % and diabetes 17,2%. Old myocardial infarction is a bit less common (15.2%), COPD in 7,9%, stroke in 6,6% and sleep apnoe in 7,6%. Thyroid gland diseases were rare comorbidities in this study. Hyperthyroidism was found in 3,3% and hipothyroidism in 6,0%. The prevalence of arterial hypertension and heart failure in this study were higer than in literature data. Frequency of arterial hypertension in this study was 98% and in literature prevalence varies from 49% to 90%, heart failure – 91% vs 6-35%. Diabetes (17.2% vs 14-20%). and myocardial infarction (15,2% vs 15-20%) prevalence in this study was similar to another paper . Stroke was less common comorbidity in this study (6,6% vs 15-20%) . The occurrence of co-morbidities is similar with the data in other papers, except for arterial hypertension and heart failure, which is significantly higher in this study. Thromboembolic events and COPD in previous anamnesis were found less often compared to similar trials.

Kopsavilkums
Ātriju fibrilācija ir visplašāk izplatītais aritmijas veids, kas saistīts ar dažādām blakussaslimšanām. Dotā pētījuma mērķis bija noteikt blakussaslimšanu prevalenci pacientiem ar persistējošu ātriju fibrilāciju, kam sinusa ritma atjaunošanai tika veikta elektriskā kardioversijas Latvijas Kardioloģijas centrā un salīdzināt ar literatūras datiem. Pētījumā tika iekļauti 150 pacienti (45 sievietes un 105 vīrieši) ar persistējošo ātriju fibrilāciju pirms sinusa ritma atjaunošanas ar elektrisko kardioversiju. Anamēzes dati tika iegūti izmantojot pacientu aptaujas anketas un medicīnisku dokumentāciju. Iekļauto pacientu vidējais vecums vīriešu grupā bija 64 gadi (min. 33, maks. 83 gadi), sieviešu grupā 67 gadi (min.37, maks. 84 gadi). 76 (51,4%) pacienti bija smēķētāji. Dotajā pētījumā visbiežāk sastopama blakussaslimšana bija arteriāla hipertensija (AH) (98,6%), no tiem 1.pakāpe tika konsatēta 29,1%, 2.pakāpe 66,2%, 3. pakāpe 2,6%. Hroniska sirds mazspēja (HSM) tika konstatēta 91% pacientu, cukura diabēts (CD) 17.2%. Vecs miokarda infarkts (MI) bija 15,2%, HOPS 7,9%, cerbrāls infarkts 6,6% un obstruktīva miega apnoja 7,6%. Vairogdziedzera slimības bija starp retāk sastopamājām blakussaslimšanām. Hipotireoze bija 3,3% un hipertireoze 6,0% pacientu. AH un HSM sastopamība šajā pētījumā bija augstāka salīdzinot ar literatūras datiem. AH dotajā pētījumā tika konstatēta 98% pacientu, literātūra AH prevalence svārstās no 49% līdz 90%, HSM – 91% pret 6-35%. CD (17,2% pret 14-20%) un MI (15,2% pret 15-20%) prevalence šajā pētījumā bija līdzīgu citu pētījumu rezultātiem. Cerebrālie infarkti tika konstatēti retāk (6,6% pret 15-20%). Blakussaslimšanu prevalence dotajā pētījumā bija līdzīga literatūras datiem, izņemot AH un HSM, to prevalence bija lielāka. Savukārt trombembolijas un HOPS tika konstatētas retāk nekā citos līdzīgos pētījumos.

Introduction

Atrial fibrillation is the most common type of arrhythmia affecting up to 10% of the population over 60 years of age, increasing in prevalence with rising age. It is characterized by uncoordinated atrial activation that can lead to embolic complications and reduction in cardiac output resulting in significant morbidity, mortality and impaired quality of life. Atrial fibrillation is associated with a 1.5 to 1.9 fold higher risk of death. (Lakshminarayan 2006: 1969)

Atrial fibrillation has strong associations with other cardiovascular diseases, such as heart failure, coronary artery disease, valvular heart disease, diabetes mellitus and hypertension. It may be connected to several of life-threatening complications, like cerebrovascular events and systemic embolism.

In order to avoid complications and reduce symptoms, atrial fibrillation can be converted, restoring normal heart rhythm, by using drugs or a controlled electrical shock. Patients with long-acting atrial fibrillation with unknown duration can be converted into sinus rhythm only by electrical cardioversion. The American College of Chest Physicians strongly recommends anticoagulation with warfarin (target INR 2 to 3) or new oral anticoagulants for at least 3 weeks before elective cardioversion if atrial fibrillation has been present for more than 48 hours or for an unknown amount of time.

Aim of the Article

The study aims to determine the prevalence of co-morbidities among patients with persistent or long-lasting atrial fibrillation undergoing electrical cardioversion in Latvian Cardiology Center and to compare these results to literature data.

Material and Methods

In this prospective study 150 patients were enrolled in 2016 with persistent atrial fibrillation undergoing electrical cardioversion in Paul Stradins Clinical University Hospital, Department of Arrhythmology**.** All patients received treatment with anticoagulants prior to electrical cardioversion. Anamnestic data was based on interviews and medical records. Following co-morbidities were included in the questionnaire: arterial hypertension, diabetes mellitus, valvular heart disease, stroke, transient ischemic attack, heart failure, cardiomyopathy, hypothyroidism and hyperthyroidism, chronic obstructive pulmonary disease, asthma and pulmonary embolism.

Chronic kidney disease stage was detected using results of biochemical analysis.

Interview included also questions about anticoagulants used before electrical cardioversion.

Results

Participants were predominantly men (105 of 150; 70%) with a mean age of 64 years (min.-33, max.-83); 45 were women (30%). Average age in women was 67 years (min.-37, max.-84). Mean body mass index in women group 31,42 kg/ m^2 (minimum 22,5 kg/ m^2, maximum 48.6 kg/ m^2, SD 6), in men group 29,6 kg/ m^2 (minimum 21,3 kg/ m^2, maximum 42,4 kg/ m^2, SD 4,4). 76 (51,4%) patients (6 women, 70 men) were smokers.

According to the guidelines, all patients with persistent form of atrial fibrillation and long-acting paroxysm should use anticoagulants at least three weeks before sinus rhythm restoration with electrical cardioversion. Before electrical cardioversion 43 (28.5%) patients used warfarin, 43

(28.5%) dabigatran, 61 (40.4%) rivaroxaban, 4 (2.7%) patients received low molecular weight heparins (fraxiparine).

All patients enrolled underwent electrical cardioversion. In all cases anterior - posterior electrode positioning was used. Sinus rhythm was restored in 43 (95%) women and in 102 men (97%). The success rate after a single discharge was 87.3 %. 2 electrical shocks were required for 9.3% of patients and 3.3% of patients benefited from a third shock. Initial discharge was 150 J in 10% of all patients. In 76.7% of patients 200 J were used, 300 J were used for 6% of patients, and 360 J for 3.3% of patients.

The most common co-morbidity in this study was arterial hypertension. 148 (98.6%) of 150 patients had arterial hypertension in previous anamnesis, 45 in women and 103 in men group. 16 (36 %) women had stage 1, 28 (61 %) had stage 2, only 1 woman had a stage 3. 72 (70%) men had stage 1, stage 2 was found in 28 (27%), 3 (2.9%) patients in men group had a stage 3. (Figure 1.)

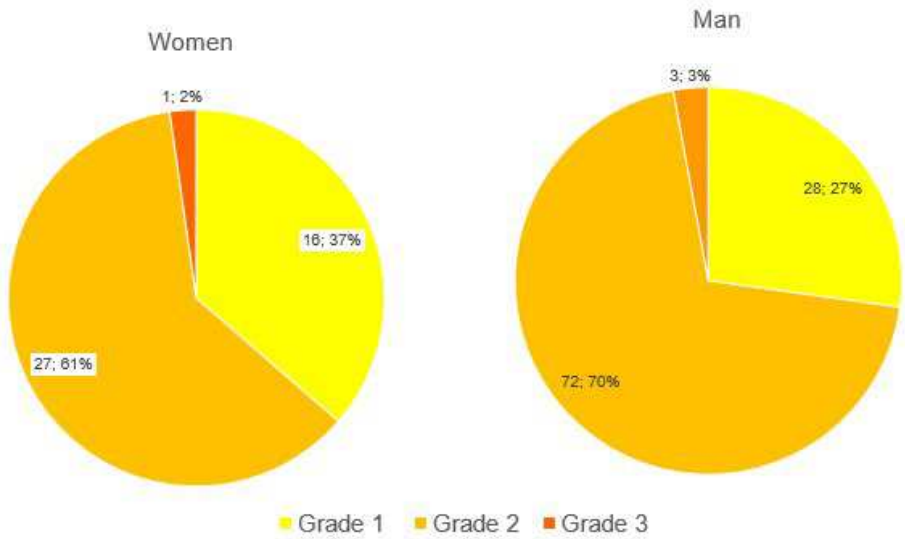

Figure 1. **Grades of arterial hypertension**

Hypertension is frequently seen in patients with atrial fibrillation during major clinical trials. In particular, it was found in 49–90% of individuals in atrial fibrillation trials. (Manolisa 2012: 240)

Chronic heart failure is also a frequent co-morbidity in atrial fibrillation. The simultaneous presence of these two conditions is common. In this study, heart failure was found in 41 (91%) women and 96 (91%) men. The prevalence of heart failure in this study population was very high. Diagnostics criteria were based on clinical features and patient's complaints. Brain natriuretic peptide and echocardiographic data were not evaluated. In comparison, the prevalence of atrial fibrillation in patients with systolic left ventricular dysfunction and chronic heart failure in literature ranges from 6% for asymptomatic patients or patients with minimal symptoms, to 15% - 35% for patients with New York Heart Association (NYHA) class II–IV symptoms.

8 (17%) women and 18 (17.4%) men enrolled in this study suffered from diabetes. Diabetes mellitus is one of the most common concomitant diseases in patients with atrial fibrillation. A multivariate analysis showed that diabetes is independently associated with atrial fibrillation. In literature, diabetes prevalence in patients with atrial fibrillation varies from 14% till 20%. (Murphy 2007: 609)

COPD is an independent risk factor for arrhythmias, especially atrial fibrillation, and cardiovascular morbidity and mortality. (Camm 2010: 2371) Patients with COPD have a 4.41 times higher risk of atrial fibrillation and COPD is present in 10-15% of patients with atrial fibrillation. Decreased pulmonary function is an independent risk factor of atrial fibrillation. (Sidney 2005: 2067) In this study only in 8% (6 men, 6 women) of all enrolled patients COPD was detected in previous anamnesis.

Obstructive sleep apnea (OSA) was a rare co-morbidity in this study, it was found only in 10 men (7.6%). The Sleep Heart Health Study reported a 4-fold higher prevalence of atrial fibrillation in obstructive sleep apnea patients. The risk of atrial fibrillation increases with the severity of OSA. In addition, OSA is more prevalent among patients with AF than in general population. A prospective study reported a strong association between these two conditions. (Gami 2004: 366)

Patients with chronic kidney disease are more likely to develop atrial fibrillation. The prevalence of atrial fibrillation in patients with moderate chronic kidney disease and hemodialysis patients is 10 to 15 times higher as compared to age matched general population. The incidence of atrial fibrillation increases as renal function decreases. In addition, chronic kidney disease is found in nearly 10-15% of atrial fibrillation patients, and atrial fibrillation is associated with increased risk of developing chronic kidney disease. (Watanabe 2009: 632) Normal kidney function or stage 1 was detected in 35 patients (25%), stage 2 in 80 participants (56%), stage 3 in 26 patients (18%), and stage 4 in 2 patients (1%). (Figure 2)

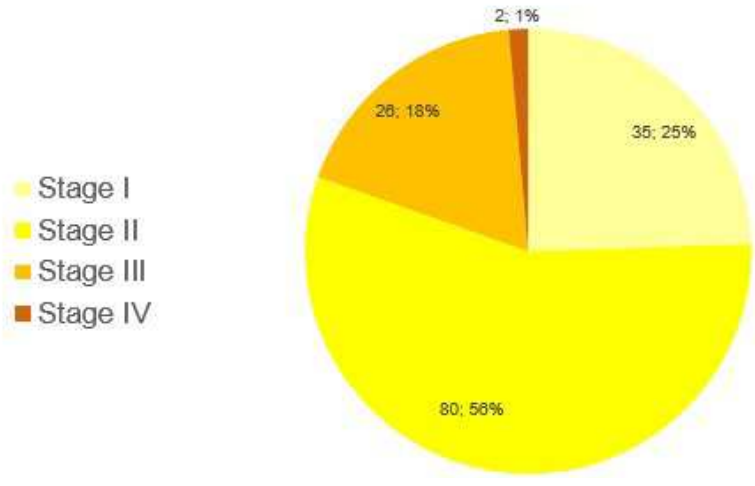

Figure 2. **Stages of chronic kidney disease**

Many studies have shown that atrial fibrillation is an independent risk factor for stroke and thromboembolic events. Atrial fibrillation is responsible for 15–20% of all ischemic strokes, increases the risk of stroke four-fold to five-fold, and is an independent risk factor for ischemic stroke severity and recurrence. Stroke and transient ischemic attack was not a frequent complication of atrial fibrillation in this study. Only 6 men (4%) and 4 women (8.8%) suffered from this complication in previous anamnesis. Three patients (2%) had pulmonary embolism in medical history.

Atrial fibrillation is an independent risk factor for myocardial infarction. The relationship between atrial fibrillation and myocardial infarction is bidirectional: each can cause the other, and both conditions probably have similar underlying pathophysiologic mechanisms. Previous myocardial infarction was found in 5 women (11%) and 18 men (17%). Atrial fibrillation often complicates acute myocardial infarction with an incidence of 6 to 21%. (Schmitt 2009: 1037)

Low serum thyrotropin concentration is an independent risk factor for atrial fibrillation. Atrial fibrillation occurs in 10 - 15% of patients with hyperthyroidism. (Jayaprasad 2005: 305).

Thyroid gland diseases were rare co-morbidities in this study. Hyperthyroidism was found in 3.3% and hypothyroidism in 6.0%.

Discussion

The most common co-morbidity in this study was arterial hypertension. The incidence of arterial hypertension (98%) is higher than in other trials where it was found in 49–90% of individuals. Additionally, heart failure was found more frequently than in similar studies. The prevalence of heart failure varies from 6% to 35% in another research compared to 91% in this study. Perceptible difference in heart failure incidence can be explained with diagnostics particularities. Diagnostics criteria were based on clinical features and patient’s complaints in this study. Brain natriuretic peptide and echocardiographic data were not evaluated.

Similar prevalence was found in diabetes mellitus which is one of the most common concomitant diseases in patients with atrial fibrillation. In this study 17% suffered from diabetes, in literature numbers range from 14 to 20%.

COPD was an uncommon co-morbidity in this study. It was found in 8% of all enrolled patients. Literature data has shown that COPD is present in 10-15% of patients with atrial fibrillation.

Thromboembolic complications were no common co-morbidity in this study. Only 4% of men and 8.8% of women had this complication in previous anamnesis. Similar studies have shown higher prevalence from 15% to 20%.

Conclusions

The occurrence of co-morbidities is similar with the data in other papers, except for arterial hypertension and heart failure, which is significantly higher in this study. Thromboembolic events and COPD in previous anamnesis were found less often compared to similar trials.

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THE INFLUENCE OF CD4+ CELL COUNT AND CD4+/CD8+ CELL RATIO ON THE RADIOLOGICAL DIAGNOSTICS OF OPPORTUNISTIC CENTRAL NERVOUS SYSTEM INFECTIONS IN HIV PATIENTS

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Abstract

The Influence of CD4+ Cell Count and CD4+/CD8+ Cell Ratio on the Radiological Diagnostics of Opportunistic Central Nervous System Infections in HIV Patients

Key words: *HIV, CD4+ cell count, CD4+/CD8+ ratio, radiology*

Introduction: HIV-related opportunistic infections of the central nervous system (CNS) are a significant threat to the health of the affected patients. In case of doubt, radiological findings can help to confirm or deny the diagnosis.

Aim: To evaluate the impact of CD4+ cell count and CD4+/CD8+ ratio on the radiological diagnostics of opportunistic CNS infections.

Materials and methods: A retrospective study of the CD4+ cell count, CD4+/CD8+ ratio and the radiological findings of HIV patients at the time of diagnosing an opportunistic CNS infection. The frequency of the radiological symptoms of the encountered infections, previously identified in literature, was compared to the laboratory measurements.

Results: The mean CD4+ cell count and CD4+/CD8+ ratio values were respectively: 104,03 cells(c.)/ml and 0,185. As the CD4+ cell count decreased below 200 c./ml the frequency of radiological symptoms increased for both computed tomography (CT) and magnetic resonance imaging (MRI). The CD4+/CD8+ ratio below 0,1 was shown to be connected with increased findings on MRI in the majority of encountered infections, except for PML, in which for both MRI and CT the ratio above 0,1 was prognostic of a more distinct radiologic symptomatology.

Conclusion: The decrease of CD4+ cell count and the CD4+/CD8+ ratio is connected to an increase of radiological findings. The radiological symptoms of PML are seen more frequent at higher CD4+/CD8+ ratios as opposed to the other CNS infections encountered in this study.

Kopsavilkums

CD4+ šūnu skaita un CD4+/CD8+ šūnu indeksa ietekme uz centrālās nervu sistēmas oportūnistisko infekciju radioloģisko diagnostiku HIV pacientiem

Atslēgas vārdi: *HIV, CD4+ šūnu skaits, CD4+/CD8+ šūnu indekss, radioloģija*

Ievads: Ar HIV saistītās centrālās nervu sistēmas (CNS) infekcijas rada nopietnus draudus skarto pacientu veselībai. Neskaidros gadījumos, radioloģiskā diagnostika var palīdzēt apstiprināt diagnozi.

Mērķis: Izvērtēt CD4+ šūnu skaita un CD4+/CD8+ šūnu indeksa ietekmi uz CNS oportūnistisko infekciju radioloģisko diagnostiku.

Materiāli un metodes: Šī ir retrospektīva HIV pacientu CD4+ šūnu skaita, CD4+/CD8+ šūnu indeksa un radioloģiskās atradnes analīze laikā, kad tiek diagnosticēta kāda CNS oportūnistiska infekcija. Radioloģisko simptomu, kuri tika identificēti literatūrā, biežums tika salīdzināts ar laboratorajiem rādītājiem.

Rezultāti: Vidējais CD4+ šūnu skaits bija 104,03 šūnas/ml un vidējā CD4+/CD8+ šūnu indeksa vērtība – 0,185. CD4+ šūnu skaitam samazinoties zem 200 š./ml, radioloģisko simptomu biežums pieaug gan kompjūtertomogrāfijā (CT), gan magnētiskajā rezonansē (MR). Šūnu indeksa vērtība zem 0,1 lielākajā daļā aplūkoto infekciju bija saistīta ar paaugstinātu radioloģisko simptomu biežumu. Pretēja saistība redzama PML gadījumā – vairāk radioloģisko simptomu redzami pie šūnu indeksa virs 0,1.

Secinājumi: CD4+ šūnu skaita un CD4+/CD8+ šūnu indeksa samazināšanās ir saistīta ar biežāku radioloģisko atradni. PML gadījumā radioloģiskie simptomi ir redzami biežāk pie šūnu indeksa vērtībām virss 0,1.

Introduction

Today, human immunodeficiency virus (HIV) remains a widespread global infection and, in spite of the efforts of the World Health Organisation and other international organisations, the incidence of this infection remains high or even increases in many regions. (UNAIDS 2016) And also in Latvia, the amount of new HIV infections has been slowly increasing up until 2015 (Slimību profilakses un kontroles centrs 2017), when Latvia had the second highest count of new HIV

infections (19,8 cases per 100’000 inhabitants) and the highest count of new cases of acquired immune deficiency syndrome (AIDS) (6,6 cases per 100’000) in the European Union and European Economical Zone. (European Centre for Disease Prevention and Control 2016)

The pathogenetic basis of the HIV and AIDS is the viruses’ affinity for the immune system’s lymphocytes which express the CD4 molecule on their surface together with either CCR5 or CXCR4 co-receptors, which are used by the virus to attach to and enter the cell. An example of such cells is T helper lymphocytes. (Harrison, 2015) These co-receptors can be found on various cells of the immune system – CCR5 is the main co-receptor for infecting macrophages, and CXCR4 – T lymphocytes. (Ances 2007) The main function of a T helper lymphocyte is mainly regulatory – via different cytokines they activate other T and B lymphocytes, as well as monocytes. (Harrison 2015) More than one mechanism which results in disrupted T helper cell function and therefore both the cellular and humoral immunity has been identified in the case of HIV infection: direct destruction of the T helper cells by the virus, the destruction of infected cells as an immune reaction and also cell death and exhaustion, caused by incorrect activation of the immune system. This negative effect on the imune system is believed to be the main cause of opportunistic infections that can be seen in HIV patients as the CD4+ T cell count decreases. (Harrison 2015) Other illneses that are characteristic for AIDS, for example, Kaposi sarcoma and lymphomas, can also partially be explained by the weakening of cellular immunity. A defect in a specific subtype of CD4+ cells, Th17 cells, causes the decrease of mucosal immunity, particularly in the gastrointestinal tract, which increases the odds of bacteria of intestinal origin spreading in the bloodstream. (Levinson 2016)

In the case of the CNS examples of these opportunistic infections are CNS toxoplasmosis, progressive multifocal leucoencephalopathy (PML), cryptococcal meningitis e.t.c. (Tan 2012). And although since the start of the era of highly active antiretroviral therapy the incidence of these infections has decreased significantly, the rate of lethal outcomes or permanent damage remains high. (CHIC 2010)

The majority of these infections have a set of radiological findings, that allows them to be diagnosed using a radiological method (for example, CT or MRI) combined with the clinical and laboratory findings.

Considering the potentially severe consequences of these infections and the fact, that most of them are treatable, appropriate diagnostics of these infections is very important. And even though a great part of the diagnostic process is based on clinical and laboratory findings, the possibility of confirming the diagnosis, when the aforementioned findings are not conclusive, can help to start appropriate treatment on time.

Methods and Materials

This study is a retrospective analysis, including data about 27 patients that were investigated at Riga East Clinical Hospitals ‘’Gaiļezers’’ and ‘’Latvijas Onkoloģijas centrs’’ in the period between January 1st, 2013 and October 19th, 2016. The mean age of the patients at the time of establishing a diagnosis was 42,33 years. The distribution between men and women was respectively 74,1% and 25,9%. The patients had been clinically and in a part of the cases, laboratorically diagnosed with a CNS infection on 37 occasions. Of these infections, the most common ones were cerebral toxoplasmosis (13 cases) and PML (12 cases). Other infections, that were diagnosed, included meningitis, encephalitis, neurosyphiliss and others, but these infections occurred relatively rarely – 1 to 3 cases per diagnosis.

Only the CT and MRI investigations, that were done before diagnosing an opportunistic infection, were analysed. A radiological symptom was considered as recognized, if they were mentioned in the appropriate diagnostic-radiologist’s conclusion about the examination. Investigations in both modalities were done according to the default protocol of Riga East Clinical University Hospital.

In addition to the radiological findings, data about the patients’ CD4+ cell count and CD4+/CD8+ cell ratio (not available in one case) at the moment of establishing the diagnosis of a CNS opportunistic infection was analysed.

To evaluate the influence of CD4+ cell count and the CD4+/CD8+ cell ratio on the radiological findings, the frequence of the symptoms was analysed at different values of the desired laboratory test.

Results

For 10 patients (37%) the CNS infection was the first HIV opportunistic infection that had caused admission to the hospital. 6 patients (22,2%) CNS infection was also the only opportunistic infection at the time. As mentioned before, in total there were 37 cases of CNS infection diagnosed, as several patients had simultaneously two infections and there were also relapses of infection. The two most common infections were cerebral toxoplasmosis and PML with 13 and 12 cases respectively. Full distribution of diagnoses can be seen in Figure 1.

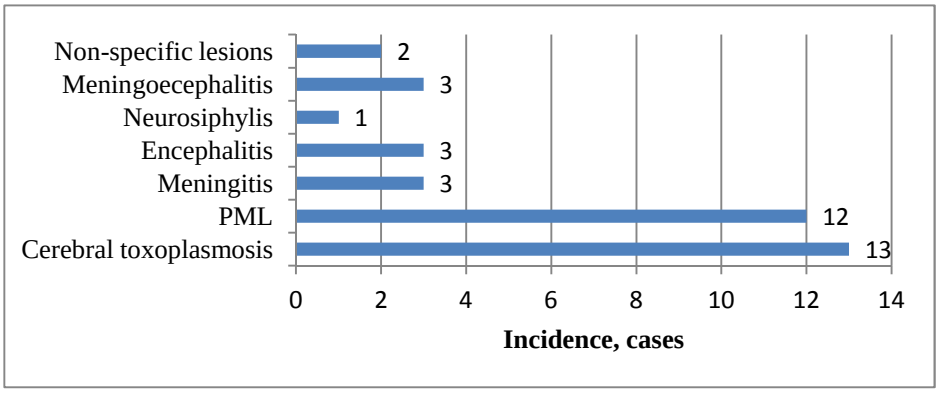

Figure 6**. Diagnoses by incidence**

The radiological symptoms characteristic to the encountered infections were identified in world literature. Originally, 11 symptoms in total were selected for native CT and MRI examinations and 4 symptoms for both modalities using a contrasting agent. From the selected, 2 symptoms in CT – symmetric atrophy and symmetrical hypodense lesions and 1 symptom in MRI – T1 asymmetric hypointense lesions were not noted in any of the infection cases. The most common symptom in CT was hypodense lesions (in 29,7% cases) which corresponds to cerebral toxoplasmosis (Smith 2008). In MRI the most common symptom was T2 asymmetric hyperintense lesions (37,8%), characteristic to PML (Osborn, 2010), followed by T2 hyperintense lesions (32,4%) and ring-like contrast enchancement (29,7%) which are attributed to cerebral toxoplasmosis (Smith 2008). The complete list of sypmtoms and their incidence are seen in Table 1.

Table 5. **Incidence of radiological symptoms**

	Number of cases	% of infection cases
CT hypodense lesion	11	29,7%
CT mass effect	4	10,8%
CT asymmetric hypodense lesions	3	8,1%
CT examination not done	24	64,9%
CT no contrast enhancement	12	32,4%
CT other type contrast enhancement	1	2,7%
MRI T2 hyperintense lesions	12	32,4%
MRI T1 hypointense lesions	2	5,4%
MRI perilesional oedema	10	27,0%
MRI T2 asymmetric hyperintense lesions	14	37,8%
MRI T2 symmetric hyperintense lesions	5	13,5%
MRI No contrast enhacement	14	37,8%
MRI contrast ring enhancement	11	29,7%
MRI contrast meningeal enhancement	3	8,1%
MRI contrast other type enhancement	9	24,3%

Nowadays, the two main systems for classifying HIV and AIDS used are the CDC (Centers for Disease Control and Prevention) classification system and the World Health Organisation Clinical Staging and Disease Classification System. The later is better suited for use in resource-constrained settings, seeing it does not rely on CD4+ cell count and other diagnostic and laboratory findings. The CDC system was last revised in 1993 and is based on the CD4+ cell count (categories 1-3) and the classification of opportunistic diseases (categories A,B,C). The diseases are dividend in Category B Conditions and Category C or AIDS-Indicator Conditions. Category C includes the infections most common in this study – cerebral toxoplasmosis and PML, as well as HIV encephalitis (Coffey 2014).

In both CT and MRI more characteristic radiological symptoms were seen at lower CD4+ cell count values, as seen in Figures 2 and 3. It can be explained by the fact that as the CD4+ cell count decreases, the immune system weakens, which allows infections to progress to more severe forms and therefore makes them easier to recognize radiologically. The CD4+ cell counts were dividend in 3 groups (0 to 50, 50 to 200 and above 200 c./mm^3) so as to better demonstrate the correlation between radiological findings and the decrease of the cell count. As it can be seen, in both radiological modalities the decrease of CD4+ cell count below 200 c./ mm^3 is connected to an increase of radiological findings. And for even more so for MRI, where the cases with the cell count below 50 c./ mm^3 contain a relative majority of all symptoms.

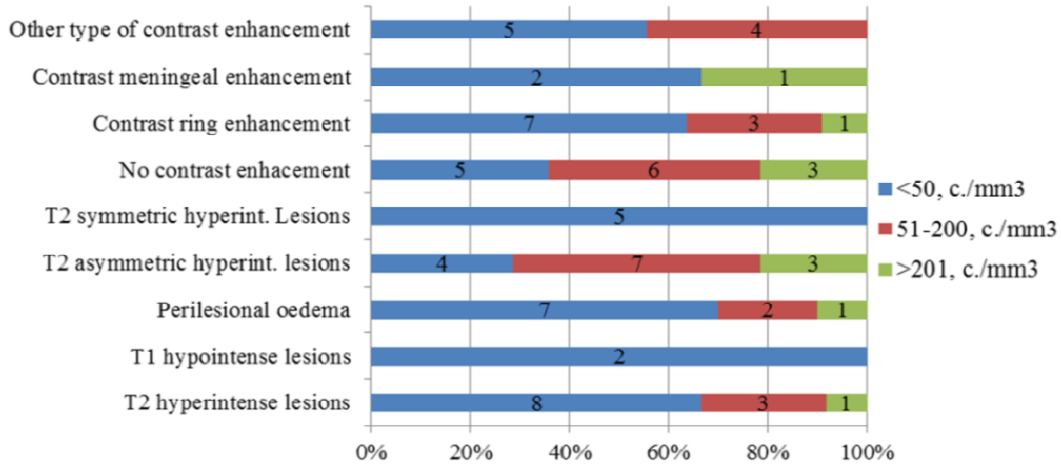

Figure 7. **MRI findings in relation to CD4+ cell count**

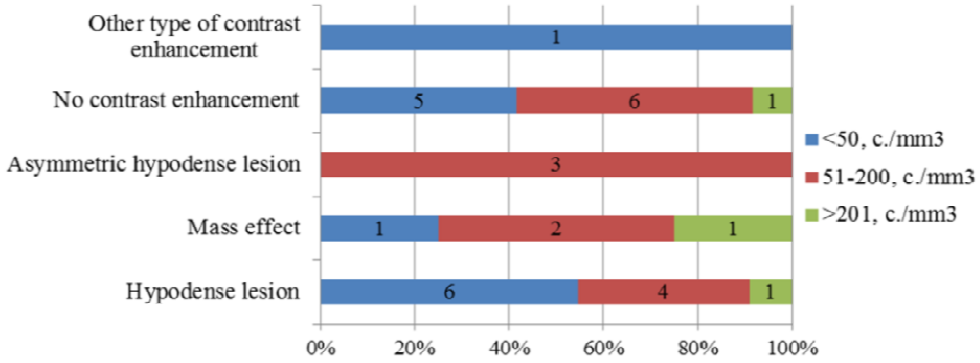

Figure 8. **CT findings in relation to CD4+ cell count**

In normal population, a CD4+/CD8+ cell ratio below 1 is considered to be an indicator of agingof the immune system and also an independant prognostic factor for mortality in seniors (Hadrup 2006). Historically, this parameter has been thought to represent the probability for the HIV infection to progress to AIDS stage, but the CD4+ cell count is considered to be more important (Lu, 2015). The results of several studies have shown that in HIV patients receiving

highly-active antiretroviral therapy, lower CD4+/CD8+ cell ratio is an indicator of higher risk of death from AIDS-unrelated causes (Lu 2015; Serrano-Villar 2013).

In the case of CD4+/CD8+ cell ratio, two distinct trends can be established for MRI – in most infection cases, a cell ratio value below 0,1 was prognostic of a more marked radiological picture. However, in the case of 2 symptoms ‘’T2 asymmetric lesions’’ and ‘’No contrast enchancement’’ which are both characteristic for PML (Osborn, 2010), the tendency was oposite – these symptoms were seen mostly when the cell ratio was above 0,1.

For CT, more radiological signs were recognised when the CD4+/CD8+ cell ratio was above 0,1 in the majority of infection cases, including, asymmetric hypodense lesions, which are also characteristic to PML (Smith 2008). For further detail, see Figures 4 and 5.

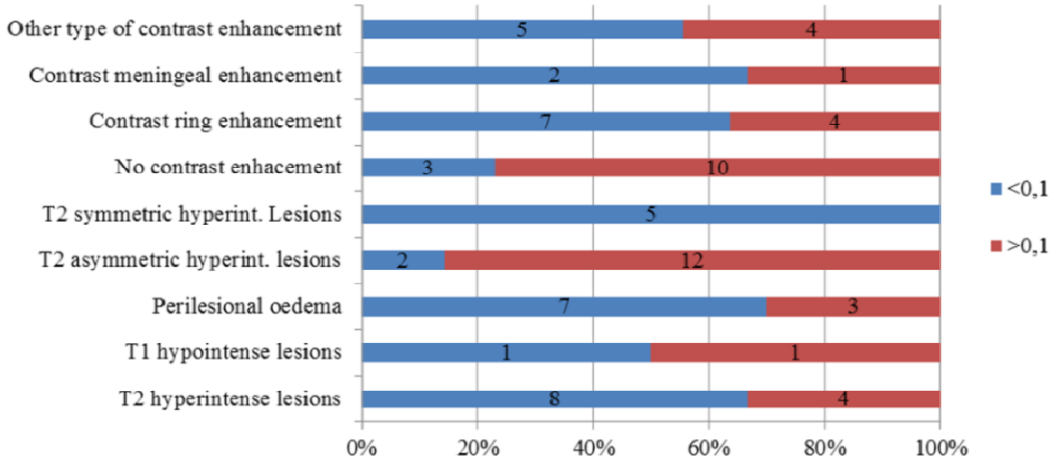

Figure 9. **MRI findings in relation to CD4+/CD8+ ratio**

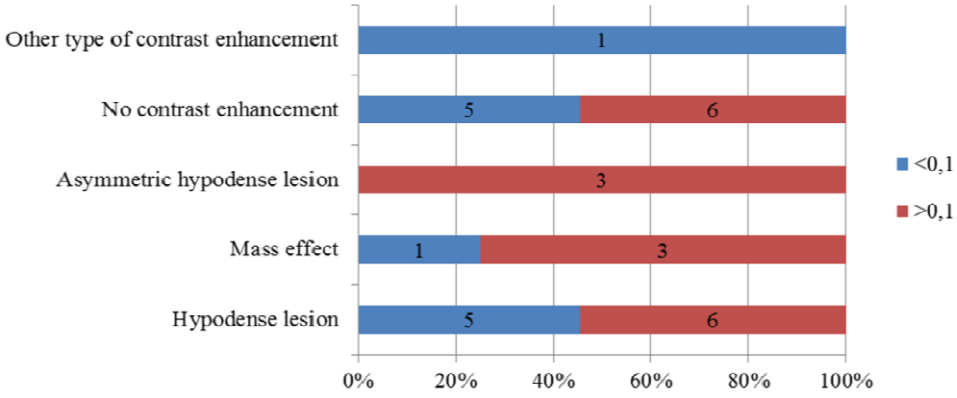

Figure 10. **CT findings in relation to CD4+/CD8+ cell ratio**

Discussion

The most common opportunistic infections of the CNS, as seen in literature, were cerebral toxoplasmosis, PML, CNS tuberculosis, criptococcosis, citomegalovirus infection and HIV encephalopathy. The most common infections of the patients included in this study were also

cerbral toxoplasmosis and PML, as well as a few patients with HIV encephalopathy, but no patients with CNS tuberculosis, criptococcosis or citomegalovirus infection were identified.

There is a wide variety of radiological findings described in literature as characteristic for certain CNS infections, but of those described radiological findings, only a part were seen in this study regularly, while others were seen rarely or not seen at all. For example, from the radiological symptoms selected from literature, 2 symptoms for CT – symmetric atrophy and symmetrical hypodense lesions and 1 symptom in MRI – T1 asymmetric hypointense lesions were not recognized at all. In another example, in CNS toxoplasmosis, small hemorrhages, which are described as one of the main signs that help distinguish it from a lymphoma (Offiah 2006), are not seen either. These discrepancies can be most likely explained with the small patient count, which limits the possibility of examining the patient at different stages of the infection, which could manifest with different radiological symptoms.

This study revealed a yet not reported correlation between CD4+/CD8+ cell ratio value above 0,1 and more distinct radiological findings in patients with PML. It could be caused by a possibly different course of the disease, depending on the state of celular immunity, but to establish and clarify this connection more studies aimed specifically at this association.

Conclusions

The two most common oppportunistic CNS infections in Latvia are cerebral toxoplasmosis and progresive multifocal leucoencephalopathy. The decrease of CD4+ cell count below 200 c./mm^3 increases the chances of an infection to be radiologicaly recognizable in both modalities. The decrease of this cell count below 50 c./mm^3 increase this chance even more for MRI investigations. A CD4+/CD8+ cell ratio below 0,1 increases the frequency of radiological findings in MRI in most infections seen in this study. However, in the case of PML the cell ratio above 0,1 is associated with a higher chance of radiological findings in both CT and MRI.

Picture 6 displays a clinical case containing characteristic radiological findings of both PML and cerebral toxoplasmosis. A brief clinical history of the patient – a 38 year old female, that was admitted after loss of consciousness and a generalised seizure. Patient notes fatigue, sweating and subfebrile temperature for the past 2 months. Neurological symptoms, like dysphasia, depression, agitation, continue while stationed. Laboratory tests do not identify any opportunistic infectious agents, but after anti-toxoplasmotic treatment is started there is significant clinical improvement. HIV RNA – 9,28 E^5, CD4+ cell count – 125 c./mm^3, CD4+/CD8+ cell ratio – 0.49. Note the asymmetrical character of the diffuse lesion as seen in both modalities.

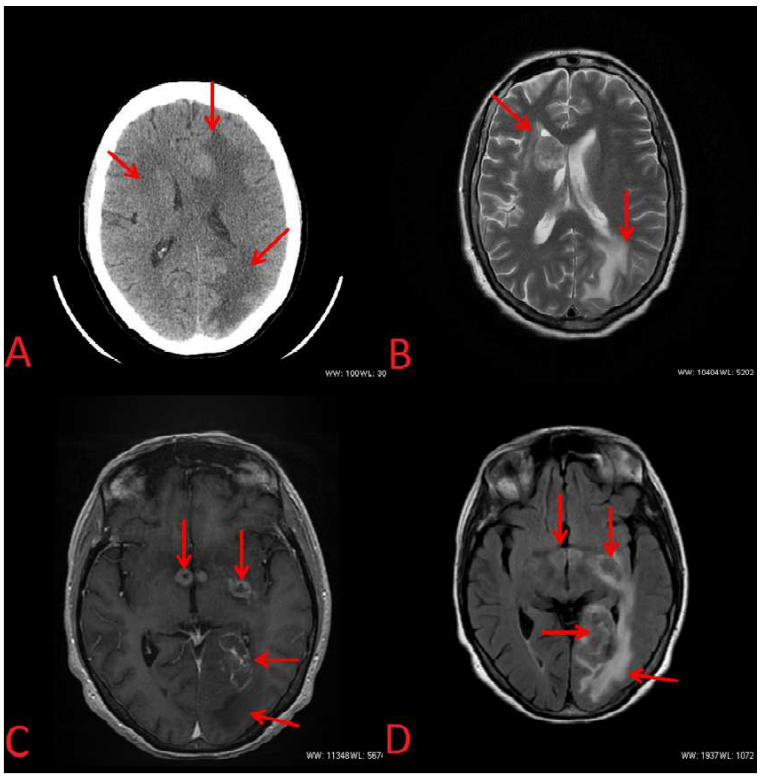

Figure 12. **Clinical case of a 38 years old female, diagnosed with both cerebral toxoplasmosis and PML. Picture contains the patient's CT and MRI images: A – axial CT image shows wide hypodense regions in the left hemisphere, as well as a slight hypodensity in the right frontal lobe. B – MRI T2 weighted image shows a non-homogenous hyperintense lesion with perileasional oedema at the anterior horn of the right lateral ventricle, but in the left occipital lobe a diffusive hyperintense region. C is a T1 weighted image with contrast administration (gadolinium 0,1mmol/kg) showing multiple hypointense lesions that show ring-like contrast enchancement. A diffusive hypointense region can also be seen in the right occipital lobe. D – a T2 FLAIR image showing multiple non-homogenous hyperintense lesions corresponding to the locations of lesions in Part C. Also – a diffusive hyperintense region in the right occipital lobe.**

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USED TREATMENT TACTICS IN NEWBORNS WITH NECROTIZING ENTEROCOLITIS IN TWO DIFFERENT TIME PERIODS: SINGLE CENTRE EXPERIENCE

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Abstract

Used treatment tactics in newborns with necrotizing enterocolitis in two different time periods: Single centre experience

Key words: *necrotizing enterocolitis, newborns, demographics, treatment, mortality*

Necrotizing enterocolitis (NEC) is the necrosis of the small and large bowel, that affects mainly preterm infants. NEC is the most common surgical emergency in newborns ~2:1000. Surgical intervention is used only for advanced cases, but there is still no sufficient data on which treatment tactic has an advantage. Study's aim was to describe the difference in NEC patient demographics, evaluate used treatment tactics and their impact on mortality reduction in newborns. A retrospective study was conducted analysing 195 newborns with NEC. Patients were divided into two groups according to time period of treatment – group 1 - 2006–2010 (n=128) vs group 2 - 2011-2015 (n= 67). Demographic data, used treatment options and mortality was compared between the groups. There was a 47.7 % decrease in NEC patient cases between group 1 and group 2. Surgical treatment was used for 28 patients (21.9%) in group 1 and 18 patients (26.9%) in group 2. No difference was found in used treatment options between both groups regarding conservative treatment 78,1% vs 73,1% (p=0.436), peritoneal drainage (PD) 7,3% vs 3% (p=0.183), laparotomy 8,6% vs 16,4% (p=0.101) and combined therapy of peritoneal drainage and laparotomy – 5,5% vs 4,5% (p=0.766). There was a tendency for drop of mortality in group 2 (30% vs 21%), but statistically insignificant (p=0.154). When evaluating efficacy of treatment options based on patient mortality between groups, only conservative treatment showed a significant improvement in group 2 (27% vs 10.2%, p=0.019). In conclusion, during past five years there has been a significant drop in cases of NEC with significantly more preterm and underweight newborns being affected, yet with a slight decline of mortality. Treatment tactics have not changed, but there is a significant increase in conservative treatment efficiency.

Kopsavilkums

Izmantotā ārstēšanas taktika jaundzimušajiem ar nekrotizējošu enterokolītu divos dažādos laika periodos: Viena centra pieredze

Atslēgvārdi: *nekrotizējošs enterokolīts, jaundzimušie, demogrāfija, ārstēšana, mortalitāte*

Nekrotizējošs enterokolīts (NEC) ir tievo un resno zarnu nekroze, kas skar galvenokārt priekšlaikus dzimušos. NEC ir biežākā neatliekamā ķirurģiskā patoloģija jaundzimušajiem ar incidenti aptuveni 2:1000. Ķirurģiskā iejaukšanās tiek izmantota tikai advancētos gadījumos, bet vēl nav pietiekamu datu, kas parādītu, kurai ārstēšanas metodei ir priekšroka. Pētījuma mērķis bija aprakstīt atšķirības demogrāfijā, izvērtēt izmantotās ārstēšanas metodes un to ietekmi uz mirstības rādītājiem pacientiem ar NEC. Tika veikts retrospektīvs pētījums, kurā tika iekļauti 195 jaundzimušie ar NEC. Pacienti tika iedalīti divās grupās atkarībā no ārstēšanās laika: 1. grupā – 2006 – 2010 (n=128) vs. 2. grupa – 2011-2015 (n=67). Demogrāfiskie dati, pielietotā ārstēšanas metode un mortalitāte tika salīdzināta starp grupām. Otrajā grupā bija 47.7% samazinājums gadījumu skaitā salīdzinot ar 1. grupu. Ķirurģiskā ārstēšana tika pielietota 28 pacientiem (21.9%) 1. grupā un 18 pacientiem (26.9%) 2. grupā. Nebija novērota atšķirība pielietoto ārstēšanas metožu izvēlē starp abiem laika periodiem attiecībā uz konservatīvo ārstēšanu (78,1% vs 73,1% (p=0.436), periotoneālo drenāžu (PD) 7,3% vs 3% (p=0.183), laparatomiju 8,6% vs 16,4% (p=0.101) un kombinēto ārstēšanas metodi ar PD un laparatomiju – 5,5% vs 4,5% (p=0.766). Bija novērota tendence uz mortalitātes samazināšanos otrajā grupā (30% vs 21%), taču statistiski nenozīmīga (p=0.154). Izvērtējot ārstēšanas metožu efektivitāti balstoties uz mortalitātes rādītājiem starp abām grupām, tikai konservatīvā terapijā 2. grupā parādīja uzlabojumu (27% vs 10.2%, p=0.019). Kopsavilkumā, pēdējo piecu gadu laikā ir novērots NEC gadījumu samazinājums, galvenokārt tiek skarti priekšlaikus dzimušie un zema dzimšanas svara jaundzimušie, bet ar tendenci uz mirstības samazināšanos. Pielietoto ķirurģisko ārstēšanas metožu taktika nav mainījusies, taču vērojams, konservatīvās ārstēšanas efektivitāte ir uzlabojusies.

Introduction

Necrotizing enterocolitis (NEC) is among the most commonly acquired gastrointestinal emergencies in neonates. It is characterized by ischemic necrosis of the intestinal mucosa, which is associated with inflammation, invasion of enteric gas forming organisms, and dissection of gas into the muscular layer and portal venous system. (Neu et al. 2011; Lee and Polin 2003; Neu et al. 1996)

Most affected are preterm infants, but up to 25% of the cases have been reported in full term infants. The incidence of NEC lies between 0.3 to 1 neonates per 1000 live births and 1% to 8% of newborns admitted to the neonatal intensive care unit. In recent decades, the incidence of NEC has increased due to more preterm and extremely low birth weight infants being born. The estimated rate of mortality associated with NEC varies between 12% and 50%, with highest rates among the extremely low birth weight infants. (Rennie 2012; Lee and Polin 2003; Neu et al. 2011; Rees et al. 2010; Fitzgibbons et al. 2009)

Pathophysiology of NEC remains poorly understood, but it is considered to be a multifactorial disease. The cause for premature infants to be in a high-risk group is developmental immaturity of key functions such as gastrointestinal motility, digestive ability, circulatory regulation, intestinal barrier function and immune defence. Other risk factors that could contribute to NEC development are feeding with bovine milk formula, colonization with pathogenic bacteria and hypoxic-ischaemic injury. (Schnabel et al. 2008; Lin and Stoll 2006; Zani and Pierro 2015)

Following the clinical diagnosis of NEC, most infants are managed non-operatively. Conservative treatment includes withholding enteral feeding, mechanical ventilation support, fluid resuscitation, inotropic support, correction of acid-base imbalance, correction of coagulopathy and/or thrombocytopenia, bowel rest, and antibiotics. Currently in the literature, there is no consensus and no evidence on which antibiotic regimen should be prescribed for infants with NEC. Depending on national protocols, cultural individualities and resistance patterns, antibiotics are prescribed accordingly (Zani and Pierro 2015).

The number of patients that require surgical intervention varies from 27% to 63%. If a persistent clinical deterioration, a sign of impending perforation or intestinal gangrene is observed surgical intervention is the treatment of choice. The latter indication is identified radiologically and is absolute, while signs of clinical deterioration are subtler. These signs include increase in abdominal distention, requirement of inotropes, hemodynamic instability, worsening laboratory values (intractable acidosis, persistent thrombocytopenia, rising leucocytosis, or worsening leukopenia), and/or sonographic evidence of decreased or absent intestinal perfusion. (Zani and Pierro 2015; Pierro 2005; Nadler et al. 2001)

Surgical treatment includes peritoneal draining (PD) and laparotomy with or without PD. Ein et al. in 1977 proposed usage PD as a surgical intervention for unstable neonates opposed to

laparotomy, which can result in higher morbidity or even death (Lee and Polin 2003). In 2006 and 2008 two studies where published comparing PD and laparotomy and neither of the studies demonstrated an advantage of one treatment over the other (Moss et al. 2006, Rees et al. 2008). The surgical objective of laparotomy is to remove necrotic tissue, control intra-abdominal sepsis and to preserve as much bowel length as possible. There are several surgical options and the surgeons' choice is mostly influenced by the site and extent of the disease as well as personal experience. These options include: enterostomy, resection with primary anastomosis and placement of proximal jejunostomy. Currently there are no published studies which could show one methods superiority over the other, but there is a multicenter randomized controlled trial (STAT: Stoma or Intestinal Anastomosis Trial) currently underway, that could answer this question. (Zani and Pierro 2015; Pierro 2005; Nadler et al. 2001)

Aim

The study aim was to describe the difference in NEC patient demographics and to evaluate used treatment tactics and their impact on mortality reduction in newborns admitted to Children's Clinical University Hospital NICU during the time period from year 2006 until 2015.

Materials and methods

A retrospective study was conducted in Children's Clinical University Hospital analysing all newborns with a diagnosis of necrotizing enterocolitis between time period of 2006 – 2015. Patient data was collected from the medical archive with the approval of the local Ethics committee and in accordance with the Helsinki Declaration. All included patients were divided into two groups according to time period of treatment: group 1 – 2006-2010 and group 2 – 2011-2015. Information about patient demographics, used treatment options and mortality was gathered and analysed using *IBM SPSS Statistics 22.0* programme. Nonparametric quantitative data was analysed using x^2 and qualitative data with *Mann-Whitney U* test. All p values <0.05 were considered significant.

Results

A total of 149 patients were included in this study. In group 1 there were 128 patients with NEC and in group 2 – 67. When comparing it with the general count of live births in these time periods (group 1 – 110,365 and group 2 – 101,415), the incidence of NEC in the first time period was 1.16 per 1000 live births, but between 2011 and 2015 the number dropped in half to 0.7 per 1000 live births. Median gestation age was lower in group 2 than in group 1 (*Md*=28 (*IQR* 25;31) vs. *Md*=29.5 (*IQR* 27;33)) as well as birth weight (*Md*=970 (*IQR* 810; 1640) vs. *Md*=1267.5 (*IQR* 962.50; 1772.50) both being statistically significant – p=0.018 and p=0.02, respectively. However, there was no statistically significant gender disparity observed between the two groups (p=0.695) (Fig. 1).

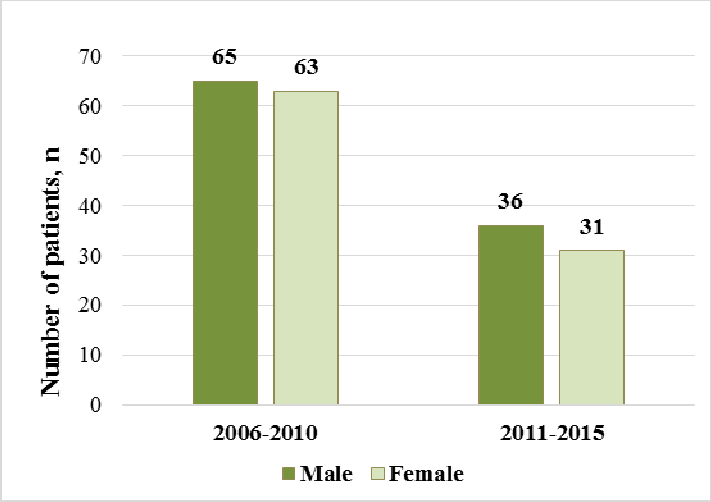

Figure 1. **Gender disparity between groups**

Surgical treatment was used for 46 patients: 28 patients in group 1 (21.9%) and 18 – in group 2 (26.9%), but others were managed conservatively (78.1% vs 73.1%, p=0.436). In the first group laparotomy (8.6%) and peritoneal drainage (7.3%) was used almost equally often, with laparotomy being the favourable choice, but combined therapy was used in only 5.5% of cases. While in the second group, laparotomy was used almost twice as often (16.4%) and PD and combined therapy was used less, 3% and 4.5%, respectively. When comparing both groups, there was no statistically significant change in surgical treatment option selection between the groups: peritoneal drainage (PD) 7.3% vs 3% (p=0.183), laparotomy 8.6% vs 16.4% (p=0.101) and combined therapy of peritoneal drainage and laparotomy – 5.5% vs 4.5% (p=0.766). Even though there was a trend that showed that laparotomy was the first choice among the surgeons in the second group (Fig. 2).

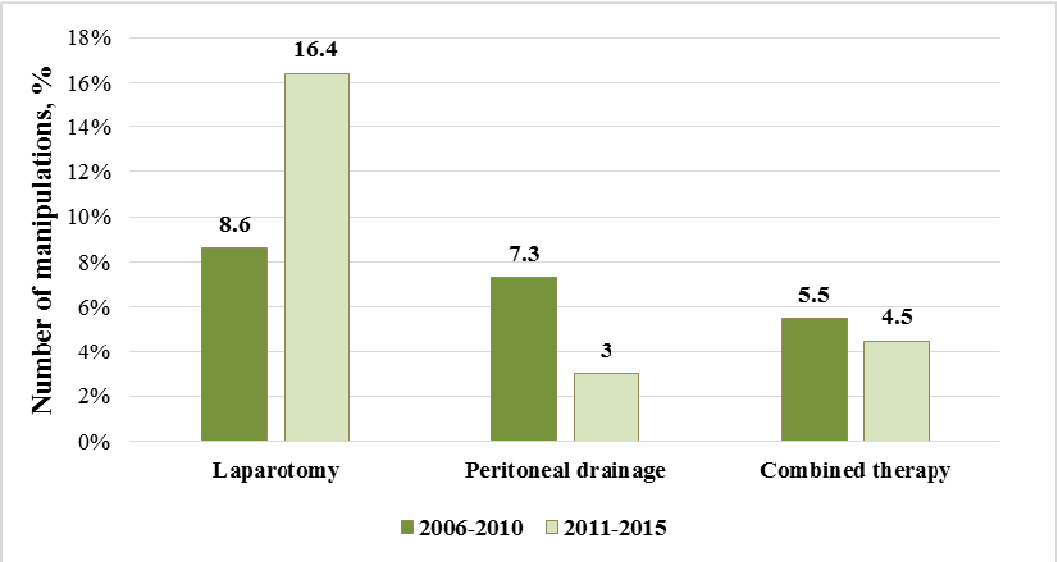

Figure 2. **Surgical treatment option comparison between two time periods**

Out of all laparotomy cases with or without prior PD (n=34), only 2 primary anastomoses were placed, with both being in group 2.

Mortality in group 1 was 30%, but in group 2 - 21%, which showed a downward trend, but when analysed it did not show any statistical significance (p=0.154) (Fig. 3).

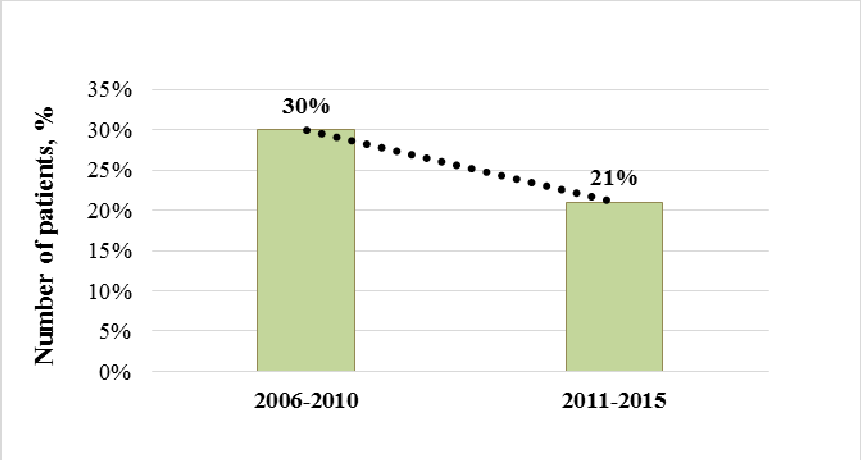

Figure 3. **Mortality in both groups**

When evaluating efficacy of treatment options based on patient mortality between groups, only conservative treatment showed a significant improvement in group 2 (27% vs 10.2%, p=0.019).

Discussion

According to the literature, incidence of NEC is from 0,3 to 1,0 per 1000 live births, but it varies between different studies. It is wise to keep in mind that the signs of NEC are usually non-specific and it can influence the diagnostic abilities, therefore, it can result in unreliable incidence rates. In our research the incidence on NEC between 2006 and 2010 was 1,16 per 1000 live births, but between 2011 and 2015 the number diminished in half to 0.7 per 1000 live births. Magnusson et al. during the period from 1998 to 2009 analysed a cohort which consisted of 1 275 735 infants and reported NEC incidence of 0,41 per 1000 live births. We can say that NEC incidence in our study is high; although there is a noticeable decrease in incidence between 2011 and 2015, it remained eminent. Many studies report various risk factors for development of NEC, such as formula feeding and fasting, thus a further study to identify and assess the influence of possible risk factors on our high incidence numbers might be in order to explain our findings and maybe find a problem target to address to lower the occurrence of NEC. (Magnusson et al. 2017; Battersby et al. 2016; Gephart et al. 2012)

NEC predominantly affects preterm infants, which was observed in this study as well. Our study showed that in the last 5 years newborns with NEC were of a lower median gestational age and birthweight, which is also a trend seen in the recent studies.

When comparing the chosen surgical treatment tactics between the time periods, there was no statistically significant change in the used surgical intervention options, however the numbers showed that in the last 5 years surgeons more often prefer to do a laparotomy and less frequently primary peritoneal drainage. This trend is with concordance with the world literature, which reports that majority of NEC survivors who underwent PD eventually required laparotomy (Ahmed et al. 1998). One of these studies is the European multi-institutional study which showed that of all 44 infants with NEC, even though 86% showed improvement after PD, 58% still underwent delayed laparotomy (Demestre et al. 2002). Yet it is still unclear from the data nowadays, whether laparotomy with bowel resection is superior to primary PD. The optimal surgical approach for patients with severe NEC is still controversial and the decision is made on a case-by-case basis, with peritoneal drainage being the first choice in unstable newborns as part of the resuscitation plan prior to laparotomy. However, the current evidence also suggests that a certain form of operative intervention does not actually affect the outcome and many variables cofactors like the patients' weight and comorbidities, as well as the timing of the procedure play the vital role in patient survival (Moss et al. 2006; Hunter et al. 2008).

NEC is a serious condition with high mortality rate that in literature ranges from 10% to 50%, which decreases with increasing birth weight (Magnusson et al. 2017; David et al. 2008). In our study mortality reached as high as 30% between years 2006 and 2010. Even though mortality rate was not statistically significant, it slightly decreased to 21% during the period from 2011 and 2015. This downward trend during the second time period might be explained with advances in conservative treatment options and management. Looking at the results, it is also worth mentioning that in Latvia, due to low population, all patients with necrotizing enterocolitis diagnosis are diverted from rural areas and treated in tertiary referral hospital, allowing to provide the best available treatment options across the country, which might also be a reason why mortality rate is lower than in some other studies.

Conclusion

During past five years there has been a significant drop in cases of NEC with significantly more preterm and underweight newborns being affected, yet with a slight decline of mortality. Treatment tactics have not changed, but there is a significant increase in conservative treatment efficiency. In future we must re-evaluate our treatment strategies regarding NEC to continue decreasing the mortality rates.

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PITX2 GENE VARIANT RS2200733 PREDICTS RISK OF LONE ATRIAL FIBRILLATION DEVELOPMENT IN LATVIAN POPULATION

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Abstract

Key words: *lone atrial fibrillation, PITX2 gene, rs2200733 variation*

Introduction: Term "lone atrial fibrillation" (LAF) was first introduced in 1954 and defined an atrial fibrillation (AF) in otherwise healthy patients without any structural heart disease. Contemporary medicine has revealed multiple risk factors, which are associated with development of AF, but still there are cases of unknown etiology. In previous studies genetic variants located near paired-like homeodomain transcription factor-2 gene (*PITX2*) were found to be associated with development of AF in different populations.

Aim: The aim of our study was to investigate the role of *PITX2* variant rs2200733 in development of LAF in Latvian population.

Materials and methods: We included 17 patients with LAF and 86 healthy controls from Latvian population in our study. LAF was defined as AF in patients younger than 65 years and no history of thyroid dysfunction, chronic obstructive pulmonary disease, chronic kidney disease, systemic inflammatory disease, diabetes, hypertension, coronary heart disease, valvular heart disease, cardiomyopathies or any other structural heart abnormalities. DNA was extracted from peripheral blood samples, and genetic analysis was accomplished via PCR-RFLP assay. Statistical analysis was performed in SPSS 20.0 software.

Results: Mean age of LAF patients was 52.9±6.5 years and 56.8±6.6 years in control group (p=0.029). In a binary logistic regression model dominant pattern of T allele inheritance (CT or TT genotypes) predicts development of LAF (OR=7.8, 95%CI=2.32–26.26; p=0.001). Homozygosity for T allele alone did not reached a statistically significant level of prediction (OR=3.6, 95%CI=0.56-23.69; p=0.176).

Conclusion: Genotypes CT and TT at PITX2 rs2200733 predict risk of development of lone atrial fibrillation in Latvian population.

Kopsavilkums

Ievads: Termins idiopātiska ātriju fibrilācija (angl. *Lone atrial fibrillation*) tika ieviests 1954.gadā un nozīmēja ātriju fibrilāciju (ĀF), kas attīstījās veseliem pacientiem bez strukturāliem sirds bojājumiem. Mūsdienu medicīna ir atklājusi daudzus riska faktorus, kas veicina ĀF attīstību, bet joprojām ir gadījumi, kad nav iespējams noteikt ĀF etioloģiju. Iepriekšējos pētījumos ir atklāta asociācija starp ģenētiskajām variācijām, kas atrodas tuvu *PITX2* (angl. *paired-like homeodomain transcription factor-2)* gēnam, un ĀF attīstību dažādās populācijās.

Mērķis: Analizēt *PITX2* gēna rs2200733 variācijas nozīmi idiopātiskās ātriju fibrilācijas (IĀF) attīstībā Latvijas populācijā.

Materiāli un metodes: Pētījumā tika iekļauti 17 IĀF pacienti un 86 veselie indivīdi no Latvijas populācijas. IĀF bija definēta kā ĀF pacientiem, kuri ir jaunāki par 65 gadiem un kuriem nav konstatētas vairogdziedzera disfunkcija, hroniska obstruktīva plaušu slimība, hroniska nieru slimība, sistēmas iekaisuma slimība, cukura diabēts, arteriālā hipertensija, koronāra sirds slimība, sirds vārstuļu patoloģija, kardiomiopātija vai cita strukturāla sirds patoloģija. DNS tika izdalīta no perifēro asins paraugiem, un ģenētiskā analīze tika veikta izmantojot PCR-RFLP metodi. Statistiskā analīze tika veikta SPSS 20.0 programmā.

Rezultāti: Vidējais IĀF pacientu vecums bija 52,9±6,5 gadi un 56,8±6,6 gadi kontroles grupā (p=0,029). Izmantojot bināro loģistiskas regresijas modeli, tika atklāta variācijas rs2200733 saistība ar T alleli dominantā iedzimšanas modelī (CT un TT genotipi) un IĀF attīstības risku (OR=7.8, 95%CI=2.32–26.26; p=0.001). T allēle homozigotiskajā stāvoklī nesasniedz statistiski ticamu rezultātu (OR=3.6, 95%CI=0.56-23.69; p=0.176).

Secinājumi: *PITX2* gēna variācijas rs2200733 CT un TT genotipi spēj paredzēt idiopātiskās ātriju fibrilācijas attīstības risku Latvijas populācijā.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia with overall prevalence 1-2%. Both incidence and prevalence are growing due to improvement in treatment of chronic cardiac

diseases and better detection of asymptomatic cases (Zoni-Berisso et al. 2014). Multiple concomitant cardiac and extracardiac pathologies increase the risk of AF development. Detection of conditions such as hypertension, coronary heart disease, thyroid dysfunction, obesity, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, sleep apnoea, smoking, excessive alcohol consumption and vigorous exercise could influence optimal therapy strategy of AF (Kirchhof et al. 2017).

Term 'lone atrial fibrillation' (LAF) was first introduced by Evans and Swans in 1954 and defined atrial fibrillation (AF) 'in the absence of heart disease or thyroid toxemia' (Evans and Swann 1954). Nowadays there is no single definition of LAF, but in general it is considered as an AF in young patients without any predisposing conditions and structural heart disease (Nair et al. 2016; Zhou et al. 2017; Blagova et al. 2016). Due to better understanding of AF pathophysiology, discovery of new cardiac diseases and misunderstanding in definition, ongoing guidelines suggest, that term LAF should not be used (January et al. 2014; Kirchhof et al. 2017). But real life practice shows that common knowledge and routine methods of investigation do not provide enough information to identify triggering event in every single AF patient. Latest studies show that the proportion of AF considered to be LAF is only 5-10% (Pison et al. 2014).

Current guidelines of European Society of cardiology highlight genetic background of AF and identify monogenic and polygenic AF as separate clinical forms (Kirchhof et al. 2017). Recent meta-analysis of genome-wide association studies established multiple genomic loci associated with AF. One of the most significant associations is located on chromosome locus 4q25, near *PITX2* (Paired-like homeodomain transcription factor 2) gene (Ellinor et al. 2012). The *PITX2* gene encodes transcription factor which is responsible for development of right-left cardiac asymmetry during embryogenesis and has a role in postnatal period, maintaining normal heart contraction (Tao et al. 2014; Syeda et al. 2017).

In previous studies genetic variation rs2200733 of *PITX2* gene was found to be associated with development of AF in different populations (Shi et al. 2009; Syeda et al. 2017; Viviani Anselmi et al. 2008; Ferran et al., 2014; Kiliszek et al., 2011; Lee et al., 2010), but data relating LAF is controversial (Henningsen et al. 2011; Olesen et al. 2012).

The aim of our study was to investigate an association of *PITX2* variation rs2200733 and risk of LAF development in Latvian population.

Material and Methods

A case-control study was performed. We included 17 LAF patients and 86 healthy individuals. LAF was defined as AF with age of onset before 65 years old, with no history of coronary heart disease, valvular heart disease, cardiomyopathies, arterial hypertension, thyroid hyper-/hypofunction or subclinical dysfunction, diabetes, chronic kidney disease, chronic

obstructive pulmonary disease, systemic inflammatory disease. Study was carried out in accordance with Helsinki declaration and all involved individuals signed informed content. The study was approved by the Central medical ethics committee of Latvia.

DNA was extracted from peripheral blood samples using commercially available kit innuPREP DNA Mini Kit (Analytik Jena AG, Germany). Variation rs2200733 was genotyped by polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) assay as previously described (Kalinderi et al. 2015).

Statistical analysis was conducted using SPSS 20.0 software. For binary and categorical (gender, genotype) outcome variables Pearson's Chi-square and Fisher's exact tests were applied. Difference for continuous variables (age, body mass index) was calculated by independent samples t-test and Mann-Whitney U test for parametrical and non-parametrical data respectively. Binary logistic regression was performed, incorporating LAF occurrence as outcome variable, rs2200733 as independent predictor and age, gender, body mass index (BMI) as covariates. Odds ratio and 95% confidence interval were calculated. P value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of case and control groups are summarized in Table 1. There was a statistically significant difference in gender distribution and age among case and control groups, body mass index did not differ significantly between groups ($p>0.05$).

Table 1. **Clinical characteristics of LAF patients and control group**

Variable	LAF patients n=17	Healthy individuals n=86	p value
Male sex (%)	82.4	37.2	0.001
Age (years)*	52.9±6.5	56.8±6.6	0.029
Age of onset of LAF (years)*	49.8±7.5	-	-
BMI (kg/m^2)*	27.3±3.3	28.8±5.6	0.483
Positive family history for AF (%)	35.3	-	-

*Continuous variables are expressed as mean value ± standard deviation
BMI – body mass index

We have compared frequencies of rs2200733 genotypes in case and control groups. Difference in genotype frequency was statistically significant (CC vs. CT vs. TT = 61 (70.9%) vs. 22 (25.6%) vs. 3 (3.5%) in control group and 4 (23.5%) vs. 11 (64.7%) vs. 2 (11.8%) in case group, $p=0.001$) (Figure 1.).

In order to assess the association of rs2200733 genotype and risk of LAF development we performed a binary logistic regression analysis. Risk allele T in dominant model of inheritance was found to be associated with an increased risk of LAF development (Table 2.).

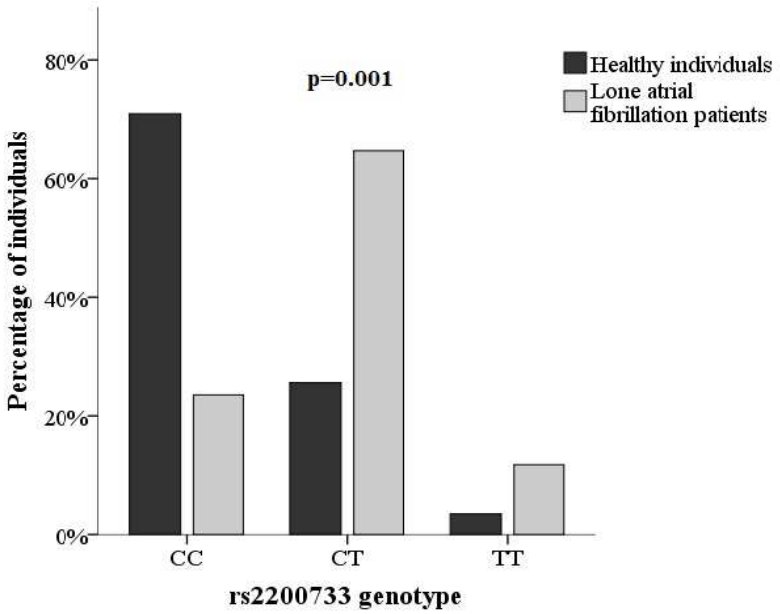

Figure 1. **rs2200733 genotypes' distribution in case and control groups**

Table 2. **Risk of lone atrial fibrillation depending on rs2200733 genotype**

Type of inheritance	Genotype	Odds ratio	95% Confidence interval	p value
Genotypic	**CC vs. CT vs. TT**	4.34	1.79-10.54	0.001
Dominant	**CT+TT vs. CC**	7.80	2.32-26.26	0.001
Recessive	**TT vs. CT+CC**	3.64	0.56-23.69	0.176

To exclude the effect of potential confounders – age, gender and BMI, an adjustment analysis was performed for dominant model of inheritance. As shown in Table 3, both magnitude of TT+CT genotypes association and statistical significance were sustained.

Table 3. **Association of rs2200733 dominant type of inheritance and risk of LAF development adjusted for confounders**

Confounder	Odds ratio	95% Confidence interval	p value
None	**7.80**	2.32-26.26	0.001
Age	7.61	2.21-26.23	0.001
Gender	5.71	1.62-20.15	0.007
BMI	9.49	2.61-34.60	0.001

Discussion

Genetic aspects of AF have raised attention lately. First genome-wide association study relating AF was performed in 2007 and discovered two strongly associated variations on locus 4q25 (rs2200733 and rs10033464). The closest gene located to 4q25 locus is *PITX2* (Gudbjartsson et al. 2007; Kaab et al. 2009).

First study regarding association of rs2200733 and risk of LAF was conducted in 2011. *Henningsen et al.* included 196 patients and 176 matching unaffected individuals of Scandinavian

ancestry and did not observe any difference in genotype distribution between groups (Henningsen et al. 2011). Later, a study with an increased population of the same ancestry was performed. It included 209 LAF patients and 534 older controls with AF risk factors. A signifficant association was found between rs2200733 and LAF (OR 1.62; 95%CI 1.16-2.27; p=0.004) (Olesen et al. 2012). Both studies included LAF cases with onset before age of 40. *Henningsen et al.* hypothesized that, due to lack of association, LAF in young patients could be related to different pathogenic mechanisms than in later onset, but further data rejected this assumption (Henningsen et al. 2011; Olesen et al. 2012). Our data shows a much greater association of rs2200733 and LAF, than previously reported (OR 4.34; 95%CI 1.79-10.54, p=0.001). This could possibly be explained by different inclusion criteria of LAF patients. We included patients who were diagnosed with LAF before age of 65.

PITX2 gene encodes a transcription factor that plays a critical role during embryogenesis, responsible for asymmetric cardiac development, for example it restricts formation of sinus node in right atrium (Franco and Campione 2003; Galli et al. 2008; Wang et al. 2014). *PITX2* has 3 isoforms, which are generated by alternative splicing and expression of *Pitx2c* isoform is specific to heart (Kirchhof et al. 2011; Syeda et al. 2017). Transcription factor, encoded by *PITX2*, has a major influence on cardiac function and structure in postnatal period also. Changes in *PITX2* expression are associated with cardiac structural and functional abnormalities. Animal models show that the upregulation of *Bmp10,* modulated by loss of *PITX2*, leads to atrial dilatation (Chinchilla et al. 2011). It is know that left atrium enlargement is a risk factor of AF development (Vaziri et al. 1994). Other function of *Pitx2* in adult heart is regulation of expression of calcium handling genes. Under expression of *Pitx2* alters calcium homeostasis (via *Atp2a2, Casq2, Plb* genes) and triggers development of arrhythmia (Lozano-Velasco et al. 2016) . Another transcriptional regulation of *Pitx2* includes genes, which preserve integrity of intercalated disc (*Ctnnb1, Dsp, Plec, Gja1, Emd*) (Tao et al. 2014).

Overexpression of *PITX2* in atrial myocytes also is associated with AF development. This is due to changes in potassium (I_{Ks}) and calcium ($I_{Ca,L}$) currents densities (Perez-Hernandez et al. 2016). I_{Ks} and $I_{Ca,L}$ are two major currents participating in cardiac action potential cycle and changes in their function is associated with electrical remodeling leading to AF (Iwasaki et al. 2011). The fact, that both increased and decreased levels of *PITX2* expression are associated with AF development, leads to hypothesis, that there is a critical level required for normal atrial function (Syeda et al. 2017).

The molecular mechanism explaining how variations located on the 4q25 influence AF development is still unknown. It is hypothesized that enhancer of *Pitx2* gene is located at the 4q25

locus and genetic variations on the 4q25 may influence its activity and *Pitx2* isoform expression in mices (Li et al. 2016), but results in humans has been contraversial (Gore-Panter et al. 2014).

Recently a novel concept of atrial cardiomyopathies has been introduced. EHRAS (European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/the Asia Pacific Heart Rhythm Society (APHRS)/the Sociedad Latino Americana de Estimulacion Cardicay Electrofisiologia(SOLAECE)) classification provides four classes with no progress in severity. First class represents morphological or molecular changes affecting only cardiomyocytes with no significant interstitial changes. Primarily cardiomyocyte-depended atrial cardiomyopathy includes cases of LAF (Goette et al. 2016). Our study revealed a strong association of 4q25 variations' rs2200733 risk genotypes and development of LAF. The potential pathogenic mechanism may be following – risk genotypes modulates function of *PITX2*, which further regulates transcription of genes encoding ion channels, calcium handling proteins, and intercalated disks. Those changes alter homeostasis and normal contraction of atrial cardiomyocytes and leads to electrical remodeling. The consequence of following process is development of atrial cardiomyopathy without structural changes and progress to LAF.

Conclusion

Genotypes CT and TT at *PITX2* rs2200733 predict risk of development of lone atrial fibrillation in Latvian population.

Acknowledgement

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TRANSARTERIAL CHEMOEMBOLIZATION OF UNRESECTABLE LIVER METASTASES FROM COLORECTAL CANCER IN PAULS STRADINS CLINICAL UNIVERSITY HOSPITAL, RIGA, LATVIA

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Abstract
Key words: *Transarterial chemoembolization, colorectal cancer, liver metastases*
About half of patients with colorectal cancer develop liver metastases. Resection is possible for only about 20% of patients. Without treatment, the median survival of patients with colorectal liver metastases is 6–12 months. Transarterial chemoembolization is a treatment option for unresectable liver metastases.
The aim of the study was to evaluate results of the transarterial chemoembolization of colorectal cancer liver metastases in interventional radiology unit of Pauls Stradins Clinical University hospital.
This study reports of 19 patients (10 men, 9 women), who underwent transarterial chemoembolization in Pauls Stradins Clinical University hospital within a period between year 2011 and 2016. In total, 52 procedures were performed, mean 3 sessions per patient. By the end of the follow up there have been 17 cases of exitus letalis. Mean survival rate after the diagnosis was 35,84 months, median 33 months (17 – 49). Mean survival after the first transarterial chemoembolization was 15,04 months, median 13 months (11 – 15). First-year survival rate after the first embolization was 42,11% (8 patients), second-year survival rate 15,79% (3 patients) and third-year survival 10,53% (2 patients). 10 patients experienced transarterial chemoembolization side-effects such as pain, nausea, vomiting, appetite loss and constipation during few days after the procedure.
Conclusion: Obtained survival rates correspond with similar studies. Unresectable colorectal cancer liver metastases can be effectively treated palliatively with transarterial chemoembolization.

Kopsavilkums
Aptuveni pusei pacientu ar kolorektālo vēzi attīstās attālas metastāzes aknās. Tikai 20% gadījumu ir iespējama to rezekcija. Nesaņemot ārstēšanu šādu pacientu vidēja dzīvildze sasniedz 6-12 mēnešus. Nerezecējamo aknu metastāžu gadījumā terapijas izvēles metode ir transarteriāla ķīmijembolizācija.
Mūsu pētījuma mērķis bija Izvērtēt Paula Stradiņa klīniskas universitātes slimnīcas invazīvās radioloģijas nodaļā veikto transarteriālu ķīmijembolizācijas procedūru iznākumus pacientiem ar kolorektāla vēža aknu metastāzēm.
Darbā tika analizēti 19 pacienti (10 vīrieši, 9 sievietes), kam Paula Stradiņa klīniskajā universitātes slimnīcā laika periodā no 2011. gada līdz 2016. gadam kopumā tika veiktas 52 transarteriālas ķīmijembolizācijas procedūras (vidēji 3 – katram pacientam). Novērošanas perioda beigās tika reģistrēti 17 nāves gadījumi. Pēc diagnozes noteikšanas vidēja dzīvildze sastādīja 35,84 mēnešus, dzīvilidzes mediāna – 33 mēnešus (17-49). Vidēja dzīvildze pēc pirmās transarteriālas ķīmijembolizācijas procedūras bija 15,04 mēneši, dzīvildzes mediāna – 13 mēneši (11-15). Pirma gada izdzīvotība pēc pirmās ķīmijembolizācijas – 42, 11% (8 pacienti), otra gada izdzīvotība – 15,79% (3 pacienti) un treša gada izdzīvotība – 10,53% (2 pacienti). Pirmo dažu dienu laikā pēc procedūras 10 pacientiem attīstījušās šādas blaknes: sāpes, slikta dūša, vemšana, apetītes trūkums, aizcietējumi.
Secinājumi: Iegūtie dati ir salīdzināmi ar līdzīgu pētījumu rezultātiem. Nerezecējamas pret ķīmijterāpiju rezistentas kolorektāla vēža aknu metastāzes var efektīvi paliatīvi ārstēt ar transarteriālu ķīmijembolizāciju.

Introduction

Colorectal cancer (CRC) is the second most common cancer in women and the third most common cancer in men worldwide. (Niederhuber 2014) For patients with CRC, the most common site for metastases is the liver. At the time of the diagnosis, approximately 20% of patients with CRC present with synchronous hepatic metastases, and almost half will eventually develop metachronous liver disease. (Jarnagin 2016)

Surgical resection is the best chance of long-term survival but only 20% of patients with liver metastases will be candidates for resection. (Niederhuber 2014, Cameron 2016) For patients with initially unresectable metastases, neoadjuvant chemotherapy permits complete resection by shrinking tumors in 12.5% to 30% of patients. (Niederhuber 2014) Currently, the first-line treatment of unresectable metastatic CRC is a FOLFOX (folinic acid , 5-fluorouracil and oxaliplatin) and FOLFIRI (folinic acid , 5-fluorouracil and irinotecan) chemotherapy drugs combination. (Jarnagin 2016)

In cases of inoperability of liver metastases and in absence of response to systemic chemotherapy, one of the options is interventional radiology procedure with drug-eluting bead transarterial chemoembolization (DEB-TACE). (Niederhuber 2014, Townsend 2016)

Transarterial chemoembolization is a palliative minimally invasive procedure conducted in order to improve survival rates of patients with CRC liver metastases. It is conducted by selectively injecting chemotherapeutic drugs into an artery directly supplying the tumor and then blocking the blood supply in the artery. Interventional radiology unit of Pauls Stradins Clinical University hospital performs drug-eluting bead transarterial chemoembolization since June 2011.

The current single-center retrospective study included 19 patient. The aim was to evaluate median overall survival and treatment response of patients with liver CRC metastases who underwent DEB-TACE.

Materials and methods

Patient population

This retrospective study included 19 patients (10 men, 9 women), with CRC liver metastases who were treated with DEB-TACE in Pauls Stradinš Clinical University hospital between June 2011 and March 2016. The clinical data was collected by reviewing the medical records from the medical archive and the CT imaging results were obtained, reviewing radiological databases of Pauls Stradiņš Clinical University hospital.

Follow-up was conducted fetom October 2016 until February 2017.

In total 52 procedures were made mean 3 sessions per patient (range 1 – 8).

All patients received palliative chemotherapy, in 16 of the patients it overlapped in time with the DEB-TACE.

Drug eluting bead transarterial chemoembolization

After infiltration of local anesthetic, the Seldinger technique is used to gain access to the common femoral artery and initial diagnostic visceral angiogram is performed to determine arterial anatomy of the liver, portal venous patency, and establish optimal location for embolization.

The use of drug-eluting beads (DEB-TACE) with the chemotherapeutic agent incorporated on polyvinylalcohol microspheres, has a dual function: a slow release of chemotherapeutic agent in a

controlled fashion and embolization of the targeted artery. (Jarnagin 2016) In DEB-TACE 100mg Irinotecan was given at each session.

Imaging

Tumor response was evaluated using computed tomography (CT) examination. The number of lesions, tumor size and location was evaluated using CT.

We selected CT examinations achieved closely before the first DEB-TACE and after the last DEB-TACE session. The first CT examinations were performed 1-3 months in advance to the first DEB-TACE and control CT were conducted 1-6 months after last DEB-TACE treatment.

The response to the therapy was assessed according to the RECIST 1.1 (Response Evaluation **Criteria** In Solid Tumors) criteria.

Statistical evaluation

The mean and median survival rates from the diagnosis of the liver metastases and from the first DEB-TACE treatment were calculated by using the Kaplan–Meier method. Survival rates were delivered in terms of 1-, 2- and 3-year survival, from the start of DEB-TACE treatment.

Statistical data were processed in IBM SPSS v22 Statistics and Microsoft Excel program.

The study was approved by Riga Stradins University Ethics committee.

Results

Mean age of the patients at the time of the first procedure was 67 years (range 52 –75).

The primary tumor was located in the colon 16% (3 patients), in the sigmoid colon 21% (4 patients), in the rectosigmoid area 21% (4 patients), in the rectum 42% (8 patients) of cases.

Primary tumor stage was as follows: 3 patients had II stage, 5 patients had III stage and 11 (58 %) patients had IV stage. In all patients, the primary tumor had been resected and all patients had received at least two lines of palliative systemic chemotherapy before DEB-TACE procedure.

Localization of metastatic lesions before the first DEB-TACE was as follows: bilobar in 11 patients, located in the right lobe in 4 patients, in the left lobe in 2 patients and for 2 patients localization was not known due to the lack of CT image.

We used RECIST 1.1 criteria in order to evaluate local tumor response. Majority of patients – 6 patients (32 %), had a partial response. Unfortinately 25 patients (25 %) had a progressive disease. The rest had stable disease (4 patients, 21 %), complete response (1 patient, 5 %) and for 3 patients (16%) the results were inestimable due to the lack of adequate CT image.

By the end of the follow up there were 17 cases of exitus letalis. Mean survival rate after the diagnosis was 35,84 months, median 33 months (17 – 49). Mean survival after the first TACE was 15,04 months, median 13 months (11 – 15).

1st-year survival rate after the first TACE was 42,11% (8 patients), 2nd-year survival rate: 15,79% (3 patients) and 3rd-year survival: 10,53% (2 patients).

10 patients experienced transarterial chemoembolization side-effects such as pain (9 patients), nausea (6 patients), vomiting (4 patients), appetite loss (6 patients), constipation (1 patient), subfebrile temperature (2 patients), bleeding from the site of catheterization (1 patient) which can also be classified as a complication. 9 Patients had no documented side effects.

Discussion

We compared collected data with 2 similar studies: "Transarterial chemoembolization of unresectable systemic chemotherapy-refractory liver metastases from colorectal cancer: Long-term results over a 10-year period" by Tatjana Gruber-Rouh *et al* 2013 (the first study) and "Salvage Therapy for Liver-dominant Colorectal Metastatic Adenocarcinoma: Comparison between Transcatheter Arterial Chemoembolization versus Yttrium-90 Radioembolization" by Kelvin Hong *et al* 2008 (the second study). Median survival after the diagnosis in the current study was 33 months and in the first study 38. There was no median survival after the diagnosis data in the second study. Median survival after the first TACE in the current study was 13 months – 14 months in the first study and 7.7 months in the second study. 1st-year survival rate after the first TACE in the current study was 42,11% with 62% in the first study and 43% in the second study. 2nd-year survival rate: 15,79% in the current study with 28% in the first and 10% in the second study. The comparison revealed that the results of the current study are similar to the given two studies.

Conclusions

The results can be compared to the similar studies. Transarterial chemoembolization is an effective and recommended treatment method for palliative treatment of patients with unresectable and chemoresistent CRC liver metastases. TACE improves survival rates of such patients. Side effects are indulgent and manageable, complications are rare.

Acknowledgements

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ACTIVATION OF VALVULAR INTERSTITIAL CELLS AND REMODELING OF EXTRACELLULAR MATRIX IN CALCIFIC AORTIC VALVE STENOSIS

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Abstract

Activation of valvular interstitial cells and remodeling of extracellular matrix in calcific aortic valve stenosis

Key words: *aortic stenosis, valvular interstitial cells, extracellular matrix, matrix metalloproteinase, immunohistochemistry*

Calcific aortic stenosis is the most common cause of aortic valve replacement in developed countries, and this condition increases in prevalence with advancing age. The primary cell types in the aortic valve are valvular endothelial and interstitial cells (VICs). Abnormal aortic valve function likely results from extracellular matrix (ECM) remodeling associated with the disequilibrium between the synthesis of ECM components and their degradation. The aim of this study was to analyze the evidence of extracellular matrix remodeling and phenotypical changes occurring in the VICs of the different histological layers of aortic valves. Immunohistochemical performance on 20 stenotic aortic valves and 11 control valves was studied by semiquantitative estimation of alpha-smooth muscle actin (α-SMA), CD34 and matrix metalloproteinase (MMP-9) expression. Activated VICs express α-SMA and significantly increase in number as respond to valve injury. Furthermore, in the ventricular layer the VICs possess the greatest capacity to differentiate into myofibroblasts. The expression of MMP-9 by activated VICs and mononuclear leukocytes was increased in stenotic valves and weakly correlated with α-SMA expression suggesting the contribution of ECM remodeling in the pathogenesis of aortic valve stenosis.

Kopsavilkums

Vārstuļa intersticiālo šūnu aktivācija un ārpussūnas matrices pārbūve kalcinēta aortas vārstuļa stenozes gadījumā

Atslēgas vārdi: *aortas vārstuļa stenoze, vārstuļa intersticiālās šūnas, ārpussūnu matrice, matrices metaloproteināze, imūnhistoķīmija*

Kalcinēta aortas vārstuļa stenoze ir visbiežākā aortas vārstuļa operācijas indikācija attīstītajās valstīs, un šīs patoloģijas prevalence pieaug līdz ar vecumu. Galvenie šūnu veidi aortas vārstulī ir endoteliālās un intersticiālās šūnas (VIŠ). Patoloģiska vārstuļa funkcija rodās ārpussūnas matrices (ĀŠM) pārbūves dēļ, kas ir saistīta ar līdzsvara izmaiņām starp ĀŠM komponenšu sintēzi un to degradāciju. Šī pētījuma mērķis bija analizēt AŠM pārbūves un VIŠ fenotipisku izmaiņu īpatnības dažādos aortas vārstuļa histoloģiskajos slāņos. Imūnhistoķīmiskās reakcija un puskvantitatīvā analīze tika veikta uz 20 stenotiskiem vārstuļiem un 11 kontroles vārstuļiem, izmantojot antivielas pret alfa-gludo muskuļu aktīnu (α-GMA), CD34 un matrices metaloproteināzi (MMP-9). Aktivētas VIŠ ekspresēja α-GMA un nozīmīgi pieauga skaitā vārstuļa bojājuma gadījumā. Ventrikulārajā slānī VIŠ bija visaugstākā spēja diferencēties miofibroblastos. MMP-9 ekspresija, ko uzrādīja aktivētās VIŠ un mononukleāri leikocīti, bija vislielākā stenozes gadījumā un vāji korelēja ar α-GMA ekspresiju, norādot uz AŠM pārbūves nozīmi kalcinēta aortas vārstuļa stenozes patoģenēzē.

Introduction

Aortic stenosis (AS) has become the most frequent type of valvular heart disease in Europe. It primarily presents as calcific AS. The prevalence of calcific AS increases with advancing age afflicting 2-7% of the population by the age of 65 years, thus the medical and economic burden is most likely to increase (Iung et al. 2003; Nkomo et al. 2006).

Calcific AS is a chronic, progressive disease. During a long latent period, patients remain asymptomatic. Sudden cardiac death is a frequent cause of mortality in symptomatic patients. AS alone is associated with a 50% increased risk of myocardial infarction or death from cardiovascular causes (Otto et al. 1997; Rosenhek et al. 2010). As soon as symptoms occur, the prognosis of severe AS is dismal, with survival rates of only 15-50% at five years (Vahanian et al. 2012).

The pathophysiology underlying calcific AS remains incompletely defined, and there are currently no effective medical treatments capable of altering its course. Furthermore, there are no reliable markers that can predict disease progression (Dweck et al. 2012).

Gross morphological characteristics are valve thickening and calcification (Akat et al. 2009). Calcific AS was regarded as a purely degenerative disease without conservative treatment options. However, in the last 15 years it has become clear that calcific AS involves cell differentiation and proliferation processes responding to several evolutionary conserved and ubiquitous pathways (Akat et al. 2009). Traditionally viewed as a degenerative process resulting from “wear and tear” with aging, calcific AS is now recognized to be an actively regulated disease (Yip et al. 2011).

Normal aortic valves are made up of 3 cusps, the arrangement of which results in even distribution of mechanical stress to the valve ring and the aorta (Thubrikar et al. 1986). Each cusp is composed of three histological layers: fibrosa, spongiosa, and ventricularis. The fibrosa, on the aortic side of the leaflet, comprises primarily collagen fibers arranged circumferentially, parallel to the leaflet margin. The spongiosa, between the fibrosa and the ventricularis, is a layer of loose connective tissue and is rich in glycosaminoglycans. The ventricularis, on the ventricular side of the leaflet, is composed of elastin-rich fibers that are aligned in a radial direction, perpendicular to the leaflet margin. (Freeman et al. 2005; Rajamannan et al. 2011).

The primary cell types in the aortic valve are valvular endothelial cells and valvular interstitial cells (VICs). Recent evidence suggests that both of these populations are heterogeneous and exhibit striking side dependent phenotypic differences that have the potential to contribute to the focal nature of calcific AS (Yip et al. 2011).

VICs are the major cell population of the cardiac valve leaflets. VICs are abundant in all layers of the heart valves and are crucial to function. These cells perform the complex biological processes that contribute to the maintenance and function of the valves through synthesis of extracellular matrix (ECM), expression of matrix-degrading enzymes (including matrix metalloproteinases [MMPs] and their inhibitors), communication and response to changes in their environment (Hajdu et al. 2011; Rajamannan et al. 2011).

VICs comprise a diverse, dynamic and highly plastic population of resident cells (Liu et al. 2007). VICs in situ have characteristics of resting fibroblasts without synthetic or destructive activity for extracellular matrix (ECM). VICs are activated during intrauterine valvular maturation,

by abrupt changes in the mechanical stress state of valves, and in disease states. These cells continuously repair a low level of injury to the ECM (Rajamannan et al. 2011; Liu et al. 2007). Once activated, VICs can differentiate into a variety of other cell types, including myofibroblasts and osteoblasts (Chen et al. 2009).

Beyond its structural role, the ECM provides biochemical and mechanical cues to adherent cells. Alterations in ECM composition and mechanics are characteristic of sclerotic diseases (Hinton et al. 2006). Abnormal aortic valve function likely results from ECM remodeling, associated with the disequilibrium between the synthesis of ECM components and their degradation. ECM remodeling is mediated by MMPs, many of which are upregulated or have increased activity in calcified aortic valves (Fondard et al. 2005; Edep et al. 2000).

MMPs are a family of 23 zinc-dependent endopeptidases that are involved in almost all physiological and pathological processes of tissue remodeling (Page-McCaw et al. 2007).

The aim of this study was to analyze the evidence of extracellular matrix remodeling and phenotypical changes occurring in the VICs of the different histological layers of aortic valves, and to describe its contribution to the pathogenesis of aortic valve stenosis.

Material and Methods

Twenty patients treated between June 2013 and April 2014 at Pauls Stradins Clinical University Hospital and undergoing aortic valve replacement surgery were selected for this study and compared with 11 samples from control group obtained at autopsy. The study protocol was approved by the Ethics Committee of Riga Stradins University and conducted in accordance with the principles stated in the Declaration of Helsinki. Autopsy material was investigated in accordance with the laws and requirements of the Republic of Latvia and the European Union.

According to the age, we divided the control group into two subgroups: elderly and young. Mean age of the patients, elderly and young controls were 70.59 (SD = 10.4); 61.43 (SD = 7.04) and 25 (SD = 5.94) years, respectively.

Transthoracic echocardiography was performed on every patient to determine the severity of aortic stenosis. Mean transvalvular pressure gradient was 44.50 mmHg (SD = 12.22).

The study of the valvular tissue was done by light microscopy, histochemistry and immunohistochemistry.

Collagenous constituents of the valvular ECM were assessed by Masson's trichrome staining. By immunohistochemistry we analyzed cell phenotypes, using antibodies to alpha smooth muscle actin (α-SMA) for activated VICs and CD34 for quiescent VICs, and the expression of the proteolytic enzyme gelatinase by using antibodies to MMP-9.

The results of immunohistochemical reactions were assessed semiquantitatively and scored as: 1+ representing that <10%; 2+: 10 – 29%; 3+: 30 – 49%; and 4+: 50% and more of field of view

was immunopositive, respectively. The expression of antigens was estimated at ×100 up to ×400 magnification, using Leica light microscope. Sections were photographed by a Leitz DMRB bright-field microscope using a DFC 450C digital camera. The data was analyzed with IBM SPSS Statistics 22.0 software package using non-parametric tests. $P < 0.05$ was considered significant.

Results

VICs phenotype was assessed by immunohistochemistry. On immunohistochemistry, activated VICs displayed marked positive α-SMA immunoreaction, but CD34 immunopositivity identified quiescent VICs.

Expression of α-SMA by activated VICs was more prominent in stenotic valves (Md = 2) compared with young (Md = 1; $p < 0.001$) and age-matched controls (Md = 1; $p < 0.001$) (Fig. 1). Furthermore, increased expression of α-SMA was observed in *ventricularis* layer (Fig. 2a) in stenotic valves (Md = 3; $p = 0.02$) and both control groups (Md = 2; $p < 0.001$). There was no difference in α-SMA expression between young (Md = 1) and age-matched controls (Md = 1; $p = 0.96$). We found clusters of α-SMA positive myofibroblasts in the close vicinity to the calcified nodules (Fig. 2b) sometimes being trapped within the calcified bone matrix. Moderate positive correlation between transvalvular pressure gradient and mean expression of α-SMA was discovered (*rho* = 0.66; $p = 0.01$).

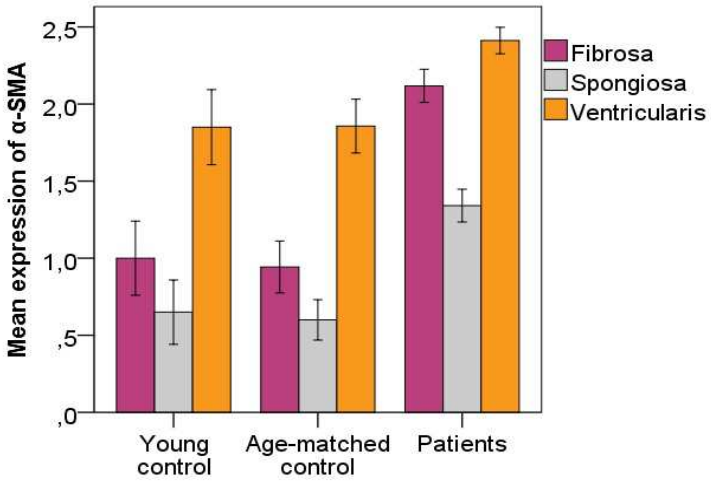

Figure 1. **Mean expression of α-SMA in different histological layers of aortic valve in young, age-matched controls and patients**

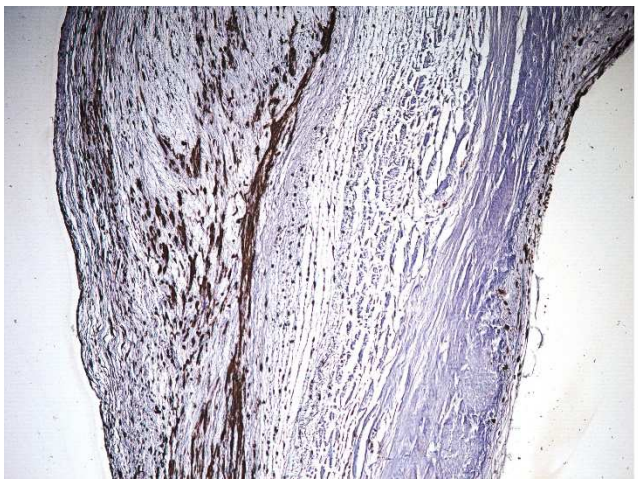

Figure 2a. **α-SMA immunohistochemistry. Low power micrograph confirms heterogeneity of the occurrence of α-SMA expression mostly referred as being ventricular (x100)**

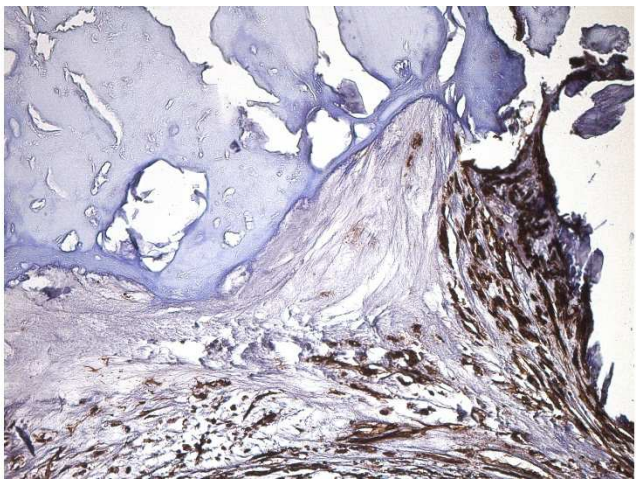

Figure 2b. **α-SMA immunohistochemistry. α-SMA positive cells heavily decorate the vicinity of calcified nodule (x200)**

CD34 positive interstitial cells were found mainly in *fibrosa* and *spongiosa* layers (Fig. 3). These mostly appeared as slender, elongated but sometimes wavy cells interspersed by collagen fibers and elastic lamina (Fig. 4a). By high power, the external appearance sometimes was interpreted as being stellate and exhibiting long dendritic processes (Fig. 4b). We observed a remarkable reduction of CD34 expression in the VICs in patients (Md = 1) when compared to both control groups ($p < 0.001$). Expression of CD34 was also reduced in age-matched controls (Md = 2) when compared to young controls (Md = 2.5; $p = 0.01$). Ratio between quiescent and activated VICs was 1.93 in young controls, 1.47 in elderly controls and 0.57 and stenotic valves.

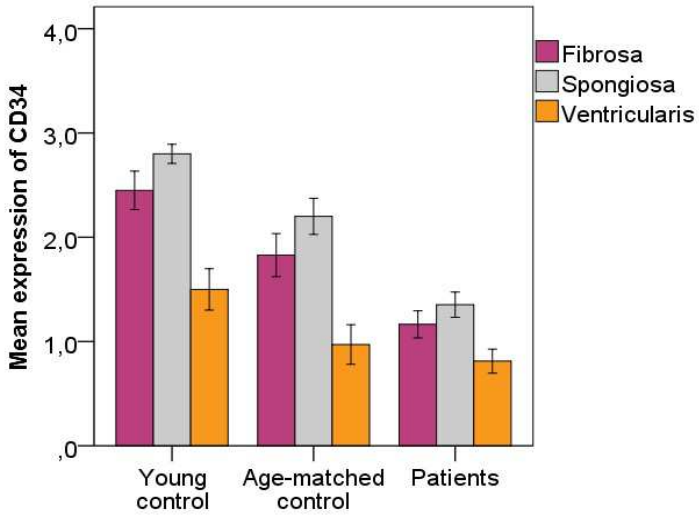

Figure 3. **Mean expression of CD34 in different histological layers of aortic valve in young, age-matched controls and patients**

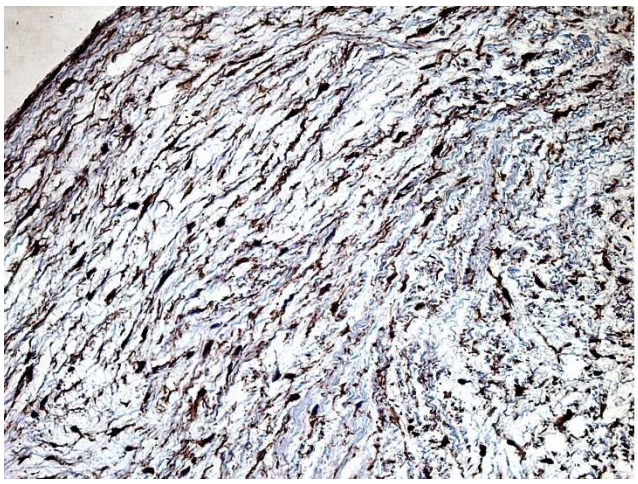

Figure 4a. **CD34 immunohistochemistry. CD34 positive VICs mostly appear as flatten and elongated, these are interspersed by distorted and fragmented elastic lamina (x250)**

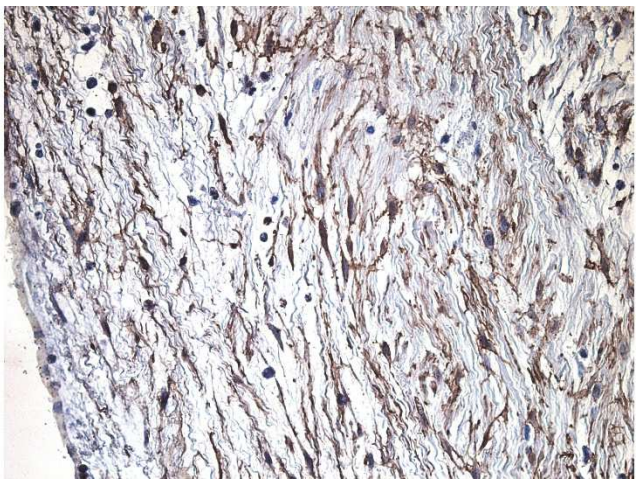

Figure 4b. **CD34 immunohistochemistry. High power micrograph reveals the stellate appearance and dendritic processes of VICs (x400)**

The expression of MMP-9 was more marked in stenotic valves (Md = 1) compared with both control groups (Md = 0; $p < 0.001$) (Fig. 5). MMP-9 expression was more enhanced in elderly controls (Md = 0) than in young controls (Md = 0; $p = 0.02$). We found that the source of the MMP-9 was activated VICs and mononuclear leukocytes. Weak positive correlations between α-SMA and MMP-9 expression (*rho* = 0.10; $p = 0.05$), and between MMP-9 and number of CD34-stained blood vessels (*rho* = 0.20; $p < 0.001$) were demonstrated.

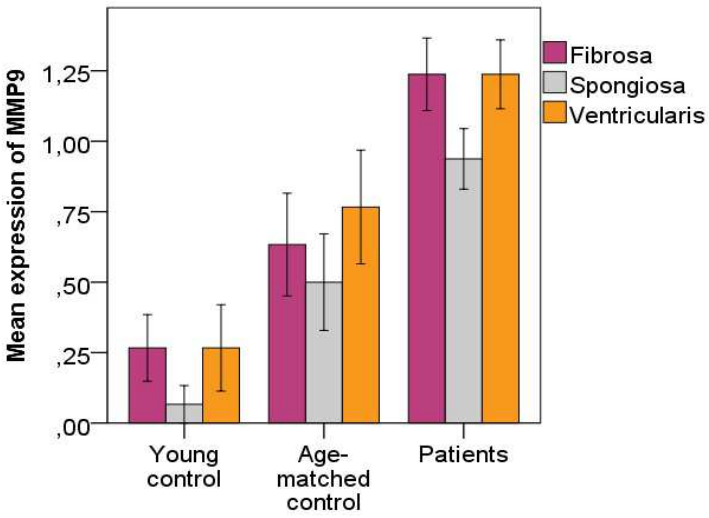

Figure 5. **Mean expression of MMP-9 in different histological layers of aortic valve in young, age-matched controls and patients**

For ECM analysis, we investigated the organization of collagen bundles by Masson's trichrome staining. In control group and *fibrosa* layer, in particular, collagen bundles were regularly

packed, compact, organized in a parallel direction. Collagen fibers appeared to be more densely packed to fulfill supportive function of degenerative valves. Often these surrounded and densely enveloped calcified nodules (Fig. 6a, 6b).

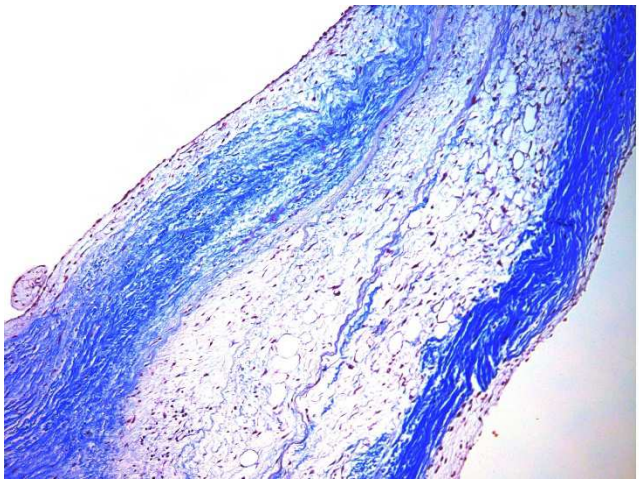

Figure 6a. **Masson's trichrome staining. Micrograph clearly demonstrates the occurrence and arrangement of collagenous ECM constituents (x100)**

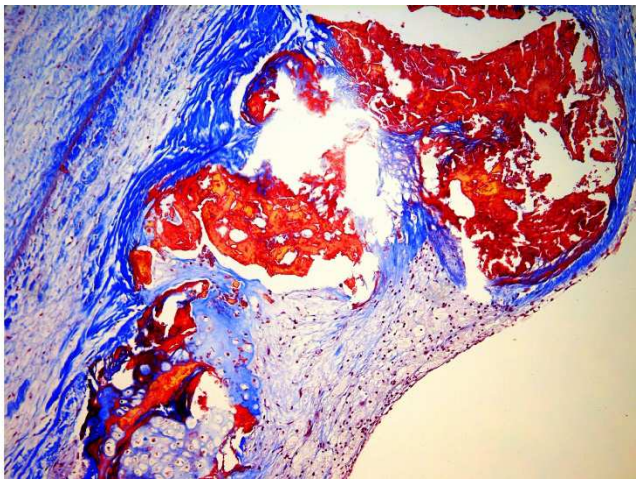

Figure 6b. **Masson's trichrome staining. Micrograph demonstrates cartilaginous and osseous transformation occurring in the affected aortic valve (x100)**

Discussion

In this study for the first time we analyzed phenotypical changes occurring in the VICs of the different histological layers of calcific stenosis affected aortic valve and compared these to the controls.

VICs play a pivotal role in valve function, both under physiological and pathological conditions. Based on their function and residing environment, five distinct phenotypes of VICs were proposed: embryonic progenitor endothelial/mesenchymal cells, progenitor VICs, osteoblastic VICs, quiescent VICs and activated VICs (Liu *et al.* 2007). Of particular interest are quiescent VICs that maintain normal structure and function in healthy adult valves, and activated VICs that regulate numerous processes in diseased or developing fetal valves (Rabkin-Aikawa *et al.* 2004).

In diseased valves VICs differentiate into myofibroblast type cells, expressing α-SMA. These activated VICs play a vital role in the pathogenesis of clinical aortic valve disease when the response to tissue injury becomes disproportionate and leads to disruption of the leaflets with excessive remodeling, scarring and calcification (Liu *et al.* 2007; Li *et al.* 2010).

The VICs in *ventricularis* layer have greater myofibroblast differentiation potential, but calcification in stenotic aortic valves occurs in *fibrosa* layer. Therefore, the VICs of different layers respond differently to the same stimuli. This distinction in differentiation potential suggests that VICs in *fibrosa* layer are inherently less sensitive to profibrotic signals. It may serve as a

homeostatic mechanism to counter many pathological microenvironmental challenges in *fibrosa* layer (Yip *et al.* 2011).

MMPs family of enzymes is involved in the ECM breakdown in normal and pathological conditions such as atherosclerosis and aortic aneurysms (Aikawa *et al.* 1998). Progressive profibrotic changes, as was investigated by increased MMP-9 expression, also occur in control samples. In this group, and especially, in elderly subjects it may represent a progressive subclinical worsening of valvular function. However, MMPs activity should be additionally estimated biochemically.

The reduced expression of CD34 in the VICs is very intriguing finding. Possible explanations are: firstly, activation and transformation of quiescent cells (fibrocytes) into active myofibroblasts and, secondly, reduction in number of CD34 positive progenitor cells (e.g. telocytes) responsible for the repair of aortic valve. Telocytes is a special type of interstitial cells that have been identified by Popescu's group; these are described as cells with extremely long and thin projections, called telopodes (Popescu *et al.* 2010). These cells have been recently identified in human heart valves, including mitral valve, tricuspid valve and aortic valve (Yang *et al.* 2014). Since telocytes are known for the participation in regeneration, it remains to be determined how these cells contribute to the valve attempts to re-establish normal structure and function following injury (Yang *et al.* 2014). Telocytes might be essential as *nurse* cells for progenitor cells (Popescu *et al.* 2012).

Conclusions

Activated VICs express α-SMA and significantly increase in number as respond to valve injury. Furthermore, in the *ventricularis* layer the VICs possess the greatest capacity to differentiate into myofibroblasts. The expression of MMP-9 by activated VICs and mononuclear leukocytes was increased in stenotic valves and weakly correlated with α-SMA expression, suggesting the contribution of ECM remodeling in the pathogenesis of aortic valve stenosis.

Acknowledgement

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DEGENERATIVE MITRAL REGURGITATION VIEWED VIA PRISM OF CELL-MATRIX INTERPLAY

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Abstract

Degenerative mitral regurgitation viewed via prism of cell-matrix interplay

Key words: *mitral regurgitation, interstitial cells, extracellular matrix, elastic fibers, matrix metalloproteinases, immunohistochemistry*

In Europe, mitral regurgitation (MR) is the second most frequent cardiac valve disease requiring surgery. Reduced incidence of rheumatic fever and increased lifespan in industrialized countries have progressively changed the distribution of etiologies, with degenerative MR now being the most common. The aim of the study was to analyze the cell-matrix interactions in distinct anatomic regions of mitral valve complex in different aged control and degenerative valves, and to determine whether there were age-specific and region-specific differences in interstitial cell phenotype and matrix composition. The immunohistochemical expression of alpha-smooth muscle actin (α-SMA), CD34, matrix metalloproteinases (MMP-3 and MMP-9) antigens was estimated semiquantitatively in 20 degenerative valves and 20 control valves. Collagen fibers were analyzed using Masson's trichrome stain, whereas elastic fibers – using Weigert's resorcin-fuchsin stain. The ultrastructure of mitral valve complex was studied by scanning electron microscopy. Activated interstitial cells were more prominent in diseased valves and were found to be the source of MMP. Fragmented elastic fibers accumulated in regions with collagen fiber degeneration. These changes in collagen and elastic fiber organization are possibly the key features in the pathogenesis of MR. Chaotic organization of collagen fibers promotes leaflet thickening, while fragmentation of elastic fibers decreases the elasticity of *chordae tendineae*.

Kopsavilkums

Šūnas-matrices mijiedarbība deģeneratīvas mitrālas regurgitācijas gadījumā

Atslēgas vārdi: *mitrāla regurgitācija, intersticiālās šūnas, ārpusšūnas matrice, elastīgās šķiedras, matrices metaloproteināzes, imūnhistoķīmija*

Eiropā mitrāla regurgitācija (MR) ir otrā biežākā sirds vārstuļu slimība, kad jālieto ķirurģiskā ārstēšana. Sakarā ar mazāku reimatiskā drudža incidenci un garāku mūža ilgumu attīstītajās valstīs, mitrālā vārstuļa deģenerācija ir kļuvusi par visbiežāko MR cēloni. Šī pētījuma mērķis bija analizēt šūnas-matrices mijiedarbību dažādos mitrālā vārstuļa kompleksa anatomiskajos reģionos dažāda vecuma kontroles grupas un deģeneratīvajos vārstuļos, kā arī pētīt vecuma-specifiskas un reģiona-specifiskas atšķirības intersticiālo šūnu fenotipā un ārpusšūnas matrices strukturā. Alfa-gludo muskuļu aktīna (α-GMA), CD34 un matrices metaloproteināžu (MMP-3 un MMP-9) antigēnu ekspresijas izvērtēšana un puskvantitatīvā analīze tika veikta 20 deģeneratīviem un 20 kontroles vārstuļiem. Kolagēna šķiedras tika pētītas, izmantojot Masona trihroma krāsojumu, savukārt elastīgās šķiedras – izmantojot Veigerta rezorcīna-fuksīna krāsojumu. Mitrālā vārstuļa kompleksa ultrastruktūras analīze veikta ar skenējošo elektronmikroskopu. Intersticiālo šūnu aktivācija un MMP ekspresija bija izteiktāka deģeneratīvajos vārstuļos. Fragmentētas elastīgāas šķiedras uzkrājās apvidos ar kolagēna šķiedru deģenerāciju. Šīs izmaiņas kolagēna un elastīgo šķiedru organizācijā ir noteicošās MR patoģenēzē. Haotiska kolagēna šķiedru izvietošanās veicina viru sabiezēšanos, savukārt elastīgo šķiedru fragmentācija samazina hordu elasticitāti.

Introduction

In Europe, mitral regurgitation (MR) is the second most frequent cardiac valve disease requiring surgery. Reduced incidence of rheumatic fever and increased lifespan in industrialized countries have progressively changed the distribution of etiologies with degenerative MR now being the most common (Iung et al. 2003). It affects about 2.5% of the general population (D'Arcy et al. 2010).

Two main etiologic classifications of degenerative disease of the mitral valve are Barlow's disease and fibroelastic deficiency. In Barlow's disease (also called myxomatous degeneration) the mitral valve show excess of tissue and leaflet thickening (Anyanwu et al. 2007). In many of these disease states the mechanical properties of valves are altered, often contributing to the poor valve function requiring surgical intervention (Stephens et al. 2011).

In asymptomatic severe chronic MR, the estimated 5-year rates of death from cardiac causes have been reported to be 14 ± 3% (Enriquez-Sarano et al. 2009). In patients with chordal rupture, the clinical condition may stabilize after an initial symptomatic period. However, left unoperated, it carries a poor spontaneous prognosis owing to the subsequent development of pulmonary hypertension (Vahanian et al. 2012).

The probability of a durable valve repair is of crucial importance. Degenerative MR due to segmental valve prolapse can usually be repaired with a low risk of reoperation (Vahanian et al. 2012). The repairability of rheumatic lesions, extensive valve prolapse, and MR with leaflet calcification is not as consistent (David et al. 2005).

Once largely considered as simple, passive fluidic functional components of the heart, cardiac valves are now deemed dynamic structures that actively remodel (Sacks et al. 2008).

The human mitral valve complex consists of the annulus, two leaflets (anterior and posterior), numerous chordae tendineae and the papillary muscles (Walmsley 1978). The mitral valve leaflets each consist of three layers that differ from each other in extracellular matrix (ECM) structure and functionality. From top to bottom, the layers are the atrialis, spongiosa and fibrosa. The atrialis is located on the inflow side of the mitral valve and has an abundance of the elastin, which allows the valve to undergo considerable stretch and then recoil back to its original shape during the cardiac cycle. The spongiosa contains a high concentration of glycosaminoglycans, which provide compressive strength for the valve. The fibrosa is the thickest layer of the valve and is comprised of dense, circumferentially aligned collagen fibers, that provide tensile strength (Kunzelman et al. 1993; Latif et al. 2005; Stephens et al. 2008).

Valvular interstitial cells (VICs) are the predominant cells found in all layers of mitral valve and are responsible for synthesizing and maintaining the ECM composition. VICs are a heterogeneous and dynamic population of cells that have a range of distinct cellular phenotypes (Blevins et al. 2006). This plasticity of VIC phenotype is crucial in heart valve development, remodeling and repair, and progression of diseased states where the myofibroblast cell type predominates (Rabkin et al. 2001). However, the interplay between the ECM and the phenotype as well as the synthetic activity of VICs, particularly in the mitral valve, has largely been overlooked (Stephens et al. 2011).

The turnover of the valvular ECM depends on a dynamic balance between synthesis and degradation. The remodeling of the ECM occurs through the action of matrix metalloproteinases (MMP). Tight regulation of matrix homeostasis maintains the functional architecture of the normal valve (Rabkin et al. 2001).

The aim of the study was to analyze the VIC-ECM interactions in distinct anatomic regions of mitral valve complex in different aged control and degenerative valves, and to determine whether there were age-specific and region-specific differences in the VIC phenotype and ECM composition.

Materials and methods

Twenty patients treated between June 2013 and April 2014 at Pauls Stradins Clinical University Hospital and undergoing mitral valve replacement surgery were selected for this study and compared with 20 samples from control group obtained at autopsy. The study protocol was approved by the Ethics Committee of Riga Stradins University and conducted in accordance with the principles stated in the Declaration of Helsinki. Autopsy material was investigated in accordance with the laws and requirements of the Republic of Latvia and the European Union. The study of the tissue structure was done by light microscopy and immunohistochemistry. The ultrastructure of mitral valve complex was studied by scanning electron microscopy.

Based on the age, we divided the control group into two subgroups: young and age-matched. Mean age of the patients, age-matched and young controls were 54.5 (SD = 14.09); 60.38 (SD = 4.6) and 30.67 (SD = 6.58) years, respectively.

Cell phenotype was determined immunohistochemically using antibodies to alpha smooth muscle actin (α-SMA) for activated VICs and CD34 for quiescent VICs. The expression of proteolytic enzymes stromelysin-1 and gelatinase was analyzed by using antibodies to MMP-3 and MMP-9, respectively. The expression of antigens was estimated at ×100 up to ×400 magnification, using Leica light microscope. Sections were photographed by a Leitz DMRB bright-field microscope using a DFC 450C digital camera.

The area and intensity of antigen expression were assessed semiquantitatively and scored for the area as: 1+ representing that <10%; 2+: 10 – 29%; 3+: 30 – 49%; and 4+: 50% and more of field of view was immunopositive, respectively. The intensity of expression was assessed from 1+ to 3+. Data processing was done with IBM SPSS Statistics 22.0 software package using non-parametric tests. P value < 0.05 was considered significant.

Collagen fibers were analyzed using Masson's trichrome stain, and elastic fibers – using Weigert's resorcin-fuchsin stain. Finally, the ultrastructure of mitral valve complex was examined under a JSM-6490LV scanning electron microscope at accelerating voltage of 10kV using SEI mode and magnification ×150 – ×6000.

Results

The area and intensity of α-SMA expression by activated interstitial cells were more prominent in the degenerative valves (Md = 1, Md = 3, accordingly) compared with both control groups (Md = 0, $p < 0.001$; Md = 0, $p < 0.001$, accordingly) (Fig. 1a, 1b). Furthermore, increased area of α-SMA expression was observed in the *atrialis* layer in the degenerative (Md = 3; $p = 0.01$) (Fig. 2a) and both control groups (Md = 3; $p < 0.001$) (Fig. 2b). We did not find statistically significant differences in the area and intensity of α-SMA expression between young (Md = 0, Md = 0, accordingly) and elderly controls (Md = 0, $p = 0.13$; Md = 0, $p = 0.10$, accordingly).

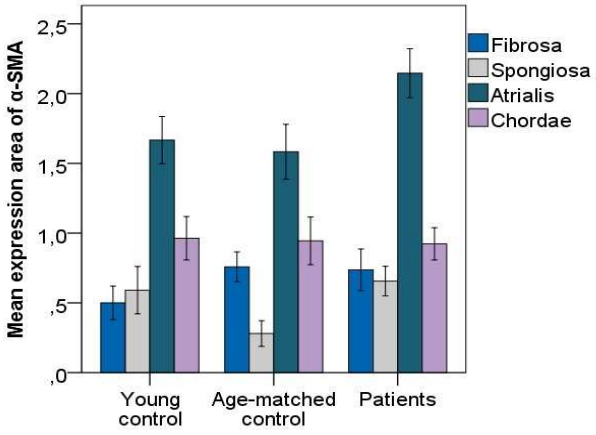

Figure 1a. **Mean area of α-SMA expression in different histological layers of mitral valve in young, age-matched controls and patients**

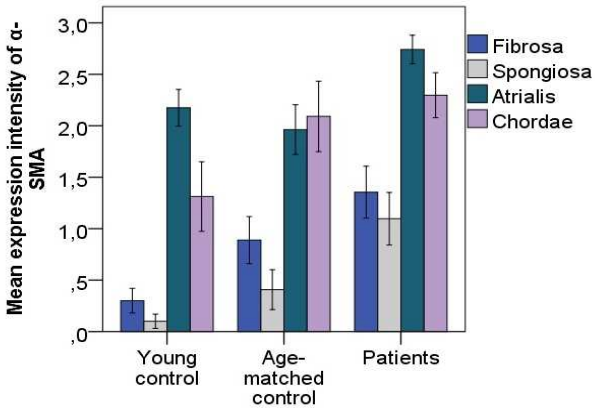

Figure 1b. **Mean intensity of α-SMA expression in different histological layers of mitral valve in young, age-matched controls and patients**

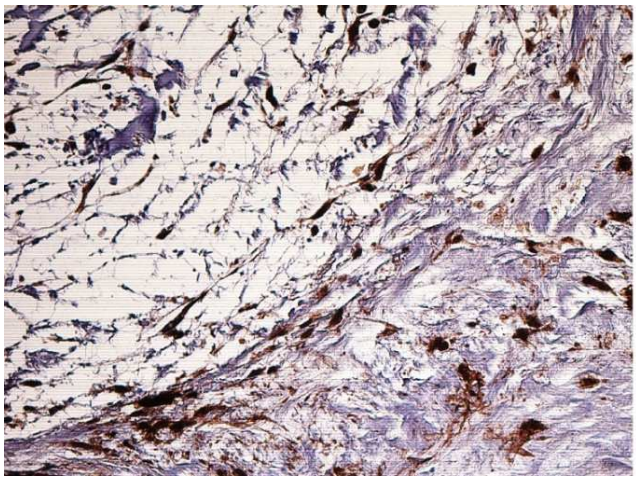

Figure 2a. **Strong expression of α-SMA exhibited by activated VICs in degenerative mitral leaflets (×100)**

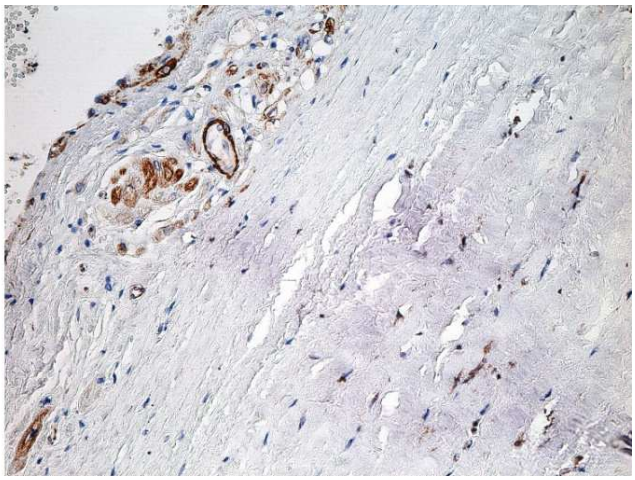

Figure 2b. **Weak to moderate expression of α-SMA displayed by activated VICs in the *atrialis* layer in young controls (×200)**

The strongest expression of CD34 was discovered in the middle – *spongiosa* layer. The area and intensity of CD34 expression by quiescent VICs were more marked in the young controls (Md = 3, Md = 3, accordingly) compared with elderly controls (Md = 2, $p = 0.02$; Md = 3, $p = 0.03$,

accordingly) (Fig. 3a, 3b). There were no differences in the area and intensity of CD34 expression between the young control (Md = 3, Md = 3, accordingly) and degenerative valves (Md = 3, p = 0.95; Md = 3, p = 0.33, accordingly) (Fig. 4a, 4b). The area of CD34 expression was larger in the degenerative valves (Md = 3) when compared to elderly controls (Md = 2; p = 0.03).

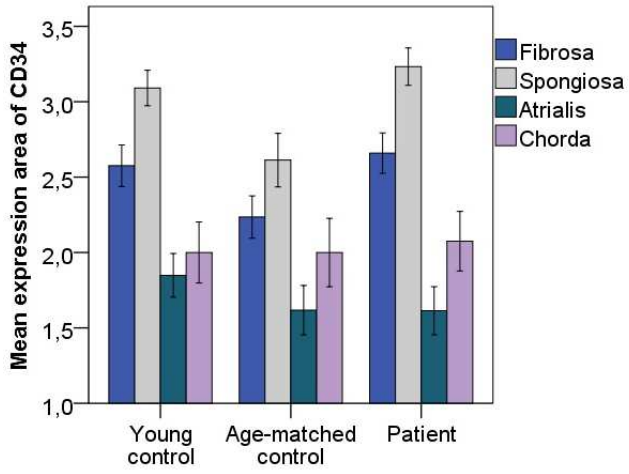

Figure 3a. **Mean area of CD34 expression in different histological layers of mitral valve in young, age-matched controls and patients**

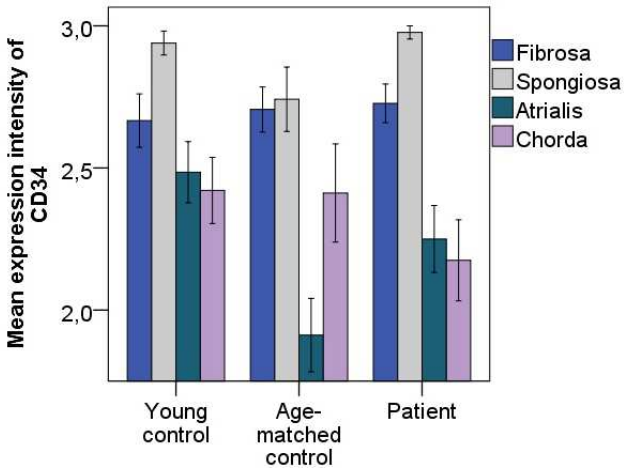

Figure 3b. **Mean intensity of CD34 expression in different histological layers of mitral valve in young, age-matched controls and patients**

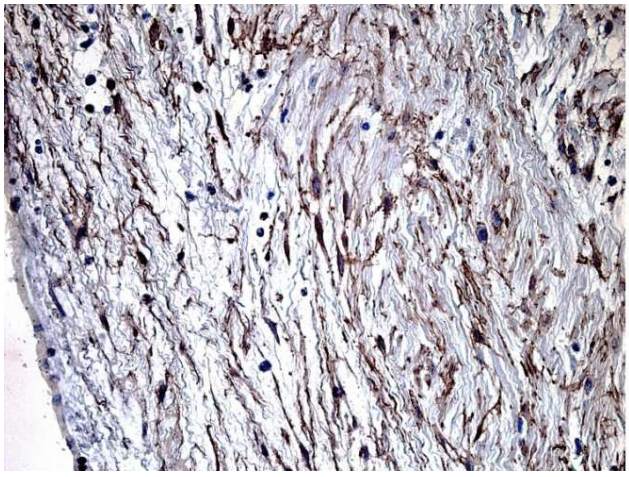

Figure 4a. **CD34-positive quiescent VICs discovered in the *fibrosa* and *spongiosa* layers of mitral leaflets in young control group (×250)**

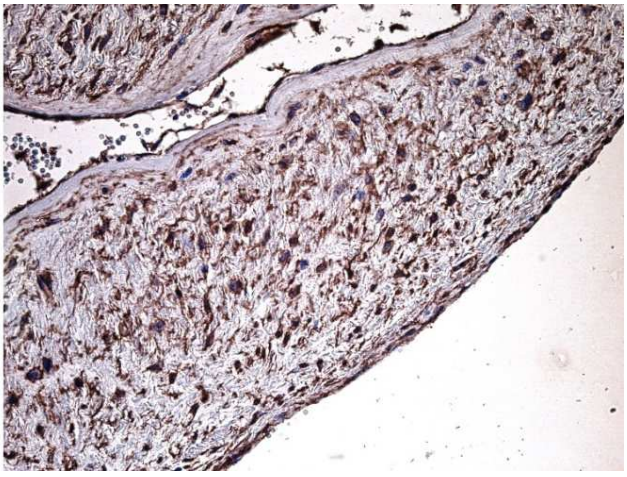

Figure 4b. **Marked expression of CD34 by quiescent VICs of *chordae tendineae* from the same subject (×250)**

The expression area and intensity of MMP-3 in the degenerative valves was more prominent (Md = 2; Md = 2) than in both control groups (Md = 1, p < 0.001; Md = 2, p < 0.001, accordingly) (Fig. 5a, 5b). We did not find statistically significant differences in the area and intensity of MMP-3 expression between young (Md = 1, Md = 2, accordingly) and elderly control groups (Md = 1, p = 0.57; Md = 2, p = 0.58, accordingly). Additionally, there were no differences in MMP-3 expression area and intensity between mitral valve leaflets and chordae in all three groups (p > 0.05).

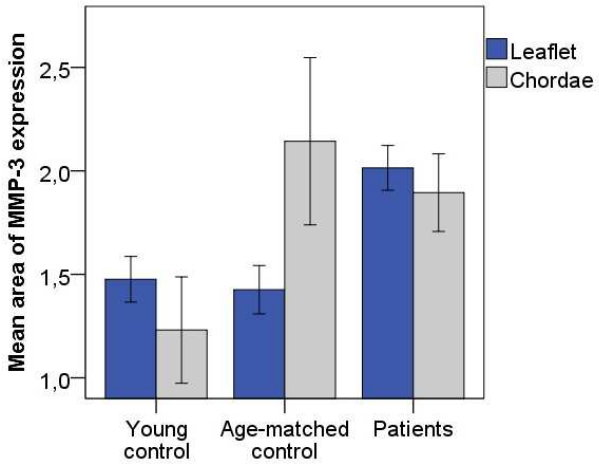

Figure 5a. **Mean area of MMP-3 expression in different anatomical regions of mitral valve in young, age-matched controls and patients**

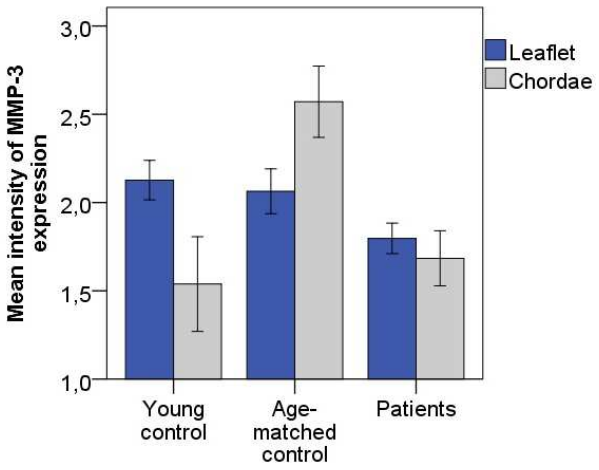

Figure 5b. **Mean intensity of MMP-3 expression in different anatomical regions of mitral valve in young, age-matched controls and patients**

Collagen bundle disruption and loss of organization was more prominent in patients with MR (Md = 2) compared with the age-matched controls (Md = 1), $p = 0.04$. In regions with active ECM remodeling we found higher intensity (Md = 2) and larger area (Md = 2) of MMP-3 expression than in areas with a parallel arrangement of collagen fibers (Md = 2, $p < 0.001$; Md = 1, $p < 0.001$, accordingly).

MMP-9 expression was significantly less prominent than MMP-3 expression and was found only in the leaflets of degenerative and control valves, but not in *chordae tendineae*.

Elastic fibers were abundant in the *atrialis* layer of mitral valve leaflets, as well as in chordae. In leaflets and *chordae tendineae* of degenerative valves we found a marked accumulation of fragmented elastic fibers. In valvular leaflets elastic fibers accumulated in regions with collagen fiber derangement and degeneration (Fig. 6a, 6b).

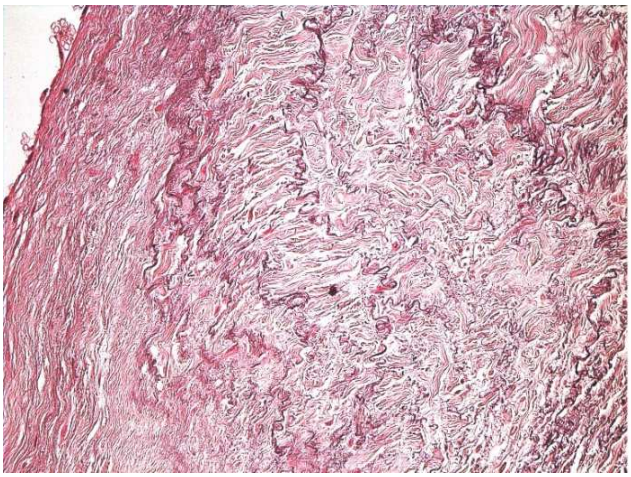

Figure 6a. **Accumulation of disorganized elastic fibers in the area of collagen disruption in degenerative leaflet (Resorcin-fuchsin staining, ×200)**

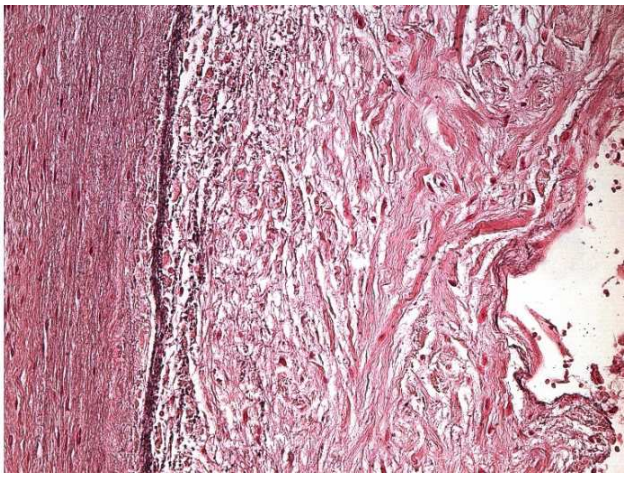

Figure 6b. **Dense elastic lamina and parallel organization of elastic fibers in the *atrialis* layer in young control group (Resorcin-fuchsin staining, ×200)**

For ECM analysis, we compared the organization of collagen bundles both in light microscopy applying Masson's trichrome staining and scanning electron microscopy. In control group (Fig. 7a, 7b), the collagen bundles appeared wavy, compact, organized in a parallel direction. But in degenerative valves (Fig. 8a, 8b), collagen bundles lost its wavy appearance, and there was found the formation of the dense fibrous lamina. We found thinning of degenerative chordae that may lead to chordal rupture (Fig. 9).

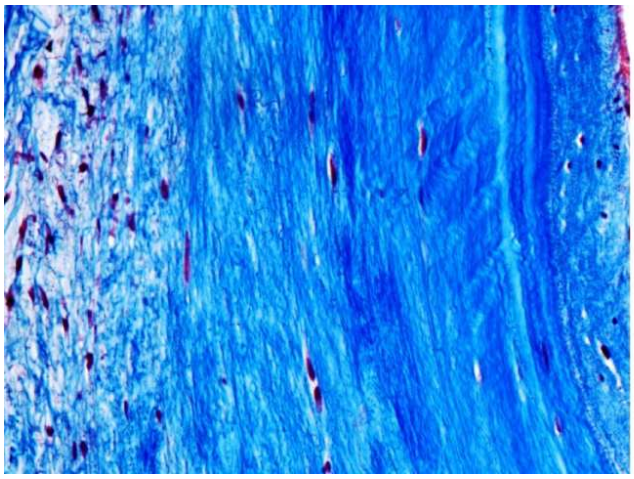

Figure 7a. **Compact collagen bundles organized in a parallel direction in control samples (Masson's trichrome staining, ×200)**

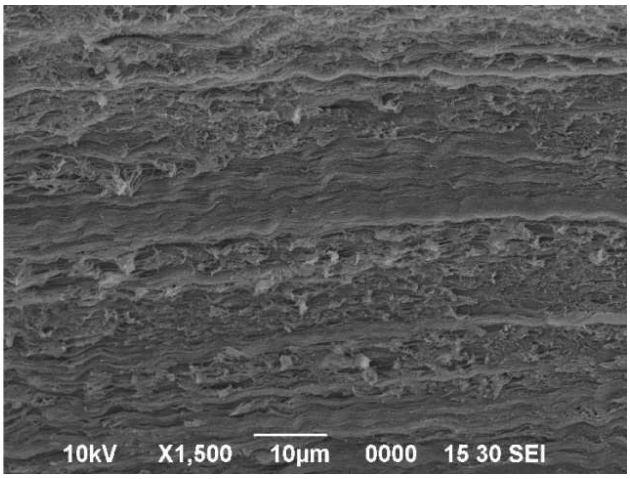

Figure 7b. **Scanning electron microscopy image of the control leaflet. Wavy, densely packed collagen fibers are organized in bundles (×1500)**

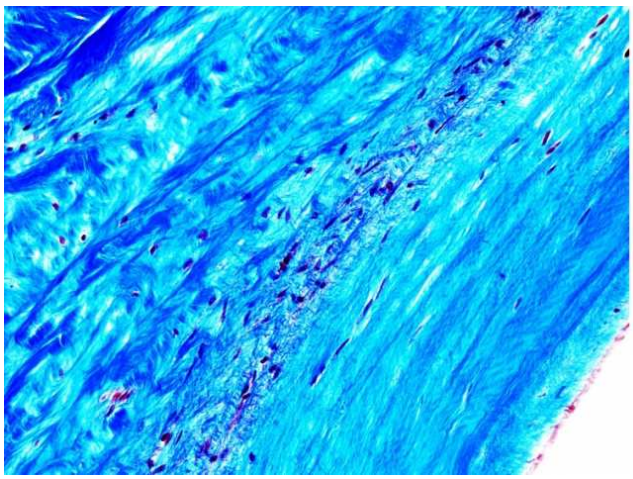

Figure 8a. **Bundles of collagen fibers demonstrate both dense and loose organization in valvular degeneration (Masson's trichrome staining, ×200)**

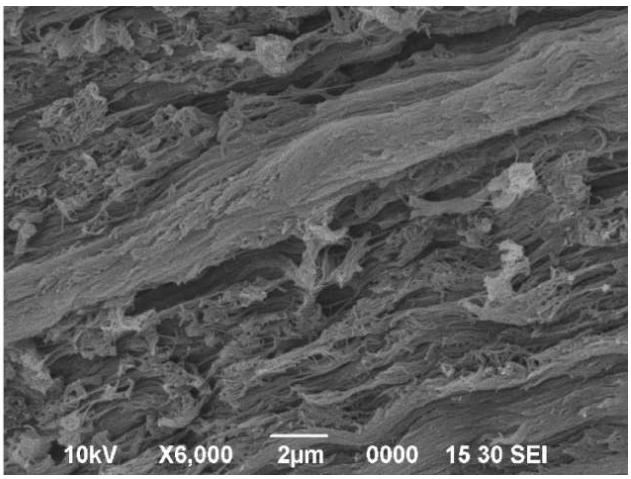

Figure 8b. **Scanning electron microscopy image of degenerative mitral valve. Disorganization of collagen bundles with the loss of the wavy appearance and formation of the fibrous lamina (×6000)**

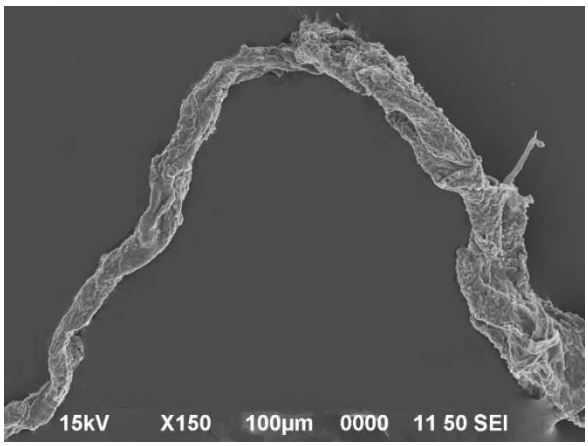

Figure 9. **Low power scanning electron microscopy image of surgically replaced *chordae tendineae*. Thinning of degenerative chordae is evident (×150)**

Discussion

For the first time we analyzed changes occurring in the VICs and ECM of the human mitral valve complex in degenerative valves, age-matched and young control subjects. Age-specific and region-specific differences in the ECM composition and VIC phenotype between mitral leaflets and chordae were accentuated.

The strongest α-SMA expression was observed in the atrialis layer, whereas the expression of CD34 was the most prominent in the spongiosa layer. Elastic fibers were abundant in the atrials layer of mitral valve leaflets, as well as in chordae. These region-specific differences may relate to the different loading patterns in these areas and also to the propensity of certain valve diseases to affect specific regions of the mitral valve complex. On the other hand, the age-specific differences could relate to the predilection of certain cardiac valve diseases to occur at certain ages (Stephens et al. 2011).

According to our results, patients with degenerative MR are younger, compared to patients with calcific aortic valve stenosis. These are in accordance with previously published data (Connell et al. 2011) evidencing that mitral valve degeneration appears distinct from age-related changes and is opposed to calcific aortic valve disease, which has a clear association with aging.

We found marked disorganization of collagen bundles and accumulation of disrupted elastic fibers both in degenerative leaflets and chordae. From a functional point of view, the disappearance of the wavy arrangement of collagen and the rupture of the collagen bundles represent a decrease of the elastic capabilities of the chordae, and is responsible for the increase in chordal length (Liao et al. 2004). Decreased elastic recovery and lengthening or rupture of the chordae contribute to the leaflet prolapse and the mitral valve insufficiency (Icardo et al. 2013).

Interest in VICs has grown in recent years as they are believed to be essential in valve tissue homeostasis and pathophysiology. VICs serve to maintain the structural integrity of the valvular

tissue through protein synthesis and enzymatic degradation. Their phenotype, which ranges from fibroblast-like to myofibroblast-like, is plastic and reversible (Rabkin et al. 2002; Rabkin-Aikawa et al. 2004;).

Phenotypic changes, that occur in the VICs of degenerative valves, present as differentiation from quiescent fibroblasts (CD34 positive) into activated myofibroblasts (α-SMA positive), with the atrialis layer having the greatest myofibroblast differentiation potential. When the phenotype of the resident VICs is myofibroblast-like, the cells are actively remodeling the ECM, indicating that VIC phenotypic state at a given time is related to the current remodeling demands of the tissue (Rabkin et al. 2002). We found increased α-SMA expression both in degenerative leaflets and chordae. It indicates that cellular and extracellular components are both involved in degenerative MR pathogenesis.

In addition to their role as matrix-producing cells, VICs express catalytic enzymes. Increased matrix degradation plays a fundamental role in the development of structural abnormalities during leaflet degeneration and also contributes to spontaneous chordal rupture (Rabkin et al. 2001; Icardo et al. 2013). MMP-3 has the ability to cleave the ECM and activate collagenase, while MMP-9 is involved in angiogenesis and inflammatory infiltration (Sternlicht et al. 2001). We found increased expression of MMP-3 both in mitral valve leaflets and chordae tendineae. It may ultimately result in chordal rupture.

The chordae is a potential target of the degenerative disease. Progression of the disease may be the reason for the late complications and the recurrent mitral regurgitation which can occur several years after surgery (Flameng et al. 2008). It may indicate that a more aggressive approach to surgery may be needed (Icardo et al. 2013).

Knowledge of cell-matrix interactions may be crucial for valve tissue engineering (Stephens et al. 2011). The stiffness of the substrate on which VICs are grown has been shown to affect the cell phenotype, in that VICs grown on rigid plastic were more spread and expressed more α-SMA than those grown on flexible polyacrylamide (Discher et al. 2005).

Conclusions

Activated interstitial cells were more prominent in diseased valves and were found to be the source of MMPs. Fragmented elastic fibers accumulated in regions with collagen fiber degeneration. These changes in collagen and elastic fiber organization are possibly the key features in the pathogenesis of MR. Chaotic organization of collagen fibers promotes leaflet thickening, while fragmentation of elastic fibers decreases the elasticity of chordae tendineae. Valve cells therefore demonstrate a variable phenotype both between and within anatomic regions of the valve.

Acknowledgement

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REAL-TIME ULTRASOUND-GUIDED PERCUTANEOUS DILATATIONAL TRACHEOSTOMY: A FEASIBILITY STUDY

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Abstract

Real-time ultrasound-guided percutaneous dilatational tracheostomy: a feasibility study

Introduction. Patients in ICU require tracheostomy for long-term ventilator support, real-time US guidance for percutaneous dilatational tracheostomy (PDT) is the method of choice.
Aim. Was to demonstrate that PDT under real-time US guidance is feasible.
Methods. Mechanically ventilated patients under deep sedation and local anesthesia underwent US-PDT. Neck anatomy was examined using palpation and US. Endotracheal tube cuff was visualized during US by inflating it with saline solution. The trachea was punctured under real-time US guidance using the acoustic shadows of the tracheal rings to identify the level of puncture. A 2 cm horizontal incision and blunt dissection was carried out after puncture at the midline between the 2nd and 3rd rings. Advancement of the needle was halted, when the aspiration of air into a saline-filled syringe and a palpable change in resistance was noted. Then guidewire was passed following dilatation and tube placement.
Results. 10 patients aged between 33 and 66 years underwent US-PDT. Diagnoses were: aneurysmal subarachnoid hemorrhage (***n***=4), severe traumatic brain injury (***n***=4), intracerebral hemorrhage (***n***=2). Procedure was successful in all 10 patients. No complications were observed in any patient during the procedure or following for up to 1 week after (median 5 days, IQR4-6).
Conclusion. US-PDT may become an alternative method to bronchoscopy assisted tracheostomy if several conditions fulfill: available bed-side US, optimal patient neck anatomy.

Kopsavilkums

Reālā laikā ultrasonogrāfijas asistētā perkutānā dilatācijas traheostomija

Ievads. Intensīvas terapijas klīnikas pacientiem ilgstošas makslīgas plaušu ventilācijas nodrošināšanai nepieciešama traheostomijas ievietošana. Reālā laikā ultrasonogrāfaijas asistētā perkutānā dilatācijas traheostomija (US- PDT) varētu kļūt par zelta standartu šai manipulācijas.
Mērķis. Parādīt, ka US-PDT ir ērti un viegli lietojama metode.
Metodes. Tika atlasīti mākslīgi ventilēti pacienti, kuri atbilst iekļaušanas kritērijiem. Procedūra veikta dzīļā sedācijā, lokālā analgēzijā. Kakla anatomija tika izmeklēta ar palpāciju un US. Endotraheālas caurules manžente tika vizualizēta ar US piepildot to ar S. NaCl šķīdumu. Pēc punkcijas 2 cm grieziens un neasā audu dissēkcija tika veita. Līmeni izvēlējas ar US viduspunktā starp otro un trēšo trahējas skrismsli. USG kontrolē punktē traheju, izmantojot gaisa aspirācijas metodi, ievada katetru, caur katetru ievada vadītajstiepli. Izveidotā kanālā ievada traheostomijas kanili, fiksē ar traheostomijas fiksējošām saitēm, pievieno mākslīgas plaušu ventilācijas aparātam, pārbauda ventilācijas parametrus.
Rezultāti. 10 pacienti vecumā no 33-66 gadiem. Diagnozes: subarahnoidālas aneirismas asinsizplūdums (n=4), smags traumatisks galvas smadzēņu bojājums (n=4), spontāns intracerebrāls asinsizplūdums (n=2). Visiem pacientiem veiksmīgi tika ievietotas PDT ar US asistēšanu. Bez akūtām sarežģījumiem procedūras laikā vai nedēļu pēc tas.
Secinājumi. US-PDT var kļūt par alternatīvu bronhoskopijas asistētai PDT, pie dažiem nosacījumiem: pieejams ultrasonografs, optimālā pacienta kakla anatomija.

Introduction

Patients admitted in ICU frequently require long-term ventilator support, which is a proven factor that prolongs ICU/hospital length of stay, associated with more poor health outcomes as well as increases expenses for patient management. (Mahafza 2012; Hunter 2014)

It is known, that long-term ventilation support could not be provided by orolaryngeal intubation, because of proven data that after 7th intubation day, tissue lesion that forms in orolarynx and trachea are not completely irreversible. The benefits of tracheostomy over prolonged intubation are: reduced use of sedation, faster rehabilitation process, reduced trauma to the oropharynx and

larynx, reduced work of breathing and improved clearance of pulmonary secretion, decreased periods of mechanical ventilation and consequently length of ICU and hospital stay. (Durbin 2005)

Nowadays bedside percutaneous dilatational tracheostomy (PDT) is the method of choice in ICU department. Several studies have demonstrated that PDT is a safe and cost-effective alternative to open, surgical tracheostomy. PDT is routinely performed with the aid of bronchoscope to further enhance the safety and accuracy of the procedure. But recently bedside real-time US guidance has emerged as a simple and noninvasive tool for different procedures as well as PDT. In Latvia this method is not widely used, perhaps because of lack of knowledge or equipment, that why this study was undertaken to proven that real-time US guidance of PDT is feasible. (Heikkinen 2000; Freeman 2001; Delaney 2006)

Aim

Our objective was to demonstrate that PDT performed under real-time US guidance is feasible.

Methods

This is a prospective case series study. Mechanically ventilated (MV) patients, who required ventilation support for longer than 7 consecutive days were included in study. Mechanically ventilated patients, without cervical spine lesions, poor anatomy, obesity (Body Mass Index $\geq$30 kg/m^2) and previous tracheostomy, underwent US guided PDT (US-PDT). Before procedure all patients were estimated in Checklist for percutaneous tracheostomy in critical care (Rajendran 2014).

The decision to perform tracheostomy was made in accordance with the usual practice at our institution. The number of days on mechanical ventilation prior to PT, and the indication for tracheostomy were recorded. All US-PDT were performed by single intensivist with 12 year experience in providing bronchoscopy assisted PDT and 8 years' experience with the use of point-of-care ultrasound for evaluation of neck anatomy prior to PT.

Propofoli 1% infusion titrated to deep sedation (RASS -5) was used for all patients during the procedure and local anesthesia with S. Lidocaini 2% 5ml. Patients were positioned optimally, mild head extension with a rolled blanket under the shoulders, before procedure initial neck anatomy was examined using palpation as well as the US and color duplex imaging for visualization of blood vessels.

A bk medical flex Focus 500® point-of-care ultrasound machine was used, with a 6 to 18 MHz linear array probe and a sterile sheath. The mode of imaging was set to maximal resolution and depth of imaging adjusted to keep the trachea just within the screen (Figure 1).

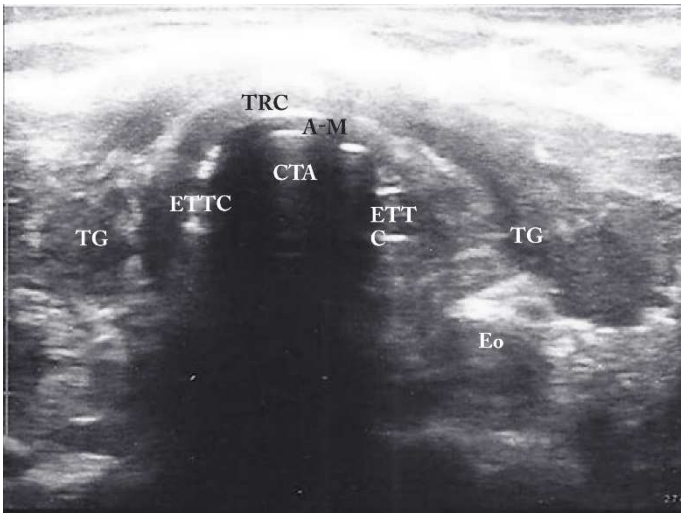

Figure 1. **Transverse view at the level of suprasternal notch. Intubated trachea, with ETT cuff filled with saline, TRC-tracheal cartilage, A-M- air mucosal interface, Comet tale artefact, TG-thyroid gland, Eo-oesophagus**

It was crucial to visualize endotracheal tube cuff, in order it not be in the needle insertion point. With or without an ETT in place, the trachea appears as an area of dirty shadowing on a sonogram because it is filled with air (Figure 1, comet tale artefact). That is why the cuff was inflated with 7 mL of saline while the probe was held in a longitudinal orientation at the suprasternal notch. The cuff was readily

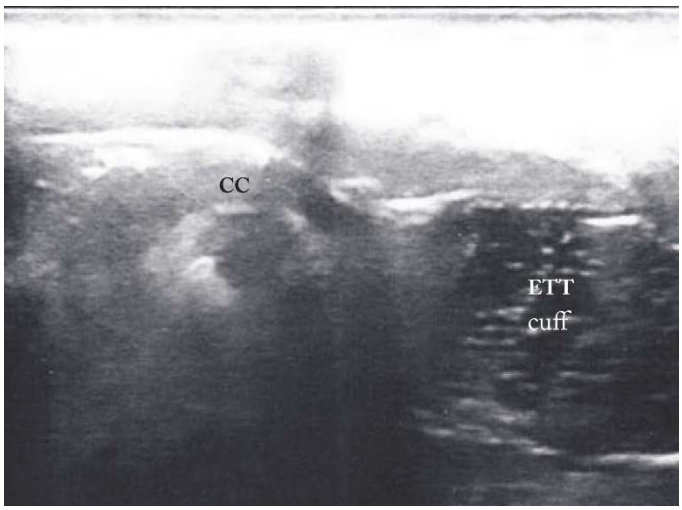

Figure 2. **Left parasagittal view at cricoid membrane. CC- cartilage cricoidea, ETT-endotracheal tube cuff, filled with saline and air burbles. visualized as an expanding anechoic sphere transiently containing hyperechoic bubbles (Figure 2)**

The probe positioned in longitudinal orientation, revealed the presence of two hyperechoic parallel lines within the trachea (Figure 3). These lines represent the outer and inner surfaces of the anterior aspect of the ETT. The saline within the cuff acted as an acoustic window allowing visualization of the tube, which had not been possible when the cuff was filled with air. When the saline is evacuated, parallel lines disappear.

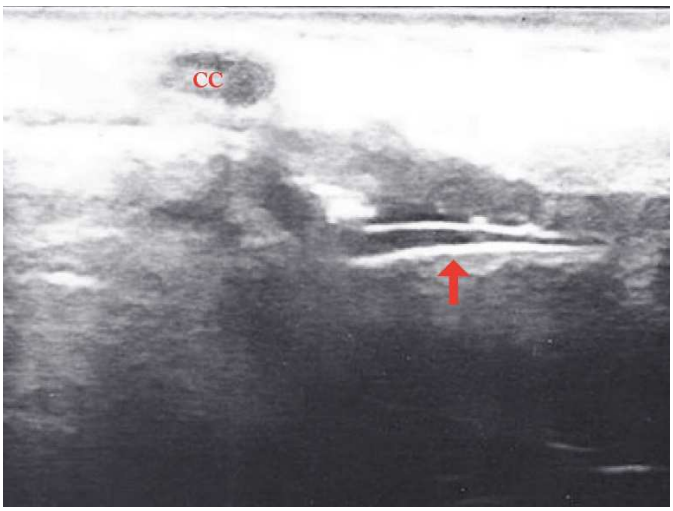

Figure 3. **Longitudinal view of intubated trachea, ETT cuff inflated with saline**

This method of confirming ETT cuff position was described by Tessaro in 2015. Then the tube was withdrawn until the cuff was positioned immediately inferior to the vocal cords. The cricoid cartilage (Figure 4, CC – cricoid cartilage) was identified using its relatively larger acoustic shadow within the anterior wall of the larynx caudal to the cricothyroid membrane and the tracheal rings identified by their relatively thin acoustic shadows within the anterior wall of the trachea. The point of tracheal puncture was selected using the following criteria: the space between the second and third rings or the third and fourth tracheal rings, as close as possible to the midline and no vascular structure in the path of the needle (longitudinal view) (Figure 4) Transverse/axial real-time imaging of the trachea was performed to permit clear visualization of the needle path up to the midline of the anterior wall of the trachea. The trachea was punctured under real-time US guidance using 14 G cannula-on-needle while observing the needle path and tracheal wall insertion by real time sonography. The needle was introduced perpendicularly to the skin and the needle path was determined by the distinct acoustic shadow ahead of the needle followed by the displacement of tissue layers seen with needle passage (Figure 5, arrow).

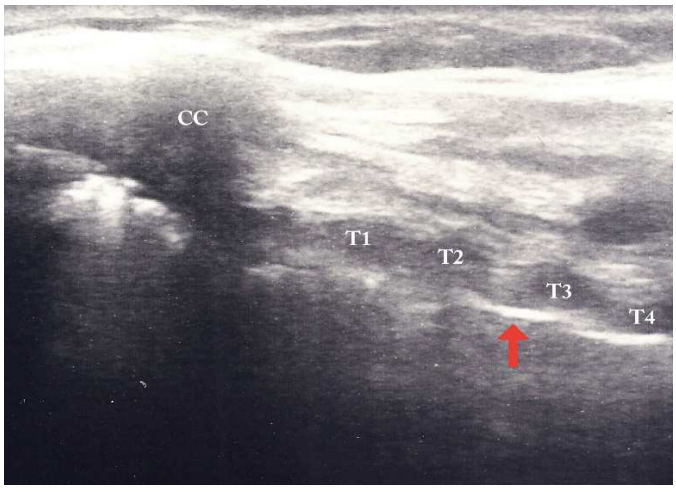

Figure 4.

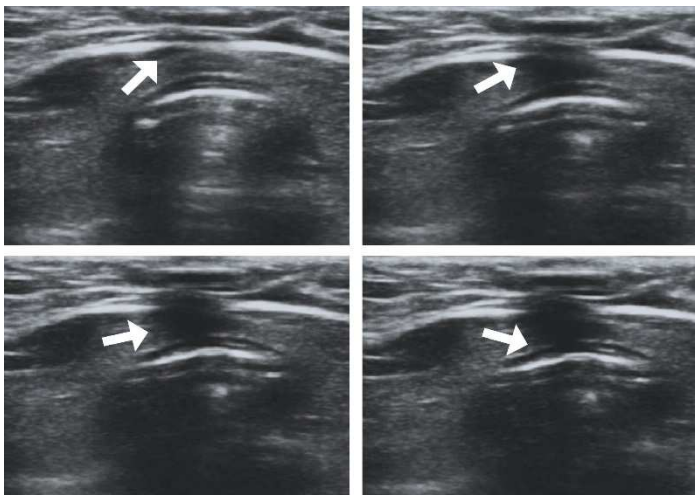

Figure 5.

Advancement of the needle was halted when the needle was seen to reach and then just pass the anterior wall, with a palpable change in resistance as the lumen was entered. The goal was to puncture the anterior quadrant of the trachea, as close as possible to the midline. Endotracheal position of the tip was confirmed by the aspiration of air into a saline-filled syringe. The needle was then angled slightly caudally to prevent retrograde passage of the guidewire. A J-shaped guidewire was introduced and the cannula removed, then an introducer dilator was passed over the guide wire to facilitate the stoma formation. 2 cm horizontal skin incision was performed on both guidewire sides.

Subsequently, blunt pretrachial and then tracheal dilatation was done as Griggs dilatation forceps was advanced over the guide wire. An appropriate size tracheostomy tube was then threaded over the guide wire into the trachea lumen. After placement of tracheostomy tube, its positon was confirmed by auscultation of bilateral equal air entry and adequate ventilation date from mechanical lung ventilation apparatus. Thereafter, tracheostomy tube was secured with straps and mechanical ventilation was continued.

Results

Sonographic examination of anatomy was possible in all enrolled subjects and no patients required conversion to standard bronchoscopic PDT. A total of 10 patients underwent US-PDT. Two patient firstly enrolled in study, were excluded after sonoscopic examination of neck anatomy. One because of diffuse thyroid gland enlargement and its cover of point of puncture, second because of individual large prethacheal veins at the point of puncture thought high risk of mentioned structure injury. The needle path could be defined using the acoustic shadow ahead of the needle followed by displacement of tissue in all patients.

Patient were aged between 33 and 66 years (median 48 years, IQR 36-60). Four patients were female. Diagnoses were: aneurysmal subarachnoid hemorrhage (SAH, n = 4), severe traumatic

brain injury (TBI, n = 4), intracerebral hemorrhage (n = 2). We successfully performed US-PDT procedure in all 10 patients. No acute complications were observed in any patient during the procedure. There were no episodes of hypoxia (pulse oximetry <90%) or unexpected extubations during the performance of PDT. No significant hemodynamic instability was observed during procedure. Following on patients for up to 1 week (median 5 days, IQR 4-6) revealed no new complications. No complications were found on bronchoscopy, including no clearly visible tracheal ring fractures and no posterior wall injury/puncture. During bronchoscopy no tracheostomy misplacement was found.

Discussion

The purpose of our study was to demonstrate the feasibility of performing percutaneous tracheostomy under real-time ultrasound guidance with actual visualization of the needle path. One should take into consideration that this research is feasibility study with only 10 patients and validation in future studies with larger sample is necessary before the results can be considered as conclusive.

In comparison to bronchoscopy assisted technique in US guided PDT performer always see the first tracheal ring. Placement of the tracheal tube above the first tracheal ring may increase the risk of late sub-glottic cicatrization and stenosis. (Walz 1999; McFarlane 1994; Heurn 1996)

In our ICU department, we perform early tracheostomy, within one week of intubation, for patients with acute brain injury, who are likely to require mechanical ventilation, or a definitive airway (because of poor mental status and the inability to cough or handle secretions) for more than two weeks. Although the benefits early tracheostomy is subject of debate, for now it is proven potential reduction in the number of ventilator and ICU days as well as improvement in patient comfort and reduced need for sedation. (Terragni 2010; Griffiths 2005; Nieszkowska 2005)

Another advantage of US-PT is the ability to avoid vascular structures anterior to the trachea and to change the point of puncture before the cut. Prior studies have demonstrated a potential role for pre-procedure ultrasound imaging in transverse section to identify vascular structures and reducing the risk of bleeding. (Hartfield 1999; Flint 2009)

Using US guided PDT some of the disadvantages of bronchoscopy can be avoided. This is crucial especially in the acute brain injury patients. Our study limitation is that ICP monitoring was not used. But previously reported observation that bronchoscopy is associated with a predictable, if transient, increase in intracranial pressure (ICP), probably caused by hypoventilation and hypercarbia. (Kerwin 2000; Reilly 1995)

Also, direct laryngoscopy has a proven effect of increasing intracranial pressure, so method of inflating ETT cuff with saline to visualize and position it is excellent method in avoiding unnecessary risk of rising ICP. As well as we need to take into the consideration that not all patient

will have adequate laryngoscopic grade of view so it is one more advantage of visualizing ETT cuff with US. And the least is that the performer in case of US visualizing of ETT cuff do not need an assistant. (Perkins 2013)

We suppose that US guided PDT should become the method of choice over bronchoscopy assisted tracheostomy in routine practice, because it can be performed by single intensivist, you do not require bronchoscopy specialist or bronchoscope itself. In case, ETT cuff is visualized by US, no assistant is need to perform direct laryngoscopy. It becomes cost-effective, because resources are not spend on additional personal, equipment usage and sterilization.

Our study is limited in being only a preliminary demonstration of the feasibility of using real-time ultrasound guidance for tracheal puncture during PDT in patients without certain factors as morbid obesity, poor anatomy (short neck, blood vessels at the point of puncture ett.), spinal lesion at cervical level, previous history of tracheostomy. Larger, randomized studies are required to better define the advantages of this technique, appropriate candidates and the safety of US-PDT. We believe our study lays the foundation for future clinical trials.

Conclusion

In our everyday practice US guided PDT is a feasible method of providing long term ventilation support. US-PDT may become an alternative method to bronchoscopy assisted tracheostomy if several conditions will fulfill: available bed-side US, optimal patient neck anatomy. Still the small patient number do not allow to make the conclusions that might be spread to overall practice, research is exploratory and provide insight to better health care. Further studies with bigger sample size must be untaken to make more objective conclusions.

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SKIN GRAFT HEALING AFTER AUTODERMOPLASTIC SURGERY FOR THERMAL BURNS

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Abstract

Skin graft healing after autodermoplastic surgery for thermal burns

Key words: *split-thickness skin graft, healing, thermal burns, autodermoplastic surgery*

Objectives:To determine the length of time it takes to achieve complete wound healing in split-thickness skin-grafted burn wounds and to identify factors that affect time to complete wound healing. Methods: Prospective study of 20 thermic burn trauma IIB, III grade pacients, who underwent autodermoplastic surgery. After transplantation patients were observed during 1st, 2nd, 4th wound dressings and on discharge. Percentage of wound surface epithelialization, presence of exudate, graft color and any possible complication were assessed.

Results80% had IIAB grade burns, 1 patient III grade burn, 3 patients had both IIAB and III grade burns. All patients were transplanted 0.3 mm thick skin autograft. 65% of skin grafts were meshed. Median time to complete wound healing is 5 weeks, minimal 3 weeks and maximum 12 weeks 50% of skin grafts had 90% wound closure at postoperative day 12. No grafts were lost to infection. Factors that significantly affected time to complete wound healing were age wound epithelialization percent observed during dressings

Conclusion: Evaluation of wound epithelialization gives information about skin graft healing already on the 3rd postoperative day (1st dressing). Results demonstrate that all patients will have 100 percent wound closure at discharge. Factors thought to influence time to complete wound healing, such as total body surface area burned, burn grade, sex, graft type, donor site, smoking and infection, did not significantly affect the authors' patient group.

Kopsavilkums

Ādas transplantātu piedzīšana pēc autodermoplastiskām operācijām sakarā ar ādas defektiem

Atslēgas vārdi: *autodermoplastika, ādas transplantāts, apdegums, piedzīšana*

Ievads. Valsts Apdegumu centrs ir vienīgā klīnika Latvijā, kur notiek pieaugušo ādas apdegumu ārstēšana, tajā skaitā, autodermoplastikās operācijas

Darba mērķis. Novērtēt ādas transplantāta piedzīšanas kvalitāti un ilgumu pacientiem ar IIB un III pakāpes termiskiem apdegumiem

Materiāli: pacienti, ar IIB-III pakāpes termiskiem apdegumiem. Pētījuma realizēšanai izstrādāts protokols, kurš atļaus novērtēt ādas transplantāta piedzīšanas kvalitāti dinamikā. Autodermoplastiskās operācijas laikā un sekojošu piecu pēcoperāciju pārsiešanu laikā, tiks ievākta informācija par ādas transplantāta piedzīšanas procesu.

Rezultāti. Pētījumā piedalījās 20 pacienti, 80% pacientiem bija konstatēti IIAB pakāpes apdegumi, III pakāpes apdegums bija 1 (5%) pacientam, bet gan IIAB, gan III pakāpes apdegumi bija 3 (15%) pacientiem. Visiem pacientiem bija pārstādīts 0.3 mm biezs ādas transplantāts. 65% ādas transplantāti tika perforēti. Nepilna biezuma ādas transplantāta donora vieta 90% gadījumos bija augšstilba priekšēja virsma. Pirmajā pārsiešanas reizē 90% no brūces virsmas bija epitelizētas 20% pacientu. 50% pacientu 12. pēcoperācijas dienā būs novērojama 90% brūces virmas epitelizācija. Mediānais laiks līdz 100% brūces epitelizācijai ir 5 nedēļas. Minimālais laiks ir 3 nedēļas, bet maksimālais 12 nedēļas. Vecums un mazāka brūces virmas epitelizācija statistiski ticami pagarina laiku līdz pilnai transplantāta piedzīšanai.

Secinājumi. Ādas transplantācija ir efektīva un kvalitatīva IIB, III pakāpes apdegumu ārstēšanas metode

Introduction

Skin grafting is a frequently used surgical method of skin defects treatment. The Republic Burn Centre is the only clinic in Latvia that provide skin burns treatment for adults including autodermoplastic operations. In 2016 in the Republic Burn Centre were carried out 108 autodermoplastic operations. Skin grafting is provided for patients with IIB, III burn degrees (according to burn classification 1999). (Savicka 2004: 63)

Burn injuries account for 1% of total traumatic incidents. According to The Republic Burn Centre data, in 2016 there were hospitalized 368 patients with burn injuries including 274 (74%) patients with thermal burns. In accordance with the World Health Organization data, patients with burn injuries have high survival rate – 96.1%. (Savicka 2004: 63)

This is due to a modern integrated approach to burn treatment, and the most significant components of it include hypermetabolic syndrome treatment, liquid substitution, burn wound infection control, an appropriate diet, and early prevention of acute respiratory distress syndrome. (Mosier 2009: 617)

In the research, had being observed the duration of time necessary for 100% burn wound healing when applying partial thickness skin grafts. There were studied patients and factors that influence skin graft healing process.

The research according to the assignment is descriptive (longitudinal) and comparative; by time – it is prospective, and by its type it is an observation research.

Methods and materials

Participants in this research included Republic Burn Centre hospital Bikernieki patients who had IIB-III burn degrees and who underwent autodermoplastic operations. All these patients received the same standard Republic Burn Centre after-operation treatment. In the research participated 20 patients. The participants had been selected by the following criteria:

1) without gender restrictions
2) 18-year-old and older
3) Able to orientate in time, place and person
4) type of the burn injury- thermal
5) IIB-III burn degrees
6) was conducted partial thickness skin graft

To implement the research was elaborated a protocol which enabled to observe skin graft healing dynamics through ongoing process. The data gathering was implemented using patients' data from anamnesis about demographical indicators, burn degree and area, patients' comorbidities. From the operation theatre protocol was gained information about skin graft thickness, perforation and the donor place. During after- operation dressing period was collected information about skin graft healing process. Skin graft healing was estimated as percentage of wound surface epithelialization.

Research protocol

Name, Surname:_____

Sex: M F

Age:_____

Diagnosis:_____

Comorbidities: is no

Is:_____

Operations date:_____

Meshing: with without

Graft thickness:_____

The donors place:_____

	1st Dressing	2nd Dressing	4th Dressing	On discharge
Wound epithelialization %				
Graft color				
Exudations				
Complications				

Results

In the research took part 20 patients, 7 (35%) women and 13(65%) men who had been hospitalized to the Republic Burn Centre with thermal burns. The patients age (median [interquartile range]) was 54 [38 – 67.25] years. Eighty percent of patients had IIAB burn degree, 1 (5%) patient had III burn degree, but both IIAB and III burn degree had 3 (15%) patients. The burn area of whole body surface area (median [interquartile range]) was 9.50% [6.50%- 15.33%]. Patients with IIAB burn degree median burn body surface area was 10%, to this group belonged also 2 patients with the biggest burn body surface area -35%. Patients with IIAB-III burn degree median burn body surface area was 8%. One patient had III burn degree with overall area 1%. 50% of patients had ≥10% overall burn body surface area.

Ten (50%) patients were smokers. The patients had the following comorbidities: 25% (n=5) arterial hypertension, 15% (n=3) Hepatitis C, 15% (n=3) diabetes. One patient had all these three diseases. Two patients needed the repeated skin transplantation because of damaged graft.

All patients had been transplanted 0.3 mm thick skin graft. 65% skin grafts were perforated, therefore increasing the surface area as 1:3. (Foto 1, 2)

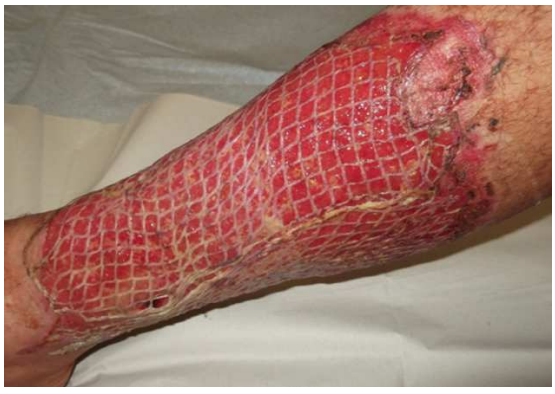

Foto 1

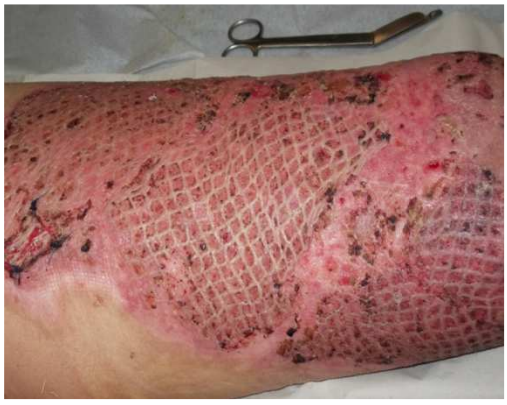

Foto 2

Partial thickness skin graft donor part of the body in 90% of cases was front surface of thigh. (Foto 3)

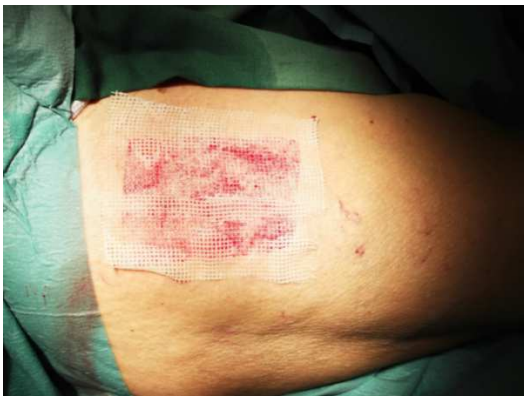

Foto 3

For one case skin graft was taken from lateral surface of shin, and for one patient the skin graft was taken both from front surface of thigh and from lateral surface of shin. 65% partial thickness skin grafts were perforated.

In Fig. 1 is shown skin graft healing percent or wound surface epithelialization percent and corresponding number of patients at the first dressing after autodermoplastic operation. Observing skin graft healing at the first dressing, was stated that 75% patients had visible 75% wound surface epithelialization. At the first dressing 90% of wound surface was epithelialized in 20% patients, but one patient had epithelialized only 30% of wound surface.

One patient did not have any visible epithelialization and also there was stated absence of skin graft in his wound. Possible explanation of this could be that the graft was lysis.

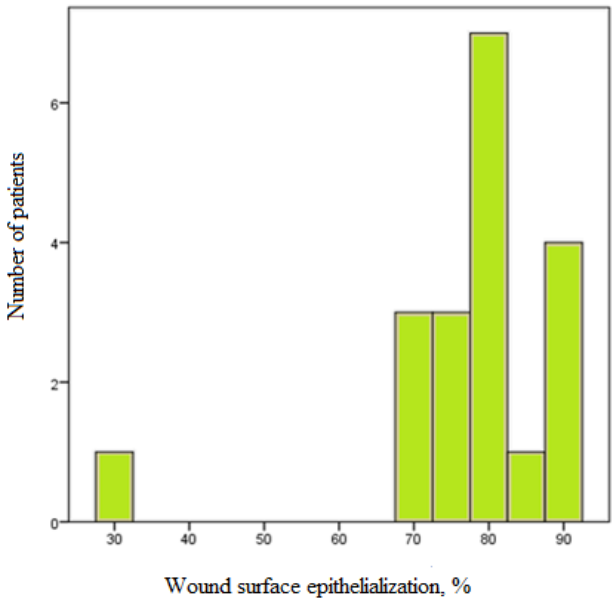

Fig. 1. **Wound surface epithelialization at the first dressing**

In Fig. 2 is shown skin graft healing percent or wound surface epithelialization percent and corresponding number of patients at the fourth dressing after autodermoplastic operation. At the fourth dressing three patients had visible complete skin graft healing or 100% wound surface epithelialization. (Foto 4, 5)

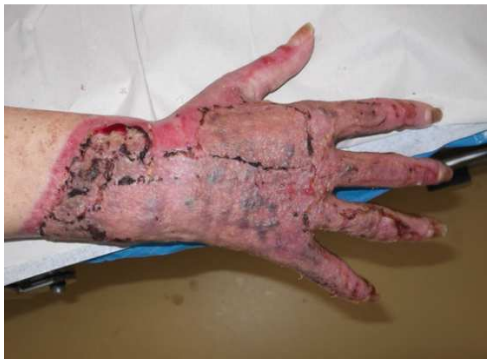

Foto 4

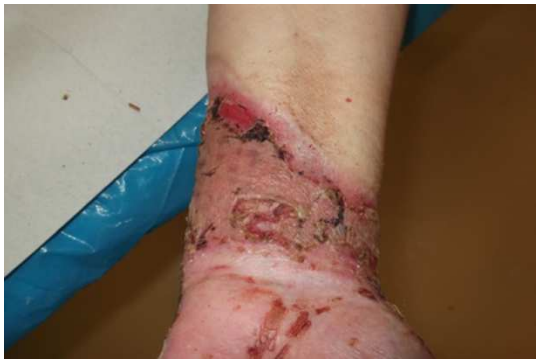

Foto 5

80% patients had 85% wound surface area epithelialization, 10% patients had visible 60% wound surface epithelialization. One patient still kept insufficient skin graft healing – only 30% of wound surface area was epithelialized.

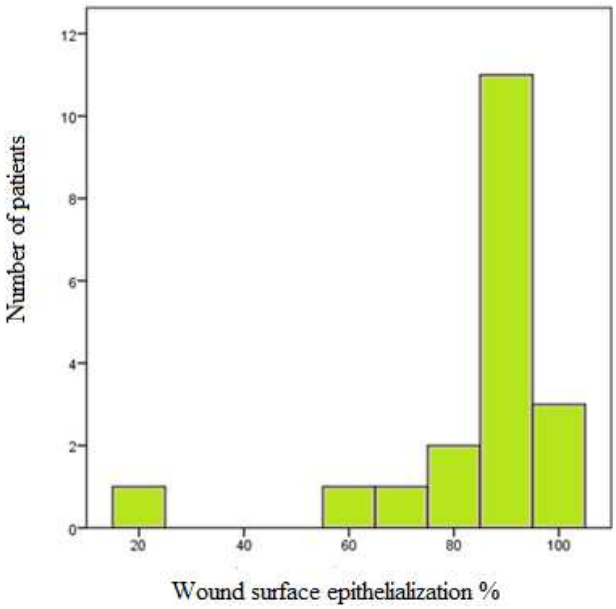

Fig. 2. **Wound surface epithelialization at the fourth dressing**

In Fig. 3 is shown time to the complete skin graft healing and the corresponding number of patients.Median time to 100% wound surface epithelialization is five weeks. Minimal time to the complete healing is three weeks while the maximal time takes 12 weeks.

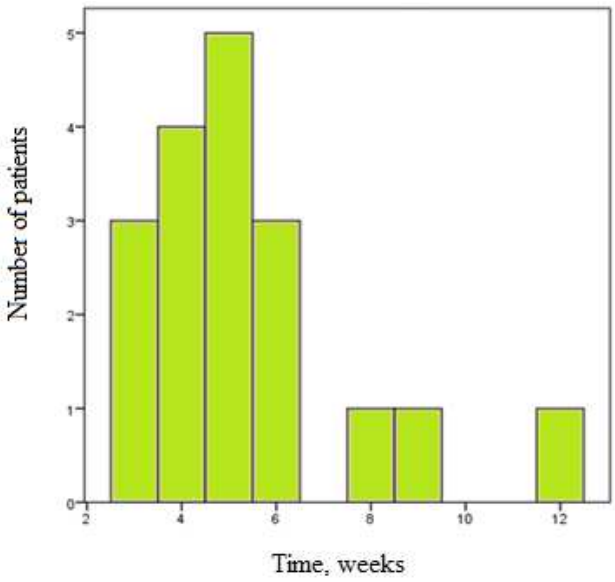

Fig. 3. **Time to 100% wound surface epithelialization**

Eighteen patients were discharged from the hospital after complete skin graft healing, 100% wound surface epithelialization. Two patients hadn't achieved the complete skin graft healing. There occurred *exitus letalis* in one patient after 4 weeks of treatment. The patient's death was unrelated to after operation complication, it was caused by his comorbidities. The patient was 76 years old, had arterial hipertension, congestive heart failure, HCV, for long time had been receiving artificial lung ventilation. The death cause was chronic decompensated heart failure, arrhythmia.

One patient did not finish treatment on account of breach of hospital regimen and regulations. At this patient's first and second dressing was observed 75% skin graft healing, at the fourth dressing – 80% skin graft healing. Further was stated partial rejection of skin graft, 30% of wound surface was not epithelialized. The reason for this unsuccessful skin graft healing was, possibly, alcohol usage after the fourth dressing. The patient needed the repeated skin grafting. In total, two patients needed the repeated skin grafting because of damaged graft. Even at the first dressing it was stated that the second patient's graft lysis and there hadn't been any signs of epithelialization. It was related to this patient'severe condition. The patient had a serious skin injury 35%, II burn degree.

Table 1**. Graft colours and wound exudate correlation with draft healing percent***

Skin graft	**Healing 1**	**Healing 2**	**Healing 4**
	p	*p*	*p*
Colour 1	0.03	0.02	0.03
Exudate 1	-	-	-
Colour 2	0.03	0.02	0.03
Exudate 2	0.08	0.03	0.03
Colour 4	0.05	0.05	0.05
Exudate 4	0.07	0.02	0.05

**with numbers 1, 2, 4 were shown correspondently the first, the second, and the fourt dressings*

The nonparametric Mann- Whitney test was applied to find out if there were statistically significant differences while observing the skin graft healing quality and graft color, the exudate substance, the size of wound surface epithelialization at the first, second, and fourth dressing (Table 1). Having analyzed these clinical indications of graft healing , was stated statistically significant difference between wound surface epithelialization percent and exudate substance in it. At the second and the fourth dressings statistically significant difference existed between wound surface epithelialization percent in wounds with increased exudate (p=0.03). Exudate in a wound is correlated with reduced wound surface healing percent. It was impossible to perform this analysis at the first dressing as 100% patients had observable exudation. At all three dressings, statistically significant difference existed between skin graft healing percent and the color of graft (white or rose).

Applying the nonparametric Mann- Whitney test for patients who had diabetes (D), was stated statistically significant difference between skin graft healing (Table 2). The patients with diabetes and the patients without diabetes didn't have any statistically significant different time to complete graft healing (p=0.19). Possibly, patients with diabetes had slower early graft healing, which could be related to slower vascularization due to microangiopathy.

Table 2. **Relation between comorbidities and graft healing***

	Healing 1	**Healing 2**	**Healing 4**
	p	*p*	*p*
AH	0.02	0.02	0.01
D	0.02	0.01	0.08

** with numbers 1, 2, 4 were shown correspondently the first, the second, and the fourth dressings*

Within the limitations of the research has been found statistically significant correlation applying nonparametric Spearman's rank correlation coefficient between quality of healing and patient's age – the older was the patient, the worse was graft healing observed at the fourth dressing (r=0.49; p=0.03).

In the research hasn't been found statistically significant difference between smoking and non-smoking patients' skin graft healing quality (p>0.05).

Discussion

It is possibly to estimate skin graft healing following the observation of wound surface epithelialization percent. For successful skin graft healing is accepted 95-100% wound surface epithelialization. (Thornton 2004, Le Cocq 2011: 502, Jewell 2007: 454.)

In this research the average time to complete (100%) skin graft healing was 5.4 (±2.3) weeks, but maximal time – 12 weeks. Literature references show less time until complete skin graft healing - 10.7 weeks. The considerable difference in minimal time necessary for 100% healing could be

explained by the presence of children amongst patients in other researches as children have faster wound surface epithelialization. On the seventh day after operation 88% patients had 95% wound surface epithelialization observable. In our research, only 30% of patients had 90% wound surface epithelialization observable on the seventh day after operation (at the second dressing).

In our research has been found a positive correlation between age and time to complete skin graft healing, the age of a patient statistically significantly influences the healing process.

Within the limitations of this research has been found statistically significant difference in wound surface epithelialization percent in patients with diabetes – similarly to other studies where authors show the greater partial graft healing percent in patients with diabetes compared with patients without diabetes.(McCampbell 2002: 157). In the literature references, there is no description of the impact of arterial hypertension on the partial graft healing after a burn injury. (Guo S.,2010:219) In the literature references and in many research studies wound infection is regarded as the first cause of graft rejection. (Unal 2005:102)

In our research, hadn't been recorded any case of graft rejection due to wound infection. Apparently, it was related to strict observance of asepsis rules and antibacterial therapy implementation.

Only two patients (10%) needed the repeated skin grafting. In other researches three (6%) patients had the repeated skin grafting.

Conclusions

- In 50% patients on the twelfth day after operation will be seen 90% wound surface epithelialization
- All patients on the discharge day will achieve 100% wound surface epithelialization, the average time until discharging is 5 weeks.
- Older patients need longer time to complete graft healing.
- There have been identified two diseases - arterial hipertonia and diabetes that influence skin graft healing process
- It has been observed that patients with diabetes have worse skin graft healing, but the time to complete graft healing is not longer.

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THE ANATOMICAL CHARACTERISTICS OF *N. TRIGEMINUS* BLOCKADE SITES

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Abstract

The anatomical characteristics of *n.trigeminus* blockade sites

Key words: *N.trigeminus, blockade sites, foramen supraorbitale, foramen infraorbitale, foramen mentale.*

The main innervation of the face is provided by branches of trigeminal nerve – the ophthalmic nerve, maxillary nerve and mandibulary nerve. All of the branches of these nerves leave bone channels through the openings, which are projected on the same imaginary line located 2,5cm lateral to the midlaine of the face – *foramen supraorbitale, foramen infraorbitale* and *foramen mentale.* According to the results the location of these openings can differ up to 0,5cm. This can cause problems with entering the local anesthesia, so it is very important to understand and clarify some outer features that could show us the most precise location of each opening.

Kopsavilkums

***N.trigeminus* zaru blokāžu veikšanas vietu anatomisks raksturojums**

Atslēgas vārdi: *N. trigeminus, blokāžu veikšanas vietas, foramen supraorbitale, foramen infraorbitale, foramen mentale.*

Sejas galveno ādas inervāciju nodrošina trijzaru nervs (*nervus trigeminus*) ar saviem zariem – *nervus ophthalmicus, nervus maxillaris* un *nervus mandibularis*. Šī nerva zari atstāj galvaskausu caur atverēm – *foramen supraorbitale, foramen infraorbitale* un *foramen mentale*, kuras atrodas uz vienas iedomātas 2,5cm laterāli no sejas viduslīnijas. Apkopojot rezultātus, secināts, ka atveru atrašanās vietas var atšķirties līdz pat 0,5cm. Tas var radīt problēmas, ievadot lokālās anestēzijas līdzekli, tāpēc ir ļoti svarīgi saprast un noteikt ārējus orientierus, pēc kuriem atveru atrašanās vietu noteikšana būtu atvieglināta.

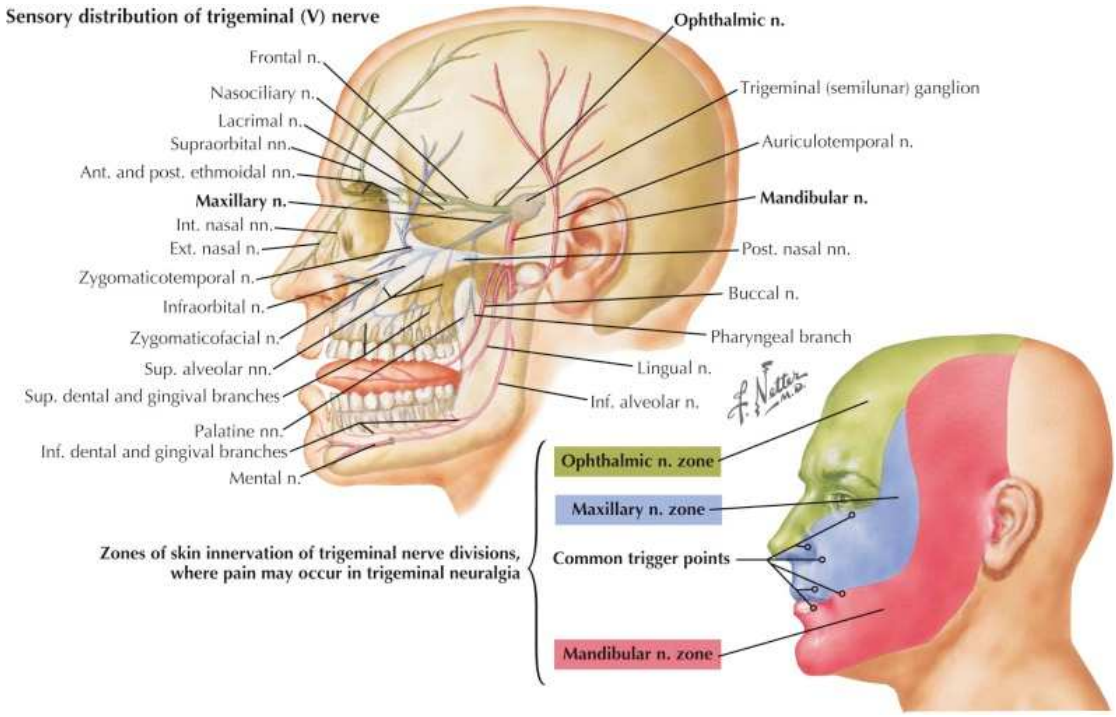
Blockade of trigeminal nerve (*n. trigeminus*) is an important stage before the surgical procedures, which are connected with skin aging, congenital facial defect correction or injuries. More often a local anesthesia is carried out of places where *n. trigeminus* branches leave bone channels through the openings – *foramen supraorbitale, foramen infraorbitale* and *foramen mentale*. Through the literature sources these openings are projected on the same imaginary line located 2,5 cm lateral to the midline of the face.

Very precise locating of the nerve branch openings in the cranium is important when administering local anesthesia, because of possible complications for patient or possible discomfort for a patient during this manipulation. It is very important to understand and clarify some outer features that could show us the most precise location of each opening. The foramen supraorbitale and mentale are palpable, but finding the exact location of foramen infraobitale may still be problematic.

The aim of this research was dissect openings *foramen supraorbitale, foramen infraorbitale* and *foramen mentale* with outgoing nerves on cadaver's face. Verify the location of the openings on the skulls, as a reference point assuming a median line of the face. Analyze obtained results and find indicators on a human face that would help to diagnose an exact location of these openings.

As materials and methods a cadaver of Anatomy and Anthropology Institute and 20 exhibited skulls in Anatomy museum of J. Primanis were used. As sources of literature other studies on the subject of the PubMed database, anatomical atlases and ClinicalKey database were used.

The trigeminal nerve with the main branches – ophthalmic, maxillary, and mandibular branches is the largest and the most complex nerve of the 12 cranial nerves (Picture 1). It is responsible for the sensory innervation of face, which is why it is used for blockades.



Picture 1. ***N. trigeminus*** **location place, branches and innervation zones**.
(*Netter's Neurology*, Jones, Vytopil 2012 year)

The *nervus supraorbitalis,* which is a branch of *nervus frontalis* one of *nervus ophthalmicus* branches, leaves bone channel through the opening *foramen supraorbitale*. *N. supraorbitalis* is responsible for skin innervation in the area of the forehead. To perform the blockade of this nerve, firstly it is necessary to palpate the opening through the skin. Then injection is followed, during which always the upper edge of the *orbita* must be palpated by the free hand to prevent that needle goes into the wrong place where it would be undesirable and can cause unwanted infections.

Foramen infraorbitale is located 2,5cm lateral from the midline of the face and 0,5-0,9cm down from the lower edge of the *orbita* or down from the medial side of the *iris* or medial line of the *pupilla*.

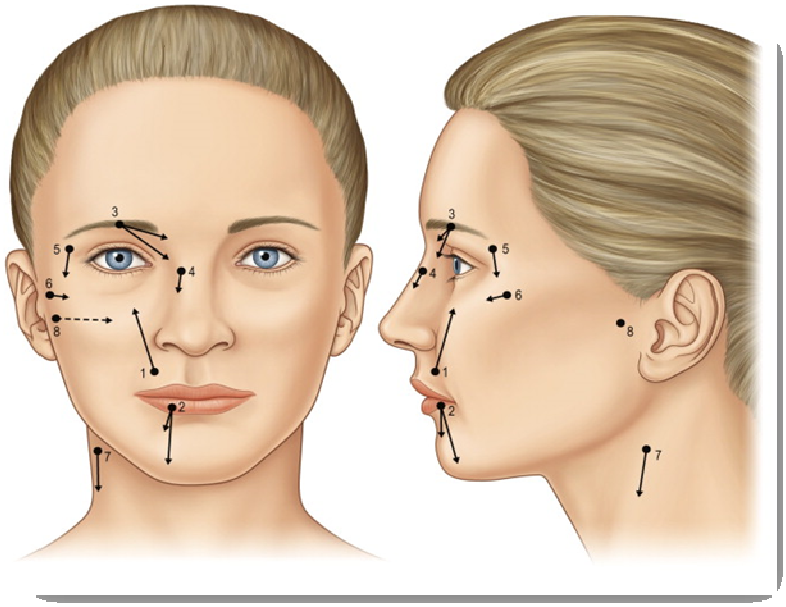
When the nerve blockade is perfomed, it is possible to make analgesia for the skin of lower eyelid and conjunctiva, also for *vestibulum nasi,* the side and wing surface of the nose. The skin of upper lip and cheek can also be anesthetized through this manipulation. Blockade can be performed in two ways – intraoral or extra oral.

When intraoral way is performed, it is necessary apply anesthetics to the gingival mucosa just below the *fossa canina* near to *sulcus vestibule*. Few minutes later when the anesthesia is exposed, injection is made by moving the needle up until it reaches the approximate location of the opening. In order to prevent the needle entering the *orbita* the palpation of the lower edge of the *orbita* with the free hand is mandatory when manipulation is performed.

If patient has dental phobia, then extra oral or facial blockade way is performed. In this case the needle is moved directly into the opening *foramen infraorbitale* through the skin, subcutaneous and muscle of the cheek.

The *nervus mentalis* which is one of the mandibular nerve branches leave the bone channel through the opening *foramen mentale*. This nerve innervates the skin of the chin and the skin and mucosa of the lower lip. The opening is located 1,1-1,5cm lower on the perpendicular line to the line of *gingiva* which is drawn through the the second premolar tooth.

The places of blockade sites are shown in the second picture (Picture 2).



Picture 2. **Local anesthesia sites of the face**.
(*Aesthetic Plastic Surgery,* Sherrell, Douglas, Walden 2009 year)

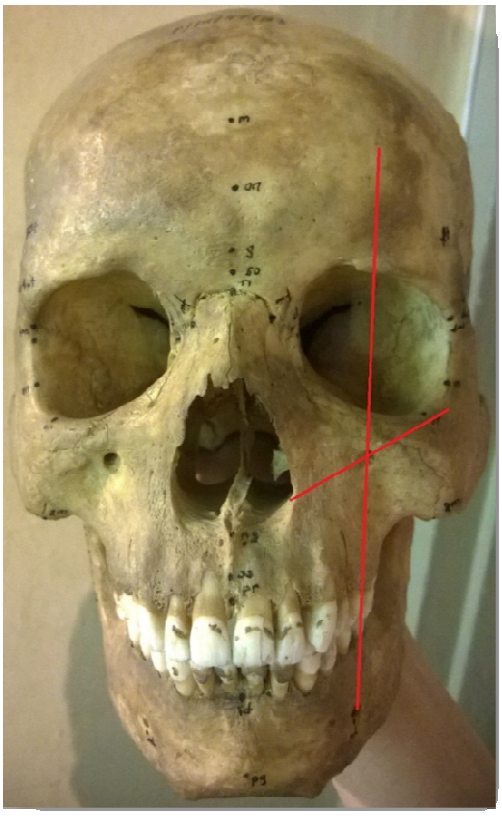
The research was done in three parts at the Anatomy and anthropology institute, and J. Prīmaņa anatomy museum. In the first part of the research, a dissection of a woman cadaver was done. From cadaver`s facial area skin, subcutaneous tissue, *corpus adiposum buccae*, some part of muscles were removed. *A. et v. facialis, n.facialis* branches and *glandula parotidea* with *ductus parotideus* were dissected. *M. orbicularis oculi* was partly detached to expose the *foramen supraorbitale* with an outgoing *n. supraorbitalis* and *foramen infraorbitale* with an outgoing *n.*

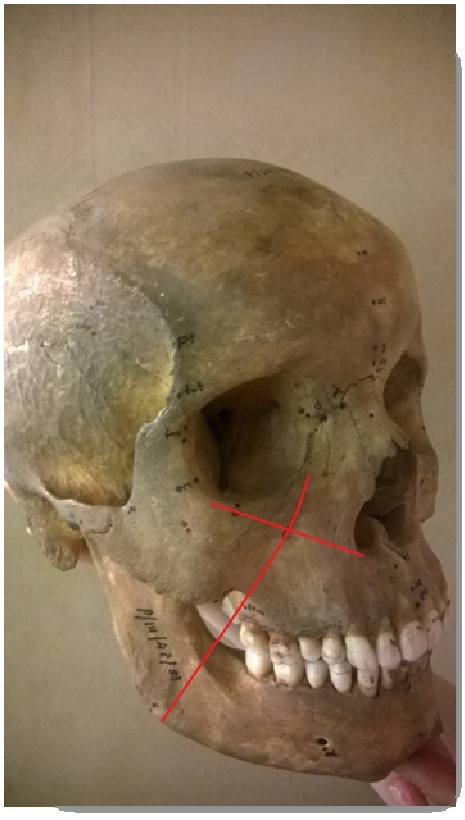
infraorbitalis. Also *m. mentalis, m depressor labii inferioris, m. depressor anguli oris* were partly detached to expose the *foramen mentale* with an outgoing *n. mentalis.*

Anatomical structures were removed from the the left side of the cadaver's face, to uncover *foramen supraorbitale, foramen infraorbitale* and *foramen mentale. Foramen supraorbitale* was located 2,5cm, *foramen infraorbitale* – 2,4cm and *foramen mentale* – 2,6cm from facial midline.

Afterwards, in the second part of the research, the measurements for 20 craniums were done with a sliding caliper. On the skulls *foramen supraorbitale* was located 2,0-2,8cm from facial midline, *foramen infraorbitale* 2,5-3,0cm and *foramen mentale* 2,4-2,9cm from the facial midline. Skull openings distance is shifted up to 0,5cm from the literature landmarks.

In the third part of the research, after analysing the acquired data, new anatomical indicators for locating *foramen infraorbitale* were determined. This opening can be found at the point of intersection between a line that connects the inferior lateral corner of the orbit with the inferior later corner of *cavitas nasi ossea* and perpendicularly to the line from *tuber frontale* (Picture 3). However, a more precise location is in the intersection of lines that connect the inferior lateral *orbita* with *cavitas nasi ossea* inferior later corner with the line that stretches from the inferior medial corner of the orbit to *angulus mandibulae* (Picture 4). There are concrete indicators that can help to find these openings with high accuracy as it was demonstrated in this research.





Picture 3 and 4. **Landmarks on the skull**. (S. Skribāne, L. Bajāre)

To conclude, each individual may have a variety of projection spaces of these three openings, which can lead to have complications in cases where local anesthetics are necessary. It is possible to find *foramen supraorbitale* through palpation, in some cases also *foramen mentale* can be found through palpation. However *foramen infraorbitale* is possible find by drawing a line from the inferior lateral corner of the orbit to *cavitas nasi ossea* perpendicularly to the line connecting the inferior medial corner of the orbit to *angulus mandibulae*. Also *foramen* mentale can be found by using *foramen* infraorbitale, because in the most cases they were located on the same line.

This research can be used for the creation of a new method for administering local anesthetics and avoiding the blocking of n. trigeminus, which would lead to a decrease in errors and patient discomfort. This research shows, that alternatives to the blocking technique are possible.

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CURRENT USE OF ANTIBACTERIAL AGENTS MAY ACT AS A RISK FACTOR FOR GUT COLONIZATION WITH ESBL PRODUCING *ENTEROBACTERIACEAE* IN ULCERATIVE COLITIS PATIENTS

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Abstract

Current use of antibacterial agents may act as a risk factor for gut colonization with ESBL producing *Enterobacteriaceae* in ulcerative colitis patients

Key words: *ulcerative colitis, ESBL, Enterobacteriaceae, risk factors, gut colonization*

Risk factors for gut colonization with ESBL producing *Enterobacteriaceae* (ESBL-E) have been studied in the general population. The described risk factors are advanced patient age, severe comorbid conditions, surgical treatment, use of immunosuppressive medication, previous and prolonged hospital stay, previous antibiotic use and international travel. The aim was to determine whether these risk factors for gut colonization with ESBL-E are applicable to ulcerative colitis (UC) patients. Rectal swabs were collected from patients hospitalized in Riga East Clinical University Hospital and Pauls Stradins Clinical University Hospital 2012 – 2015 with clinically, endoscopically and histologically confirmed UC diagnosis. *Enterobacteriaceae* were cultured, analyzed for ESBL presence. Patients were interviewed regarding the risk factors for gut colonization with ESBL-E. 92 patients with confirmed UC diagnosis were included in the study. 11 (12%) of the UC patients were colonized with ESBL-E. We found that three patients who were currently using antibiotics were colonized with ESBL-E, whereas two of the current antibiotic users were not colonized with ESBL-E (p=0.011). No statistically significant differences were found between patients with and without gut colonization with ESBL-E regarding other risk factors: age, gender, smoking, autoimmune diseases, surgical treatment, previous hospitalizations, previous antibiotic use and international travel. Current antibacterial medication use might be a risk factor for gut colonization with ESBL-E in UC patients.

Kopsavilkums

Pašreizēja antibiotiku lietošana ir iespējamais riska faktors zarnu trakta kolonizācijai ar ESBL producējošām Enterobaktērijām čūlainā kolīta pacientiem

Atslēgvārdi: *čūlains kolīts, ESBL, Enterobaktērijas, riska faktori, zarnu kolonizācija*

Vispārējā populācijā ir pētīti vairāki riska faktori zarnu trakta kolonizācijai ar ESBL producējošām Enterobaktērijām (ESBL-E). Aprakstītie riska faktori ir lielāks vecums, smagas blakus slimības, ķirurģiska ārstēšana, imūnsupresīvo medikamentu lietošana, iepriekšēja un ilga hospitalizācija, iepriekšēja antibiotiku lietošana, starptautiskie ceļojumi. Darba mērķis bija noteikt, vai šie riska faktori zarnu trakta kolonizācijai ar ESBL-E ir piemērojami arī čūlainā kolīta (ČK) pacientiem. No pacientiem, kuri no 2012.-2015. gadam bija stacionēti Rīgas Austrumu klīniskās universitātes slimnīcā un Paula Stradiņa klīniskās universitātes slimnīcā ar klīniski, endoskopiski un histoloģiski apstiprinātu ČK diagnozi, tika paņemtas rektālās iztriepes. Enterobaktērijas tika kultivētas, analizētas uz ESBL klātbūtni. Vizītes laikā veikta pacientu aptauja, iegūstot demogrāfiskos datus un izvērtējot iespējamos zarnu trakta kolonizācijas riska faktorus. Pētījumā iekļauti 92 pacienti ar apstiprinātu ČK diagnozi. 11 (12%) ČK pacientu bija kolonizēti ar ESBL-E. Pētījumā konstatēts, ka trīs pacienti, kuri intervijas dienā lietoja antibiotikas bija kolonizēti ar ESBL-E, savukārt, divi no tiem, kuri lietoja antibiotikas, nebija kolonizēti ar ESBL-E (p=0,011). Pētījumā netika atrastas statistiski ticamas saistības starp vecumu, dzimumu, smēķēšanu, autoimūnām slimībām, ķirurģisku ārstēšanu, iepriekšēju hospitalizāciju, iepriekšēju antibiotiku lietošanu, starptautiskiem ceļojumiem un zarnu trakta kolonizāciju ar ESBL-E. Pašreizēja antibiotiku lietošana konstatēta kā iespējamais riska faktors ambulatoro ČK zarnu trakta kolonizācijai ar ESBL-E.

Introduction

Inflammatory bowel diseases (IBD) consists of the two main forms – ulcerative colitis (UC) and Crohn's disease. It is currently estimated that IBD affects more than 2.2 million people in Europe and more than 5 million people over the world. Ulcerative colitis is characterized with chronic inflammation in the colon and the most commonly affects adults aged 30 – 40 years. UC starts in the rectum, extends to proximal segments of the colon and has relapsing and remitting inflammation of mucosa. The prevalence and incidence of UC has been increasing worldwide. The highest incidences of UC have been reported in the northern Europe (24.3 per 100 000), Canada (19.2 per 100 000) and Australia (17.4 per 100 000). (Conrad et al. 2014; Harlan et al. 2016; Burisch and Munkholm 2013; Ordás et al. 2012; Ungaro et al. 2016).

Patients with IBD are more than twice as likely as the general population to require hospitalization. Among those who are hospitalized, almost 20% will require readmission within a one-year period. IBD patients have also other healthcare contacts, including clinic and emergency department visits. Frequent healthcare contacts, regular use of antibiotics and other disease specific medications can cause IBD patients to become susceptible to antimicrobial-resistant organisms. According to the researches, the most commonly isolated multidrug resistant microorganisms (MDR) in IBD patients are ESBL producing *Enterobacteriaceae*. (Vaisman et al. 2013; Leung et al. 2012).

Due to the frequent use of antimicrobial agents in hospitals and outpatient settings, the number of infections and colonization with ESBL-E is increasing every year. This is an important problem because infections with ESBL-E has increased morbidity and mortality rates. (Bradford 2001; Coque et al. 2008; Peralta et al. 2012; Pfeifer et al. 2010; Shaikh et al. 2015; Skippen et al. 2006). Risk factors for infection and colonization with ESBL-E in the general population include advanced patient age, severe underlying diseases, surgeries, immunosuppressive therapy, previous and prolonged hospital stay, exposure to antimicrobial drugs, admission to the intensive care unit, venous and arterial catheters, urinary catheterization, intubation/tracheostomy and living in a healthcare facility. (Skippen et al. 2006; "The New β-Lactamases — NEJM," n.d.; Cordery et al. 2008; Laupland et al. 2008; Ministry of Health Malaysia 2001; Tham et al. 2013). Travelling has been identified as one of the most important risk factors for ESBL-E carriage. (Tham et al. 2013; Lübbert et al. 2015; Woerther et al. 2013; Barreto Miranda et al. 2016; Kantele et al. 2016; Reuland et al. 2016). Patient colonization with MDR microorganisms is a risk factor for the development of infection and infection with these microorganisms are associated with longer hospital stay, higher costs, and higher mortality. (Bradford 2001; Vaisman et al. 2013; Wehkamp et al. 2016).

Risk factors for gut colonization with ESBL-E have been studied only in USA and Canada. These studies revealed that we cannot apply all of the general population risk factors to the IBD

patient population and therefore additional researches in this field are necessary. (Vaisman et al. 2013; Leung et al. 2012).

Similarly, the incidence of UC and ESBL-E differs between regions and countries. Therefore, it is important to find out the prevalence of gut colonization with ESBL-E in UC patients and determine possible risk factors for gut colonization in each region and country.

According to recent literature data, changes in commensal microbiota and defects in epithelial barrier play an important role in the etiopathogenesis of UC. UC patients form an inadequate immune response against endogenous commensal microbiota. (Wehkamp et al. 2016; Bamias et al. 2005; Conrad et al. 2014; Kasper, Faugi, Hauser, Longo, Jameson, n.d.; Ohkusa and Koido 2015).

Dysregulation of intestinal immune system in genetically predisposed individuals leads to acute and chronic inflammation. There is a hypothesis that the commensal microbiota, pathogenic microorganisms and their metabolic products and normal epithelial structure have a very important role in the disease development. (Wehkamp et al. 2016; Bamias et al. 2005; Ohkusa and Koido 2015; Ordás et al. 2012).

Material and methods

A cross-sectional pilot study was conducted in a Riga East Clinical University Hospital (RECUH) Gastroenterology, Hepatology and Nutrition Clinic in Latvia between September 2015 and September 2016. All ulcerative colitis patients, hospitalized between 2010 – 2015 in RECUH and Pauls Stradins Clinical University Hospital were selected, evaluated according to inclusion and exclusion criteria and asked to participate in the study. Patients who met all inclusion criteria were enrolled in the study.

Inclusion criteria: out-patients with clinically, endoscopically and histopathologically confirmed UC diagnosis, age between 18 – 80 years, patients who agreed to participate in the study and signed the informed consent form.

Exclusion criteria: patients under 18 years and over 80 years, patients with indeterminate colitis, patients who refused to participate in the study.

The study was conducted according to Helsinki Declaration, reviewed and approved by the local Ethics committee.

Patients were asked to participate in out-patient interviews regarding the demographic data (age, gender) and risk factors for gut colonization with ESBL-E. During the patient visit rectal swabs were obtained and delivered to the RECUH Centre for Laboratory Medicine, Microbiology laboratory.

In this study a following risk factors for gut colonization with ESBL-E were analyzed: gender, age, smoking, hospitalization during the past 12 months, current and previous use of

antibiotics, autoimmune diseases, surgical treatment during the past 12 months and international travel.

Fecal biomaterials were collected in *Amies (Oxoid*, UK) transport media and transported to the Microbiology laboratory within 24 hours. Microbiological testing was conducted in two phases – ESBL producing *Enterobacteriaceae* cultivation and identification of isolated bacteria strains. For the cultivation of the fecal biomatherial *Brilliance™ ESBL* (*Oxoid*, UK) screening plates were used. All isolated bacteria were identified using *Vitek 2 Compact system* (*bioMerieux*, France). ESBL production was confirmed using synergy tests – ESBL and Amp-C inhibiting (containing also clavulanic acid and cloxacillin) discs (*Rosco*, Denmark), according to the EUCAST guidelines. ("EUCAST: Resistance mechanisms," n.d.).

An original study protocol in the *Microsoft Office Excel* program was created. Statistical analysis performed in IBM SPSS v20.0 program using nonparametric tests, including *Mann-Whitney U* test and *Fisher's* exact test. All p values <0.05 were considered significant.

Results

A total number of 92 patients with confirmed UC diagnosis, 56.50% (n=52) male and 43.50% (n=40) female patients were included in the study. Patient mean age was 44.28 (SD=15.52) years. During the interview we found that 41.30% (n=38) of the patients had never smoked, 37.00% (n=34) of the patients were former smokers and 21.70% (n=20) of the patients were active smokers. Study shows that ESBL producing *Enterobacteriaceae* colonize UC patients gut in 12.00% (n=11) of the cases. The most commonly isolated ESBL-E was *Escherichia coli* (n=9; 81,80%), (Fig. 1).

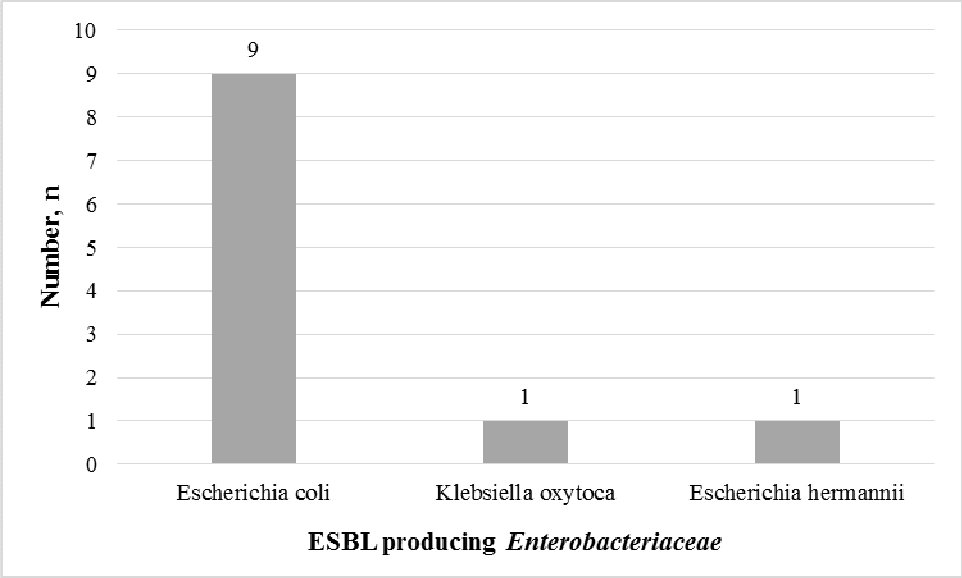

Figure 1. **Isolated ESBL producing *Enterobacteriaceae***

No statistically significant difference was observed between patient gender and gut colonization with ESBL-E (p=0.523), (Fig. 2).

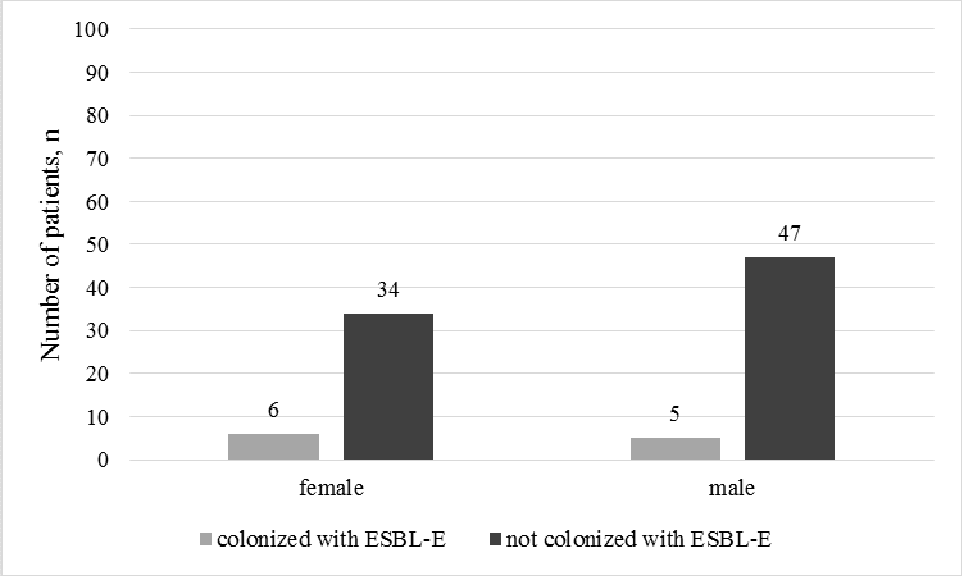

Figure 2. **Ulcerative colitis patients gender and gut colonization with ESBL-E**

Statistical analysis showed no difference (p=0.145) between mean age in patients who were colonized with ESBL-E (44.95 (SD=15.14)) and patients who were not colonized with ESBL-E (39.36 (SD=18.10)).

No statistically significant difference (p=0.939) was observed between smoking habits and gut colonization with ESBL-E (Fig. 3).

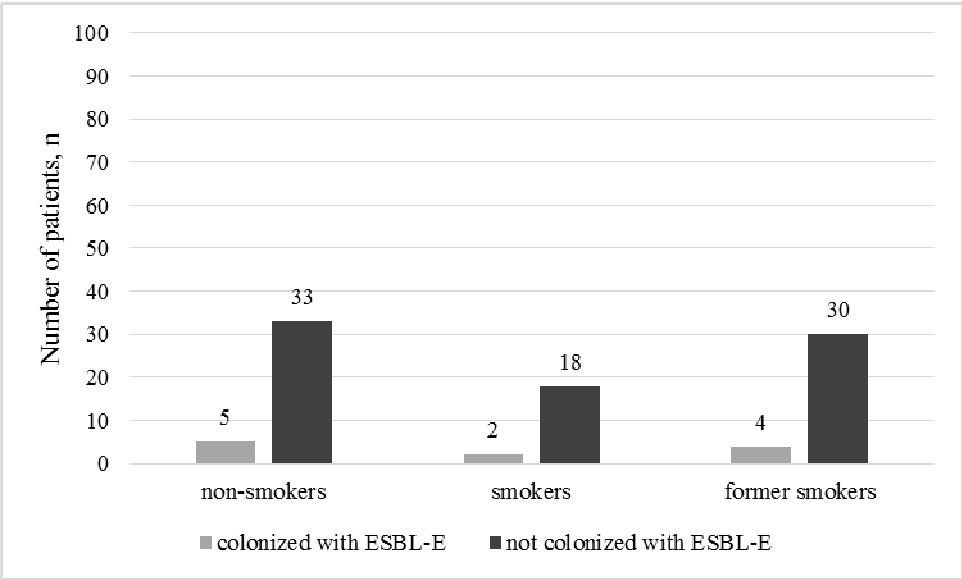

Figure 3. **Ulcerative colitis patients smoking habits and gut colonization with ESBL-E**

During the past 12 months 32.60% (n=30) of the patients were hospitalized. No statistically significant difference (p=0.333) was found between hospitalization in the past 12 months and gut colonization with ESBL-E (Fig. 4).

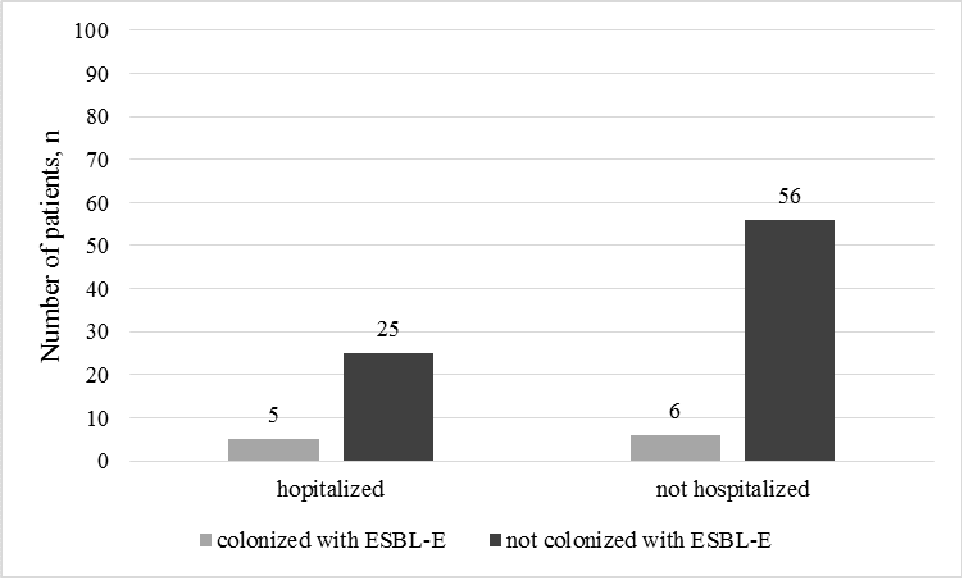

Figure 4. **Hospitalization during the past 12 months and gut colonization with ESBL-E**

Study shows that on the day of the interview 5 (5.40%) patients were taking antibiotics and 87 (94.60%) were not taking them. We found a statistically significant difference (p=0.011) between current antibiotic usage and gut colonization with ESBL-E (Fig. 5).

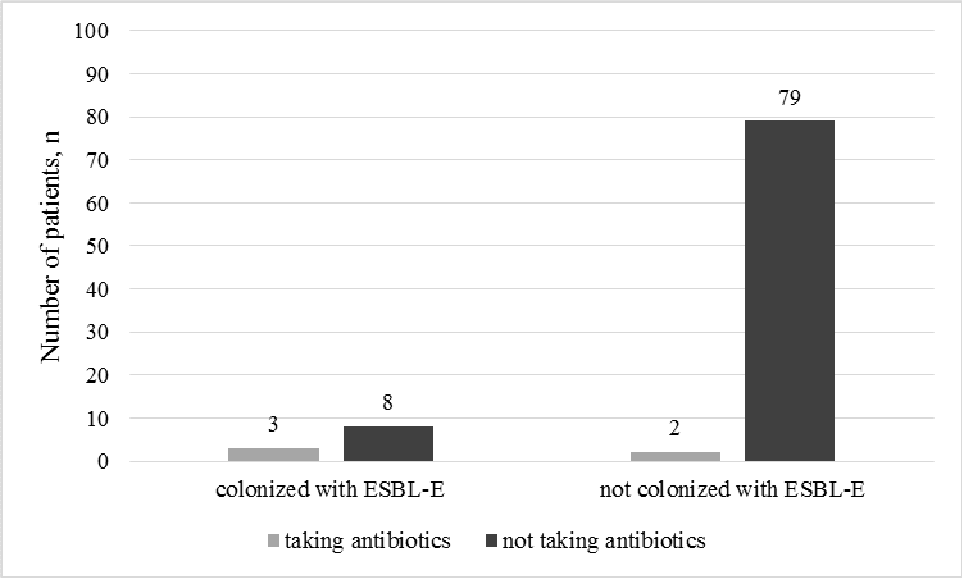

Figure 5. **Current usage of antibiotics and gut colonization with ESBL-E**

Ulcerative colitis patients in the past 12 months were using antibiotics in 40.20% (n=37) of the cases. Analyzing usage of antibiotics during the past 12 months we did not find statistically significant difference (p=0.302) between this usage and gut colonization with ESBL-E (Fig. 6).

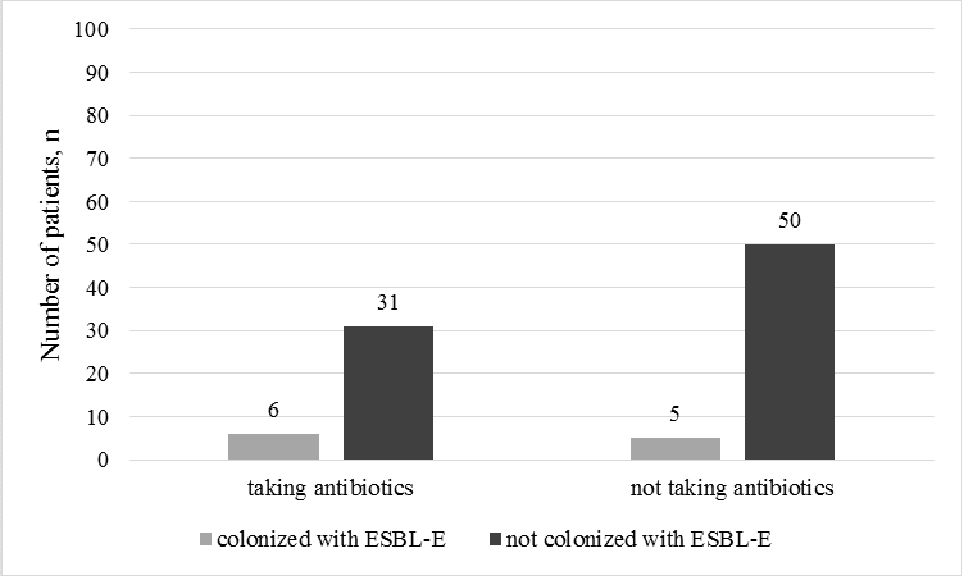

Figure 6. **Usage of antibiotics during the past 12 months and gut colonization with ESBL-E**

Autoimmune diseases had 10.90% (n=10) of the patients and type 2 diabetes had 3.30% (n=3) of the patients. None of the patients whose gut was colonized with ESBL-E had these diseases.

During the past 12 months 59.80% (n=55) of the patients were travelling to other countries. No statistically significant difference (p=0.340) was found between international travel in the past 12 months and gut colonization with ESBL-E (Fig. 7).

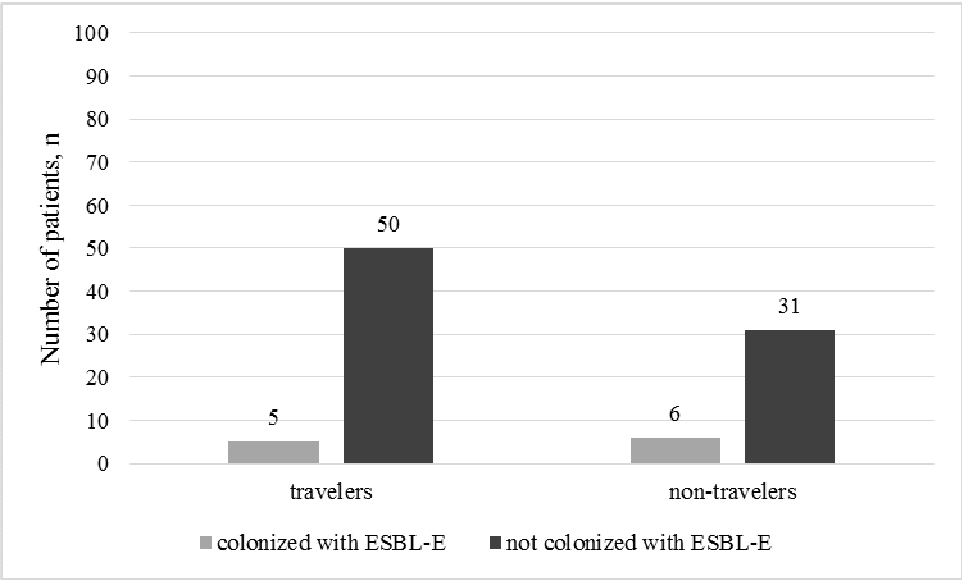

Figure 7. **International traveling and gut colonization with ESBL-E**

During the past 12 months 7.6% (n=7) of the patients had surgical procedures. We did not find statistically significant difference (p=0.843) between performed surgeries in the past 12 months and gut colonization with ESBL-E (Fig. 8).

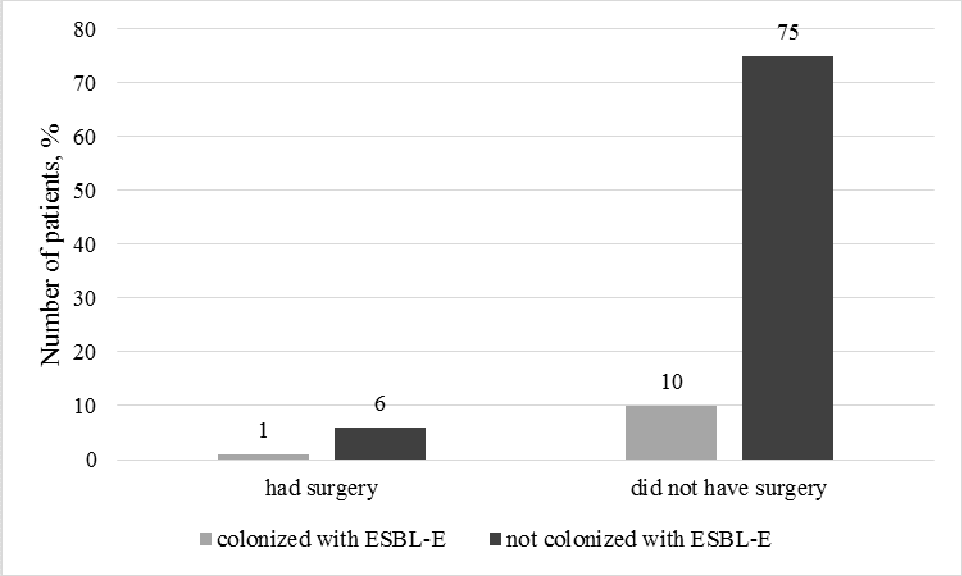

Figure 8. **Surgical procedures during the past 12 months and gut colonization with ESBL-E**

Discussion

Infections and colonization with ESBL-E is an outstanding and important problem in the world, which continues to grow. It is clear that infections and colonization with ESBL-E prolong hospitalization, increase costs and increase morbidity and mortality. (Bradford 2001; Vaisman et al. 2013; Wehkamp et al. 2016; Kassakian and Mermel 2014). The problem is that these microorganisms are multi-resistant to multiple classes of antibiotics and it is difficult to choose the most efficient empirical ESBL-E infection treatment. (Kassakian and Mermel 2014; Tham, n.d.).

In databases of scientific researches can not be found reports from European countries regarding ulcerative colitis patients gut colonization with ESBL-E. However, similar results showed studies about outpatient ulcerative colitis patients from Canada and USA. Colonization with ESBL-E was detected in 11.1% of the outpatient cases, while colonization prevalence with ESBL-E in hospitalized UC patients was established only in 4.1% of the cases. (Vaisman et al. 2013; Leung et al. 2012). Our study reveals that UC patients gut was colonized with ESBL-E in 12% of the cases. Comparing our findings with the literature, we can say that UC patients gut colonization with ESBL-E is high and it means that not only in Canada and in USA, but also in Latvia UC patients colonization with ESBL-E is a significant problem.

In the general population, the most common bacterial isolates from ambulatory patients are *E. coli* and *K. pneumoniae*. (Coque et al. 2008; Kassakian and Mermel 2014). One study about UC patients' colonization with ESBL-E described that 82% of all isolated bacteria were *E. coli*, 9% - *K. pneumoniae* and 9% - *P. mirabilis*. (Leung et al. 2012). Our study had similar results - *E. coli* was the most frequently isolated bacteria, 81.8% of the cases. The other bacteria (*K. oxytoca* and *E.*

hermannii) were not isolated in similar studies. It is probably due to regional differences, because isolated bacterial strains vary in each country and region. (Bradford 2001; Coque et al. 2008).

A large number of studies in a variety of other diseases have been conducted to clarify colonization and infection prevalence and to determine possible risk factors for the acquisition of multidrug resistant bacteria. (Mehrgan and Rahbar, 2008; Spanu et al., 2002; Cordery et al., 2008). Gut colonization with ESBL-E in UC patient population was studied only in Canada and in USA, and specific risk factors in this population are still not clear. It is important to determine the possible risk factors and identify the colonization, because it increases the risk of infections and might influence the severity of the UC disease.

We analyzed a several possible risk factors for gut colonization with ESBL-E, including, age, gender, smoking, hospitalization during the past 12 months, current and previous use of antibiotics, autoimmune diseases, surgical treatment during the past 12 months and international travel. From all the above-mentioned risk factors only current use of antibiotics was statistically significant. Other studies with IBD patients demonstrated hospitalization in the past 12 months, use of antibiotics in the past three and 12 months, current use of antibiotics, previous treatment with vancomycin or cephalosporin as possible risk factors. (Leung et al., 2012; Vaisman et al., 2013). Other risk factors were analyzed based on the studies in different disease populations. (Reuland et al. 2013; Ben-Ami et al. 2006).

In the general population, male sex serves as risk factor for infection and colonization with ESBL-E. (Ben-Ami et al. 2006; Nakai et al. 2016). In our study, gut colonization with ESBL-E was approximately the same in both sexes, thus suggesting that colonization with ESBL-E and sex are not connected.

Travelers to the countries with a high prevalence of antimicrobial resistance might be at increased risk for the acquisition of ESBL-E. (Reuland et al. 2016; Barreto Miranda et al. 2016; Kantele et al. 2016). In some parts of Asia, the community prevalence of ESBL-E has reached nearly 70%, whereas it is still below 10% in Europe. The risk of ESBL-E acquisition vary with travel destination, duration and style. (Barreto Miranda et al. 2016). People who are colonized most commonly return from Asian countries and India, and colonization may last for six months or even longer. (Barreto Miranda et al. 2016; Reuland et al. 2016). We included and analyzed international travel as one of the possible risk factors for gut colonization with ESBL-E, but it has not proven itself as a risk factor in UC population. The reason might be that after travelling ESBL-E carriage duration in the gastrointestinal tract is individual for each person and we did not take rectal swabs from each traveler in the exactly the same time.

Further studies including larger patient groups are needed to gain a better understanding on ESBL-E acquisition mechanisms and they should develop novel strategies to reduce and prevent

such colonizations/infections. Early identification of IBD patients with ESBL-E colonization and infection during hospitalization may potentially reduce overall morbidity, mortality and economic burden attributable to these emerging pathogens.

Conclusions

1. Study shows a high gut colonization rate (12%) with ESBL-E in ambulatory UC patients.
2. The most commonly isolated bacteria was *Escherichia coli* (81.80%).
3. Current antibiotic use might be a risk factor for gut colonization with ESBL producing *Enterobacteriaceae* in ambulatory UC patients.
4. Further studies including larger patient groups are needed to analyze other acquisition risk factors, to gain a better understanding on ESBL-E acquisition mechanisms and to develop strategies to decrease and to prevent ESBL-E colonization.

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SUMMARY OF THE 10 YEAR EXPERIENCE OF APPLICATION OF BIOLOGICAL TREATMENT IN CHILDREN WITH JUVENILE ARTHRITIS

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Abstract

Summary of the 10 year experience of application of biological treatment in children with Juvenile arthritis

Key words: *Juvenile idiopathic arthritis, biological therapy, JADAS, ACR Pedi*

Several groups of drugs are used for the treatment of Juvenile idiopathic arthritis (JIA), only immunosuppressive and biological therapy stops the development of destruction and disability.

The aim of the study is to summarize biological treatment experience in children with JIA, assessing an ACR Pedi and JADAS criteria after one year treatment.

Materials & methods. A retrospective analysis of 55 patients with JIA who were treated with biological therapy at the Latvian Children's Clinical University Hospital.

Results. Abataceptum was used in 14% cases, the improvement were observed in 82% of cases. JADAS after a year of treatment: decreased activity is in 55% of cases. Adalimumabum was used in 33% of cases, improvement were stated in 80% of cases. JADAS: decreased activity is in 56%. Etanerceptum was used in 36% cases, improvement were observed in 67% of cases. JADAS: decreased activity is in 44% of cases. Tocilizumabum was used in 17% cases, improvement were observed in 92% of cases. JADAS: in 85% of cases there are decreased activity.

Conclusion. The ACR Pedi response criteria do not used as the quantification of absolute disease activity or comparison of absolute responses amongst patients, therefore the definition of disease activity states based on JADAS may help to foster the implementation of treat-to-target strategy, which aims to achieve and maintain a tight control of the disease.

Kopsavilkums

Bioloģiskās terapijas 10 gadu pieredzes apkopojums bērniem ar Juvenilu artrītu

Atslēgvārdi: *Juvenils idiopātisksartrīts, bioloģiskā terapija, JADAS, ACR Pedi*

Juvenils idiopātisks artrīts (JIA) ārstēšanā pielieto vairākas medikamentu grupas, bet tikai imūnsupresīvā un bioloģiskā terapija aizkavē destrukcijas un invaliditātes attīstību.

Darba mērķis. Apkopot bioloģiskās terapijas pieredzi bērniem ar JIA, izvērtējot ACR Pedi un JADAS kritērijus pēc viena bioloģiskās terapijas gada.

Materiāli un metodes. Retrospektīvi tika analizēti 55 JIA pacientu dati, kuri tika ārstēti ar bioloģisko terapiju Bērnu klīniskās universitātes slimnīcā Latvijā.

Rezultāti. Abataceptum tika lietots 14% gadījumu, 82% gadījumu tika konstatēts uzlabojums. JADAS pēc viena gada terapijas: aktivitātes samazināšanās 55% gadījumu. Adalimumabum tika lietots 33% gadījumu, 80% gadījumu konstatēts uzlabojums. JADAS: 56% gadījumos aktivitātes samazināšanās. Etanerceptum - lietots 36% gadījumu, 67% gadījumu konstatēts uzlabojums. JADAS: aktivitātes samazināšanās 44% gadījumu. Tocilizumabum - lietots 17% gadījumu, 92% gadījumu konstatēts uzlabojums, izvērtējot ACR Pedi. JADAS: 85% gadījumu slimības aktivitāte samazinājās.

Secinājumi. ACR Pedi terapijas efektivitātes kritēriji nedod iespēju noteikt absolūto slimības aktivitāti, tāpēc JADAS vērtības noteikšana palīdz ārstējošam ārstam sekot slimības aktivitātes pārmaiņām un apzināties, vai pielietotā terapija ir mērķtiecīga un efektīva un vērsta uz slimības stingru kontroli.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common autoimmune disease among the children population, the prevalence of JIA is 1 per 1000 (Beukelman et al. 2011). Untreated disease can cause the damage of the internal organs, premature incapacity for work and increases the risk of mortality.

Several groups of drugs are used for the treatment of JIA, but only immunosuppressive (disease-modifying antirheumatic drugs) and biological therapy stops the development of destruction and disability. (Petty et al. 2016: 188-204)

Disease activity and effectiveness of the treatment of JIA can be assessed by using different scales. Effect of the treatment and improvement of the clinical course of the disease mostly are rated by an ACR Pedi (American College of Rheumatology) criteria for treatment efficacy, but recently has increased popularity of JADAS (Juvenile Arthritis Disease Activity Score) criteria. These criteria are a new approach to evaluation of disease activity in Juvenile idiopathic arthritis patients. In Latvia JADAS criteria are not widely used yet. (Consolaro et al. 2016)

Level of the response to therapy are evaluated by using American College of Rheumatology pediatric therapy efficacy criteria (ACR Pedi criteria) (Giannini et al. 1997; Latvijas Pediatru reimatologu biedrība 2016). ACR Pedi therapy efficacy criteria are: 1) physician global assessment of disease activity; 2) parent/patient global assessment of wellbeing; 3) functional assessment - using Childhood Health Assessment Questionnaire (CHAQ); 4) number of joints with active arthritis; 5) number of joints with inactive arthritis; 6) Erythrocyte sedimentation rate. (Giannini et al. 1997) The result is evaluated over time with comparing ACR Pedi criteria before starting the therapy and three to six months after starting the therapy — it is calculated in percent that shows how big was an improvement. (Consolaro et al. 2016) ACR Pedi-30 is defined as at least 30% improvement from baseline in at least 3 of the 6 variables with no more than 1 of the remaining variables worsening by 30% or more. ACR Pedi-50, 70 - at least 50% or 70% improvement from baseline in at least 3 of the 6 variables with no more than 1 of the remaining variables worsening by 30% or more. (Quartier 2010)

Six continuous months of inactive disease on medication defines clinical remission on medication, while 12 months of inactive disease off all anti-arthritis (and anti-uveitis) medications defines clinical remission off medication. (Wallace et al. 2004)

First scale for evaluation the activity of Juvenile idiopathic arthritis was developed in 2009 and was called JADAS (Juvenile Arthritis Disease Activity Score). The final version of the JADAS included the following 4 measures: 1) physician global assessment of disease activity; 2) parent/patient global assessment of; 3) Number of joints with active arthritis; 4) Erythrocyte sedimentation rate — normalised 0 to 10 scale. (Consolaro et al. 2014) Sedimentation rate is normalised to 0 to 10 scale using the following formula: (ESR(mm/h) – 20)/10. Before performing any calculations any ESR which is less than 20mm/h (ESR <20mm/h) is converted to 0, ESR which is more than 120mm/h (ESR >120mm/h) is converted to 10. (Mourão et al. 2014)

JADAS value is calculated by adding up all four JADAS components. (Consolaro et al. 2014)

JADAS and its cut-offs constitute an easy and flexible method to guide therapeutic investigations aimed at pursuing tight disease control. (Table 1).

Table 1. **JIA disease activity evaluated by original JADAS and cJADAS**
(Consolaro *et al.* 2014)

	JADAS10/71	JADAS27	cJADAS10
Oligoarthritis			
Inactive disease	≤1	≤1	≤1
Low disease activity	≤2	≤2	≤1.5
Moderate disease activity	2.1-4.2	2.1-4.2	1.51-4
High disease activity	≥4.2	≥4.2	≥4
Polyarthritis			
Inactive disease	≤1	≤1	≤1
Low disease activity	≤3.8	≤3.8	≤3.8
Moderate disease activity	3.9-10.5	3.9-8.5	2.51-8.5
High disease activity	≥10.5	≥8.5	≥8.5

Children with systemic arthritis, rheumatoid factor (RF) positive polyarthritis, RF-negative polyarthrytis, or extended oligoarthritis were included in the polyarthritis group. The oligoarthritis group included patients with persistent oligoarthritis. (Consolaro *et al.* 2016)

The definition of disease activity states based on the JADAS may help to foster the implementation of a treat-to-target strategy, which aims to achieve and maintain a tight control of the disease. (Consolaro *et al.* 2014)

Material and methods

A research „10 year biological therapy experience summary for children with juvenile idiopathic arthritis" was performed in Children's Clinical University Hospital.

326 JIA patients were treated with biological therapy in Children's Clinical University Hospital from 2004 year until 2017. During this time 203 patients have used Etanerceptum. Adalimumabum used in JIA treatment in Latvia since 2009. Adalimumabum was used in 61 patients therapy. Abataceptum is used in JIA treatment in Latvia since 2011 and it was used in 32 patients therapy. Tocilizumabum used in JIA treatment in Latvia since 2010 and in the time period up to 2017 it was used in 28 patients therapy. Two patients have used Anakinrum.

During the research time biological drugs were used in 91 JIA patients treatment. All patients were randomly selected and 55 children with Juvenile idiopathic arthritis who were treated with biological disease-modifying drugs were included in the research. Data from Children's Clinical Univeristy Hospital medical records and out-patient cards were used in the research.

The necessity of the biological therapy in case of JIA patient were discussed and decision to start medication was made by the Children's Clinical University Hospital rheumatologist council evaluated ACR Pedi therapy effectiveness criteria, patient general condition, therapy indications and contraindications .

Level of the response to therapy is evaluated by using therapy efficacy criteria (ACR Pedi criteria). The result was evaluated over time with comparing ACR Pedi criteria before starting the

therapy and one year after starting the therapy — it was calculated in percent that shows how big was an improvement.

JADAS value was calculated by adding up all four JADAS components. The result was evaluated over time with comparing JADAS value before starting the therapy and one year after starting the therapy.

The obtained data were entered in Microsoft Office Excel2007 database. Statistical analysis was performed in Microsoft Office Excel and SPSS version 22.

Descriptive statistics was performed and also were used conclusive statistical nonparametrical methods to analyze the difference in the analysis. With Wilcoxon Signed Ranks Testwas approved JADAS value decrease statistical credibility.

The research was coordinated and approved by Riga Stradins University Ethics Committee decision No. 148 / 26.01.2017. The research was also approved by Children's Clinical University Hospital Education and Science Department. Patients data protection and confidentiality were assured.

Results

67.3% (n=37) from the in study included 55 patients were girls and 32.7% (n=18) were boys. This children's average age at the beginning of therapy with biological agents were 9.62 (SD ±3.87) years, the youngest patients were 1 year old and the oldest — 17 years old. Average disease duration before the start of the biological therapy was 2.45 (SD ± 2.78) years.

The most common reason to start the biological therapy were traditional disease modifying antirheumatic drug (*Methotrexatum* (MTX)) insufficient theraupeutic effect (76.3% of cases), while in 23.7% of cases were observed MTX poor tolerance and side effects.

In 67% of cases were used only one biological agent (Figure 1), in 33% there were required one biological agent change to other biological agent because of insufficient therapeutical effect or side effects. In this cases the majority (29%) the biological agent were changed once, in 2% biological agents were changed twice and also in 2% the biological agents were changed three times during the therapy.

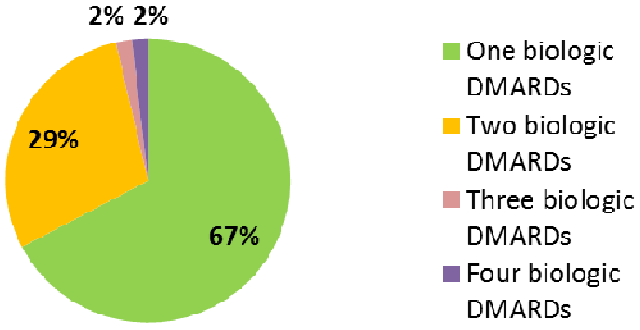

Figure 1. **Number of patients using one or more biological DMARDs**

Evaluating ACR Pedi criteria, most frequently (80% of all cases) were stated an improvement (Figure 2). The most effective drug was *Tocilizumabum* – after one year of treatment 92% of cases stated an improvement.

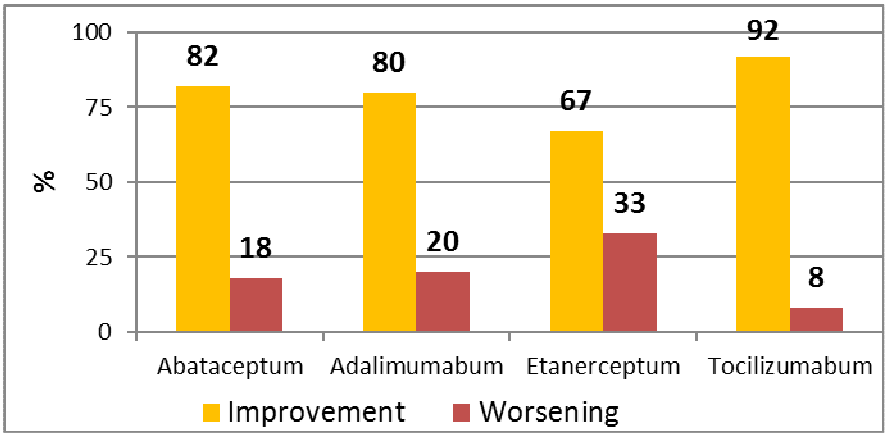

Figure 2. **ACR Pedi criteria changes after one year of the biological therapy**

After one year of treatment with *Adalimumabum* improvement were stated in 80% of cases: the most common (in 40%) improvement of 70% (ACR Pedi 70) were observed. Deterioration, improvement for less than 30% were observed in 20% of cases. In cases of using *Etanerceptum* the improvement were observed in 67% of cases and improvement for 70% (ACR Pedi 70) were diagnosed in 30% of cases. Deterioration, improvement for less than 30% were observed in 33% of cases. In cases of using *Tocilizumabum* the improvement were observed in 92% of cases (31% of cases — ACR Pedi70, 31% — ACR Pedi50). Deterioration, improvement for less than 30% were observed in 8% of cases. After one year treatment with *Abataceptum* the improvement were observed in 82% of cases: in most cases (37%) the improvement were by ACP Pedi50. Deterioration, improvement for less than 30% — 18% of cases (Figure 3)

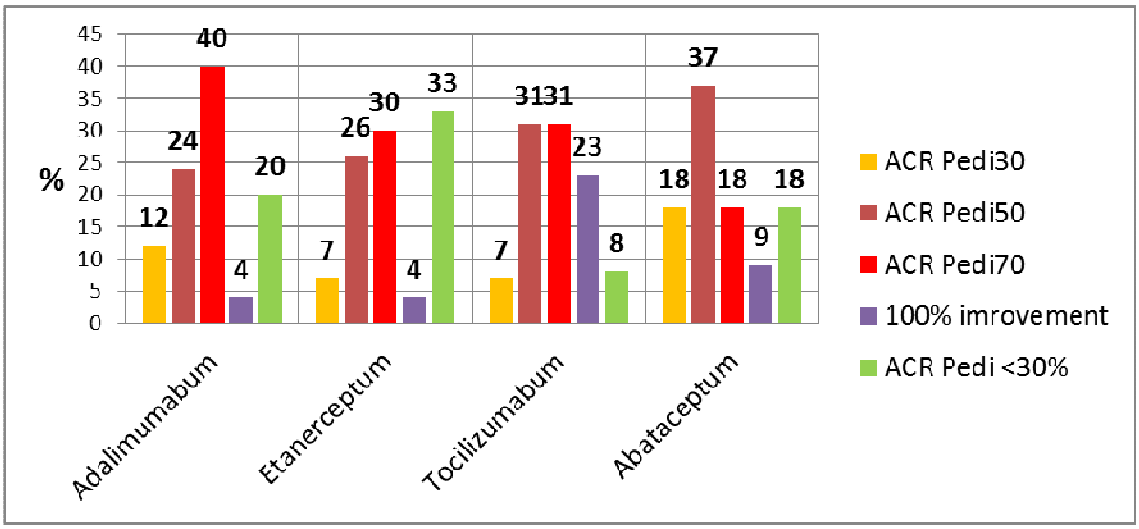

Figure 3. **ACR Pedi criteria changes after one year of the biological therapy**

Evaluating JADAS after a year of treatment level of disease activity decreased only in 60% of cases.

Comparing JADAS value before the start of the therapy and one year after the treatment disease activity in cases of using *Abataceptum* in 45.5% of cases has not changed and in 54% disease activity has decreased. Using *Adalimumabum* - in 44% disease activity was unchangeable and in 56% disease activity has decreased. In cases with *Etanerceptum* – in 51.9% of cases disease activity was unchangeable, in 44.4% disease activity has decreased but in 3.7% of cases disease activity has increased. The most effective drug was *Tocilizumabum* – in 15.4% of cases disease activity was unchangeable and in 84.6% disease activity has decreased (Figure 4).

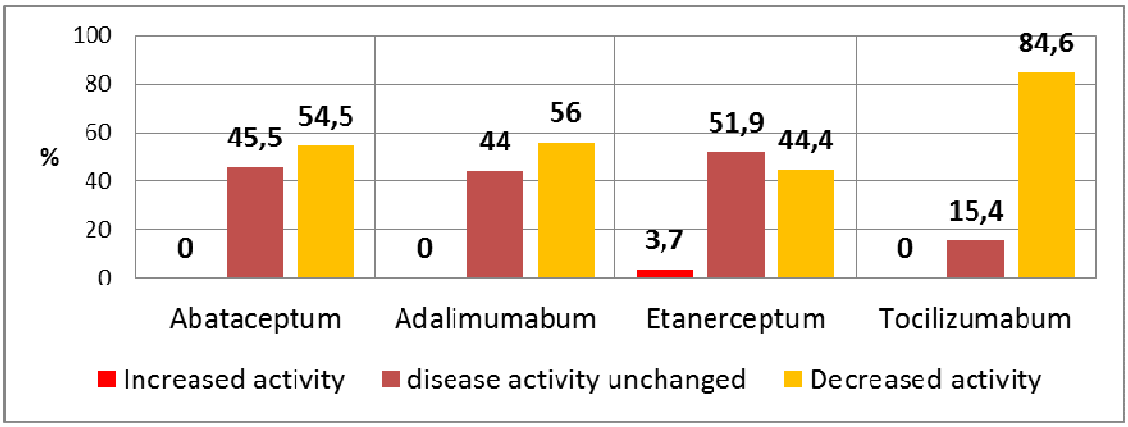

Figure 4. **Disease activity changes after one year of the biological therapy (evaluating JADAS)**

All patients with improvement in ACR Pedi30 were compared by JADAS before start of the treatment with biological agent and one year after the treatment. In 87.5% of cases the disease activity was unchangeable but in 12.5% it has decreased. 71.3% of patients has decreased disease activity by ACR Pedi50 and in 28.6% it was unchangeable. In cases of ACR Pedi 70 in 87.4% the disease activity has decreased and in 12.6% it was unchangeable. In cases where improvement was 100% disease activity has decreased by 100%. Patients with deterioration, improvement for less than 30% in 93.8% disease activity were unchangeable and in 5.9% disease activity has increased (Figure 4).

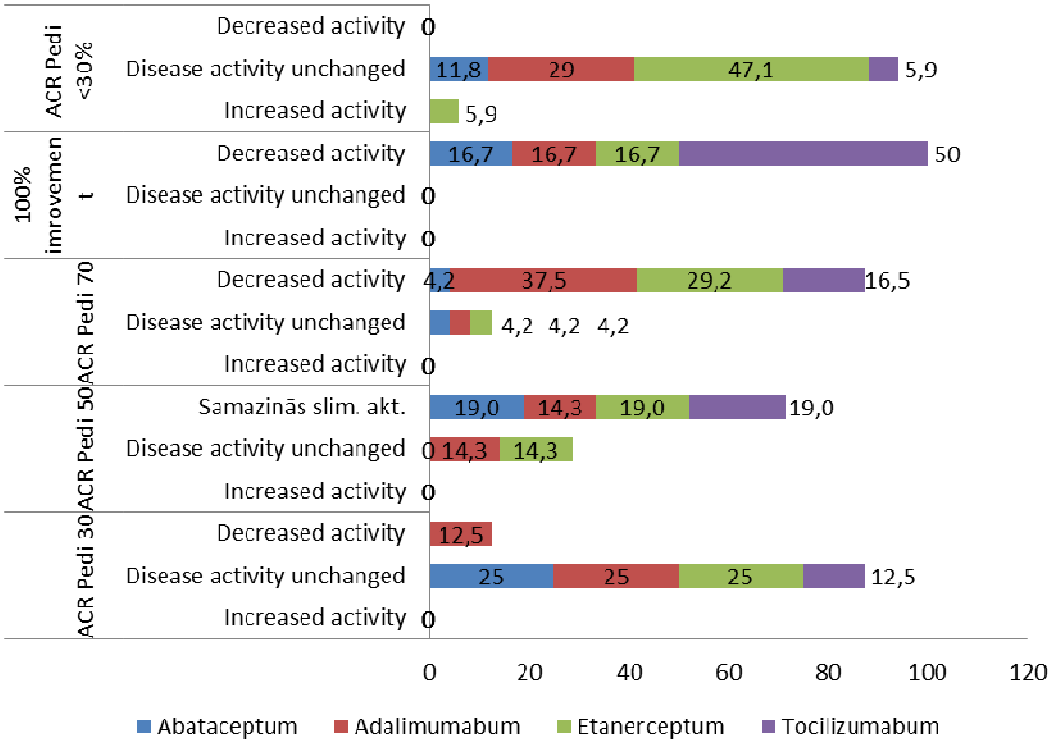

Figure 5. **Disease activity changes in comparison with ACR Pedi criteria changes**

Discussion

In this research the group of patients do not represent all children with juvenile idiopathic arthritis. During the time period from 2004 until 2017 in Children's Clinical University Hospital with biological agents were treated 326 patients. 203 patients have used Etanerceptum.. Adalimumabum is used for JIA treatment in Latvia since 2009 and it was used in therapy for 61 patient. Abataceptum is used for JIA treatment in Latvia since 2011 and it was used in 32 patients therapy. Tocilizumabum is used for JIA treatment in Latvia since 2010 and during this time until 2017 it was used in 28 patient treatment. Two patients have used Anakinrum. During the research time biological therapy were used in treatment for 91 patient. From this patients only 55 children were randomly selected and included in the research.

In the research obtained occurence percentage of the JIA type can not be compared with literature data mentioned patient percentage of JIA types, because in the research were not analysed JIA types among Latvian children. Biological agent were selected for therapy according into JIA clinical guidelines referred treatment algorithms according to the ACR four therapy groups which were made by an JIA treatment experts. (Latvijas Pediatru reimatologu biedrība 2016)

Preparing the research it was found that the JIA is more common in girl population, which coincides with literature data. (Petty et al. 2016: 188-204)

The most common reason to start the biological therapy is the insufficient effect of traditional disease-modifying antirheumatic drugs (Methotrexate). It was confirmed by in the literature

mentioned information and also this research results. However, the biological agents can not provide a sufficient theraupetic effect after one year of treatment and as a result there is the need to change one biological agent to another. (Beukelman et al. 2011) In most cases a positive therapeutic effect was expected after one biological agent change.

JIA therapy level of the response was evaluated by using an ACR Pedi treatment effectiveness criteria. (Latvijas Pediatru reimatologu biedrība 2016) Comparing ACR Pedi criteria before treatment with biological agents and one year after before starting the therapy was determined percent of the improvement of the disease and the effectiveness of the applied therapy. (Consolaro et al. 2016)

However, using the ACR Pedi effectiveness criteria can not show an absolute disease activity and can not make a cross-cheking for a response to the therapy. For this purpose has been created JADAS scale. (Luca et al. 2013) JADAS scale includes four from six in clinical practise used ACR Pedi criteria – only this criteria that indicate disease activity not the damage caused by the disease. (Consolaro et al. 2014)

The research data shows that the improvement by ACR Pedi criteria does not approve a desrease of the disease activity, which is assessed by JADAS scale. Evaluating the ACR Pedi criteria in most cases (approx. in 80%) have seen an improvement, while only in a slightly more than a half of the cases (approx. 60%) was observed the decrease of the disease activity after a one year treatment with biological agent.

AS JADAS scale includes four from the six in the clinical practice used ACR Pedi criteria, defining an ACR Pedi criteria is also possible to determine the JADAS scale value. JADAS scale value helps physician to determine changes in the disease activity and be aware of wheter the applied therapy is targeted and effective. This is why it is desirable to use JADAS scale in clinical practice. (Mourão et al. 2014)

Conclusions

1. Evaluating the ACR Pedi criteria before starting treatment with the biological agent and after one year of treatment in the majority of cases was observed an improvement of the JIA.
2. The most effective biological agent is *Tocilizumabum* – after a one year treatment in 92% of cases was observed an improvement of the JIA by ACR Pedi criteria.
3. Evaluating JADAS scale before the start of the biological therapy and after one year of treatment a slightly more than in a half of the cases was observed decreased disease activity.
4. ACR Pedi therapy effectiveness criteria does not allow to determine an absolute disease activity, that why JADAS scale value helps physician to follow to disease activity changes and understand that applied therapy is targeted, effective and focused on the strict control of the disease.

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RISK OF OBSTRUCTIVE SLEEP APNEA SYNDROME IN LATVIA

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Abstract
Key words: *sleep apnea, obesity, hypertension, heart attack*
Introduction: Obstructive sleep apnea (OSA) is characterized by recurrent airway collapse during sleep associated with oxygen desaturation and leading to development of several chronic diseases, including arterial hypertension (AH), coronary heart disease, heart attack and even death. It is the most common type of sleep-disordered breathing. The estimated OSA distribution in developed world ranges between 3-7% however there has not been much research done amongst Latvian population.
Aim, Material and Methods: The purpose of this study is to establish the prevalence of high risk OSA (HR-OSA), intermediate risk (IR-OSA) and low risk (LR-OSA) in primary care population and identify OSA risk correlation with AH, neck circumference (NC) and body mass index (BMI). The survey is carried out in general practices in Latvia. We have collected data from six general practices (GP) in Riga and two out of Riga, 132 individuals in total, aged 22-79. Patients underwent standardized OSA questionnaire, systolic and diastolic blood pressure (SBP, DBP), pulse, oxygen saturation, BMI and NC.
Results: 12 patients were identified with HR-OSA and 41 patients with IR-OSA (31,06%). 11 of the HR-OSA group (91,66%), 27 of the IR-OSA (65,85%) but just 7 of LR-OSA (8,86%) had AH (for SAP p=0,000; R=0,570; for DAP p=0,000, R=0,345). Our current study shows that 10 patients of HR-OSA group (83,33%), 22 of IR-OSA (53,66%) but just 5 of LR-OSA (6,33%) have elevated NC (p=0,000, R=0,486). 4 HR-OSA (33,33%) patients, 6 of IR-OSA (14,63%) but only 1 LR-OSA (1,27%) patient had BMI greater than or equal with 35 (p=0,000; R=0,478).
Conclusion: The risk of OSA is strongly associated with NC, BMI, SAP and DAP. BMI greater than 35 is more a sensitive indicator of increased risk of OSA than NC greater than 40cm. Consequently, for patients with an increased BMI, NC, AH and additional sleep disorders in anamnesis, it is important to perform OSA questionnaires to diagnose, prevent and treat this condition timely.

Kopsavilkums
Ievads: Obstruktīvai miega apnojai (OMA) ir raksturīga atkārtota elpošanas apstāšanās miega laikā augšējo elpceļu nosprostojuma dēļ ar tai sekojošu skābekļa koncentrācijas samazināšanos arteriālajās asinīs. Tā tiek uzskatīta par neatkarīgu riska faktoru vairākām hroniskām slimībām, kā, piemēram, arteriālai hipertensijai (AH), koronārai sirds slimībai, insultam un pat nāvei. OMA izplatība pasaulē svārstās no 3 līdz 7%, bet pētījumi par OMA izplatību Latvijas iedzīvotāju vidū trūkst.
Mērķi, materiāli un metodes: Noteiktu augsta OMA riska (AR-OMA), vidēja OMA riska (VR-OMA) un zema OMA riska (ZR-OMA) izplatību Latvijas primārās aprūpes līmenī, kā arī noteikt OMA riska korelāciju ar AH, kakla apkārtmēru (KA) un ķermeņa masas indeksu (ĶMI). Pētījums tika veikts sešās ģimenes ārstu praksēs Rīgā un divās ārpus Rīgas. Tika aptaujāti 132 pacienti vecumā no 22 līdz 79 gadiem. Katrs pacients aizpildīja standartizētu OMA anketu, kā arī papildus tika veikti sekojoši mērījumi - sistoliskais un diastoliskais asinsspiediens (SAS un DAS), sirds ritma frekvence, skābekļa piesātinājumu perifērajās asinīs ar pulsa oksimetru, ĶMI, KA. Datu bija apstrādāti Microsoft Excel un SPSS 20 programmās.
Rezultāti: 12 pacientiem bija AR-OMA (9,1%), 41 pacientiem bija VR-OMA (31,1%). 11 pacientiem AR-OMA grupā (91,66%), 27 pacientiem VR-OMA grupā (65,85%), bet tikai 7 pacientiem ZR-OMA grupā (8,86%) bija AH (SAS p=0,000; R=0,570; for DAS p=0,000, R=0,345). Pētījums rāda, ka 10 AR-OMA pacientu (83,33%), 22 VR-OMA pacientu (53,66%), bet tikai 5 ZR-OMA pacientu (6,33%) bija palielināts KA (p=0,000, R=0,486) . 4 pacientiem ar AR-OMA (33,33%), 6 pacientiem ar VR-OMA (14,63%), bet tikai 1 pacientam ar ZR-OMA (1,27%) ĶMI bija lielāks par vai vienāds ar 35 35 (p=0,000; R=0,478).
Secinājumi: OMA riskam ir cieša saistība ar ĶMI, KA, SAS un DAS. ĶMI lielāks nekā 35 ir jutīgāks OMA riska faktors kā KA lielāks par 40 cm. Līdz ar to, pacientiem ar palielinātu ĶMI, KA, AH un miega traucējumiem anamnēzē ir svarīgi veikt OMA sijājošo diagnostiku ar standartizētu OMA anketu, lai būtu iespējams slimību diagnosticēt un ārstēt laicīgi.

Introduction

Obstructive sleep apnea (OSA) is a very common upper airway obstructive disease, which significantly impairs quality of life and causes a serious hazard to the health in long term. OSA occurrence in the world ranges from 2-4.5% in Asian countries (Punjabi 2008), 2-9% in North America and 7-14% in Spain (Young 2002). Although those affected by OSA are identified by clinical signs like respiratory arrest, loud snoring at night and sleepiness during the day. It is said that about 80% of OSA cases are not diagnosed (Bonnie 2015).

OSA main risk factors are present in males aged over 50, in postmenopausal women (Patil 2007) as well as obesity which is one of the major elements (Bonnie 2015). The main indicators of obesity is the body mass index (BMI) and neck and waist circumference. Studies have revealed that the neck circumference (NC) better correlates with the severity of OSA than BMI (Warner 2009). Alcohol consumption, smoking and sedative medication usage before sleep plays an important role in the OSA pathogenesis as well (Bonnie 2015).

OSA has been associated with arterial hypertension (AH), heart attack, cardiovascular disease (CVD), sudden death (Warner 2009), chronic obstructive pulmonary disease (Chaouat 1995) and it impairs glucose control in patients with second type diabetes (Renee 2010). OSA and acute coronary syndrome (ACS) has been widely studied and show a significant correlation (Jaffe 2013). In a study of 105 patients who were hospitalized with the diagnosis of ACS (non-complicated myocardial infarction), OSA with apnea- hypopnea index (AHI) greater or equal than 15 was diagnosed in 69 patients or 65.7% (Chi-Hang Lee 2009). While conducting an 8.7 year study with 5422 patients without heart attack but with OSA anamnesis diagnosis, 93 patients developed ischemic heart attack and this showed strong correlation with OSA. Also number of cases increased linearly along with the AHI (Tamanna 2016). OSA is an important risk factor in car accidents caused by pathological drowsiness, falling asleep at the wheel of a car (Tregear 2009).

Polysomnography (PSG) is the "gold standard" in the diagnosis of OSA (Chaouat 1995) but for screening there can be used different questionnaires like, for instance, Berlin questionnaire, ASA checklists, STOP BANG questionnaire and Epworth Sleepiness Scale.

Treatment with continuous **positive** airway pressure **therapy** is the leading method of treatment (Yang 2013), which is also available in Latvia but the costs are not covered by the government at the moment. Whilst OSA is being actively studied and treated worldwide, the author has observed that the disease is not adequately diagnosed and treated in Latvia.

Material and methods

Research took place in various GP practices in Riga and also in smaller towns outside the capital. Patients observed were both men and women in age range from 22-79.

A patient questionnaire was used for the research. The basis of it was a STOP BANG scale as well as number of questions about patients' comorbidities and driver status.

There were 132 respondents, 73% women and 27% men.

Statistical data processing was carried out using a program IBM SPSS Statistics V.22. $P < 0.05$ was accepted as statistically significant value. Median and percentile (25; 75) were used for nonparametric data.

Following tests were used for the data analyses - Pearson Chi-square test (analyses of gender, AH, NC and co-morbidities), Shapiro-Wilk test of normality (evaluation of data normal distribution), Kruskal-Wallis test (analyses of BMI and OSA ratio), Fishera Exact test (BMI and gender analysis) and MedCalc easy-to-use statistics program (BMI, NC sensitivity and specificity calculation).

Results

Study included 132 patients in age group 22 to 79, of which 27.3% (n = 36) were men and 72.7% (n = 96) - women. The average NC was 37.6 cm ± 3.5 cm, the average BMI was 26.2 ± 5.5 and the mean systolic blood pressure (SBP) was 128.9 ± 17.0 mm Hg. 59.9% (n = 79) of patients had low OSA risk, 31.1% (n = 41) had a moderate risk factor and 9.1% (n = 12) of patients were in a high risk category.

Using **Pearson's chi**-squared test, it reveals that the gender significantly correlated with the risk of OSA. Men were mostly at a medium OSA risk (47.2% of men) where 27,8% had low OSA risk and 25.0% had high OSA risk. Women were mostly at a low OSA risk (71.9% of cases) where 25.0% had medium OSA risk but a high OSA risk was present just in 3.1% cases.

BMI was calculated using the formula: $\frac{\text{weight (kg)}}{\text{height}^2(\text{m}^2)}$. BMI median value was 25.17 (IQR 22,22; 29,36) and the minimum value was 17 but maximum value - 49.

Based on BMI patients were devided into six groups (1st table). 41% of patients had normal body weight and almost a quarter (24%) were obese.

We found a statistically significant correlation between male BMI and OSA risk group ($p = 0.031$). 54.5% of men with normal body weight had a low OSA risk, 18.2% medium and 27.3% high.

Overweight men were mostly at medium OSA risk - 65%, 23% had low risk and 12% had high risk. Nobody who was obese had low OSA risk. Those with first degree obesity, half (50%) were at medium and half (50%) were at high risk. There were just a few respondents with second and third degree obesity therefore it was difficult to analyze those groups.

Similarly women's BMI significantly correlated with the OSA risk ($p = 0.001$). All of women with low weight (100%) had low OSA risk. 79.1% of women with normal weight had low OSA

risk, 21% were at medium risk and 0% of high OSA risk. 81% of overweight women had low OSA risk, 19% were at medium risk and none of this group was at high risk. The group of first degree obesity was mainly at low OSA risk (60%), 33% had moderate risk but 7% had high risk. Second degree obesity was presented mainly with medium OSA risk (71%), 14% had low and high was also present in 14%. The group with third grade obesity all (100%) were at high OSA risk.

NC of 72% respondents was less than 40cm (n = 95), 28% (n = 37) was higher. NC statistically significantly correlated with the risk of OSA (p = 0.000). 77.9% of individuals whose NC was less than 40 cm were at low OSA risk, 20% were at medium but just 2,1% at high risk. Meanwhile, only 13.5% of people whose neck diameter was more than 40 cm were at low OSA risk from which most of them had medium risk (59.5%) but 27% of respondents had high risk (2nd table).

This study showed that the sensitivity of BMI for men is 66.7% and specificity 78.8% but for women sensitivity is 25.0% and specificity 98.9%. While NC sensitivity for men is 30.8% and specificity 90.0%, for women sensitivity is 18.2% and specificity -98.8%

AH statistically significantly correlated with the risk of OSA (P = 0.000). In low OSA risk group, 91.1% of patients were free of AH. In medium risk group - 65.9% had AH but in the high risk group AH was diagnosed in 91.7% of patients (3rd table).

Angina statistically significantly correlated with the risk of OSA (p=0.003). Overall angina was observed in 6% of respondents. Of those who noted angina, 37.5% was at low, 12.5% at moderate and 50.0% at high OSA risk. In turn, those who did not note angina, 61.3% were at low, 32.3% at moderate risk but only 6.5% at high OSA risk.

Diabetes statistically significantly correlated with the risk of OMA (P = 0.000).

Overall, diabetes had 6% of the respondents. Of those who have diabetes, 0% were on low OSA risk, 57% were at medium OSA risk and 43% - at high OSA risk. Of those who did not have diabetes, 63% were at low OSA risk, 30% at medium but just 7% at high OSA risk.

Discussion

While OSA is a common and widely studied disease, it is not diagnosed and effectively treated in Latvia enough.

This research covers a study of medium and high OSA risk prevalence in primary care level in Latvia and OSA relationship with different risk factors and comorbidities, for instance, BMI, NC, AH, diabetes and angina.

The study showed that 31% of respondents had medium OSA risk but 9% of respondents had high OSA risk. Summarizing the literature on the epidemiology of OSA, there was not found a large amount of reliable research on OSA risk in different populations but all the studies have focused on proven OSA disease. Therefore, the data of epidemiology obtained in this study is not comparable with other studies.

This study shows that BMI has a statistically significant link with OSA risk (p = 0.000) which coincides with the literature (Warner 2009; Schafer 2002). Both, women and men with an increasing degree of obesity are also at a higher risk of OSA.

The literature shows that OSA patients have higher NC than general population as well as the fact that it better correlates with the severity of the OSA than BMI (Renee 2010). This study confirmed that NC statistically significantly correlates with the severity of the OSA in patients with NC under 40cm only 2% have high OSA risk but in patients with NC over 40cm - 27% of patients have high OSA risk. However, BMI is generally more sensitive and more specific indicator comparing to NC which does not agree with the literature (Warner 2009).

One of the main risk factors mentioned in the literature is the male gender that also coincides with the findings in present study. In this study, 25% of men had high OSA risk while only 3% of female respondents were in the same category.

AH is one of the main OSA complications and literature shows that even at the 1st level of OSA (AHI <5 times per hour) the risk that AH will develop within the next 4 years is 42%. (Young 2002). This study has shown that the most common level of risk in patients with AH is medium OSA risk (60%) with high OSA risk following in 26% of patients.

Although the literature suggests that OSA causes resistant AH that does not respond to three different classes of antihypertensive medication (Logan 2001), it was not possible to analyze that in this study as many respondents could not name drug names or active substances that they are using daily.

A statistically significant correlation was observed between diabetes, angina and OSA (p = 0.000 and 0.003) which agrees with the literature. In this study, 50% of patients with angina were at high OSA risk and 43% of patients with diabetes were at high OSA risk. From the literature, 14.7% of OSA patients with AHI ≥ 15 have type 2 diabetes but in patients with AHI below 5, type 2 diabetes was only in 2.8% of patients (Reichmuth, 2005)[11]. The study on the OSA prevalence in ACS shows that 65.7% of patients with it were also diagnosed with OMA (AHI ≥ 15) (Chi-Hang Lee 2009).

Conclusion

Neck circumference above 40 cm and obesity are very significant OSA risk factors whilst the BMI is a more sensitive and specific indicator than neck circumference.

There is also a significant correlation between the OSA and co- morbidities such as diabetes and angina.

Therefore, an OSA screening with standardized questionnaires and, if necessary, followed by polysomnography test should be done for patients with sleep disorders and increased BMI, NC, hypertension and cardiovascular disease in anamnesis.

It would be necessary to include more male respondents in further studies so the data could be more comparable between the genders.

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DO RHEUMATOID ARTHRITIS DISEASE ACTIVITY, SEROPOSITIVITY AND SEVERITY PREDICT CEREBROVASCULAR EVENTS?

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Abstract
Key word: *Rheumatoid arthritis, cerebrovascular disease, stroke, carotid artery intima media thickness*
Patients with rheumatoid arthritis (RA) have increased risk of developing cardiovascular disease when compared to the general population.(Zubieta 2012)
This study investigated whether the atherosclerotic lesions in brachiocephalic vessels, carotid intima-media thickness (CIMT), cerebrovascular(CV) risk factors and smoking, as well as level of disease activity and severity, seropositivity are associated with the risk of developing clinical cerebrovascular disease in patients with RA. Therefore a case–control study was performed within the retrospective cohort of patients with RA. Cases were patients who developed their first stroke after diagnosis of RA; controls were patients with RA without CVD. Cases and controls had similar RA disease duration. Traditional and disease-specific risk factors for stroke were collected. The data was analysed using logistic regression analysis.
Our results showed that cases of stroke were gender independent.
Primary arterial hypertension, non-severe atherosclerotic plaques and older age of patients were associated with stroke cases in RA patients.
Other traditional and disease specific risk factors, as well as seropositivity, RA disease activity and severity were not associated with CV events in RA patients in our study.

Kopsavilkums

Vai reimatoīdā artrīta slimības aktivitāte, seropozitivitāte un smagums ir saistīts ar cerebrovaskulāriem notikumiem?

Atslēgas vārdi: *Reimatoīdais artrīts, cerebrovaskulārā slimība, insults, intima media arteria Carotis*
Pacientiem ar reimatīdo artrītu ir palielināts kardiovaskulāro slimību risks salīdzinājumā ar pārējio populāciju.(Zubieta 2012).
Pētījuma mērķis bija izpētīt vai slimības aktivitāte, seropozitivitāte, aterosklerotiskās izmaiņas brachiocefālos asinsvados, intima -media komplekss a.Carotis , cerebrovaskulārie riska faktori un smēķēšana ir saistīti ar insultu risku pacientiem ar reimatoīdo artrītu. Retrospektīvā gadījuma-kontroles pētījumā tika iekļauti pacienti ar reimatoīdo artrītu, kuriem attīstījies cerebrovaskulārs notikums-insults, bet kontroles grupā pacienti bez cerebrovaskulāriem notikumiem.Pacienti atlasīti ar vienlīdzīgu reimatoīdā artrīta slimības ilgumu. Reimatoīdam artrītam, insultam specifiskie riska faktori tika analizēti, izmantojot loģistiskās regresijas datu statistisko apstrādes metodi. Mūsu pētījumā reimatoīdā artrīta aktivitātes, seropozitivitātes saistību ar cerebrovaskulāru notikumu attīstību pierādīt neizdevās Reimatoīdā artrīta pacientiem arteriālā hipertenzija, pacientu vecums un hemodinamiski maznozīmīgas aterosklerotiskās izmaiņas brachiocefālos asinsvados pozitīvi korelēja ar insulta attīstību.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects 0.5-1% of the adult population. RA has been shown to be associated with substantial cardiovascular comorbidity, but most of the available evidence originates from studies on the risk of myocardial infarction and cardiovascular mortality (Meune 2010). In contrast to the risk of myocardial infarction related to RA, the results from studies on the risk of stroke have been inconsistent, which may reflect the diverse causes of stroke, including atherothrombosis, thromboembolism and haemorrhage.

Guidelines by the European League Against Rheumatism (EULAR) has recently updated recommendations for cardiovascular disease risk management in patients with RA 2015/2016 (Agca 2017) suggesting a need to screen for asymptomatic atherosclerotic plaques by use of carotid

ultrasound, considering it as a part of CVD risk evaluation in patients with RA. New evidence strengthens the notion that the excess risk of CVD morbidity and mortality in patients with RA is related to both traditional and novel CVD risk factors. Novel risk factors include inflammation, presence of carotid plaques, anticitrullinated protein antibody (ACPA) and rheumatoid factor positivity, extra-articular RA manifestations and functional disability (Liao 2013).

It is acknowledged that the risk of cerebrovascular disease is increased among RA patients and this remains an underserved area of medical need. Considerable evidence indicates that patients with RA have an increased incidence of cardiovascular (CV) morbidity and mortality in both men and women (Sangha 2000). Several large, prospective epidemiologic and interventional studies with 39 520 RA patients have assessed the increased risk of cerebrovascular accident (CVA). Overall, there was found a 41% increase in the risk of CVA in patients with RA comparing to general population. (Zubieta 2012)

Despite several novel and RA disease-specific risk factors that have been associated with an increased risk of CVD, there is still uncertainty if these factors will meaningfully improve cerebrovascular (particularly stroke) risk prediction in patients with RA.

A case-control study was performed in a cohort of patients with RA matched by gender and disease duration to detect stroke cases and possible novel risk factors recommended by EULAR (European League Against Rheumatism) estimating carotid arteries intima-media thickness (CIMT) and atherosclerotic changes of brachiocephalic arteries with relation to age, gender, RA disease activity and severity, seropositivity, traditional CV risk factors and smoking history.

Material and Methods

Patients

This was a case-controlled retrospective study of patients with RA that lasted from 2012-2016. Patients diagnosed according to the 1987 American College of Rheumatology criteria and or who fulfilled the 2010 criteria for RA, with disease duration >6 weeks and without prior disease-modifying antirheumatic drug use, were included in the study.

Comprehensive information on comorbidities (including CVD) and the course of the disease was regularly collected and stored in an electronic database. Access to the medical files of each patient was available, which included the periods before and after diagnosis of RA; the registration of comorbidities and medical events was therefore complete.

Cases for this study were patients who developed a cerebrovascular disease (ischaemic stroke and haemorrhagic stroke) after the diagnosis of RA. Cases were selected if the diagnosis was verified by radiologist in MRI or CAT scan. Controls were selected randomly from the cohort of patients with RA, aiming to have similar disease duration (exposition time to inflammation) for cases and controls.

Assessment of disease activity and severity

In the cohort, disease activity was prospectively assessed using the DAS28. The DAS28 is a measure of disease activity in rheumatoid arthritis. DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment. DAS 28 is calculated from the 28-tender joint count, 28-swollen joint count, C-reactive protein and the patient's global assessment of disease related general health on a visual analogue scale. Disability was assessed using the disability index of the Health Assessment Questionnaire (HAQ).

Disease severity was assessed using X-ray proved erosions in small hand and feet joints, musculosceletal sonography of synovial joints, as well as performed joint replacement surgery.

Assessment of seropositivity

Circulating biomarkers - rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti CCP) antibodies were analysed from frozen serum or plasma by ELISAs tests.

Assessment of cerebrovascular risk factors

Traditional cerebrovascular risk factors were obtained including female gender, metabolic dysfunction, hypertension, diabetus mellitus, and smoking, dyslipidaemia with high triglyceride levels, low serum high density lipoprotein (HDL) and high LDL levels. Lipids were assessed from serum samples. The atherogenic index was calculated. It is defined as the base-10 logarithm of the ratio of plasma triglyceride to high density lipoprotein cholesterol.

Body mass index (BMI) was calculated from height and weight at baseline. Diabetus mellitus was regarded as present if the diagnosis was made before the event or censoring.

Brachial blood pressure was measured according to the European Society of Hypertension guidelines (Mancia 2013) using OMRON M7 apparatus (Kyoto, Japan). The average of the last two measurements was reported. Hypertension was defined as a history of hypertension, use of antihypertensive medication before the event or censoring or systolic office blood pressure ≥140 mm Hg and/or diastolic office blood pressure ≥90 mm Hg.

Information on smoking history and occurrence of clinical cerebrovascular disease (ischaemic and haemorrhagic stroke) was assessed at entry visits and obtained from medical records or patients.

Carotid ultrasound imaging

B –mode ultrasonographic examinations of the brachiocephalic vessels were performed with GE Vivid-7 scanner (GE Vingmed Ultrasound) using a 12 (10-14) MHz linear matrix array transducer. An experienced sonographer performed all examinations. Intima-media thickness (IMT) measurements were performed bilaterally in the far wall of the common carotid artery (CCA) over a 5 mm segment, from about 15 to 10 mm proximal to the start of the carotid bulb. Before an image was stored for analysis, we ensured that both the near wall and far wall were visualized with sharp

edges, indicating an insonation of about 90^0 to the vessel wall, to avoid overestimation of IMT and plaque size. Atherosclerotic plaques in the CCA, vertebral artery, subclavian artery and the internal carotid artery (ICA) were identified bilaterally in the longitudinal view when both IMT observations of far wall and near wall had sharp edges as protrusions into the lumen ≥1,5mm. In cases of doubt about the presence of a plaque, it was verified by a cross-sectional image obtained by rotating the probe 90^0. Plaque areas were analysed only if a sharp delineation of the plaque was obtained.

Statistical analysis

The statistical analyses were undertaken using IBM SPSS statistics V.22.0 (IBM, Armonk, New York, USA). Normally distributed continuous data were expressed as mean and SD and non-normally distributed continuous data as median and IQR. Categorical variables were presented as numbers and percentages. Cases of stroke and controls were compared by disease activity variables and risk factors using the Mann-Whitney U test (for continuous variables) or the Pearson's X^2 test or Fisher's exact test (for dichotomous variables).

Results

There were 105 patients (females 81%) with RA at the moment of case and control selection. They ranged in age from 21-84 years. Ten patients were selected as cases who had suffered from stroke, 95 controls were randomly selected. The case and control group were matched by disease duration. The mean RA disease duration for all patients was 5.2 (± 6.7) but median 2 years (IQR 1-7). The mean disease duration did not statistically differ between case and control groups respectively 6.13 (±8.85) years vs control group 5.09 (±6.5) p= 0.644

Patients with stroke were mostly females (80%), with a mean age of 67.25 age (± 10.45) years. Study cases and controls were matched by gender Fisher's exact test (p=0.05). Stroke patients were significantly older compared to control RA patients respectively 66.30± 9.67 vs 56.60 ±14.84 (p=0.046).

We found that patients with stroke have suffered from arterial hypertension (HTN) in 100% of cases, but in the control group only 56% (p=0.005).

Body mass index (BMI) in all RA patients was evaluated. Mean BMI was26.6 (±5.1), median BMI was 25.8 (IQR 22.8-30.3). BMI did not differ between case 28.06 (±4.88) and control 26.46(±5.14) groups (p=0.351).

A statistically significant association stroke cases with BMI (p=0.329) was not found, as well as with atherogenic index (p=0.156). Median of atherogenic index (AIP) was calculated in case group 0.018 vs control 0.118.

Diabetes was found in 10% of cases and 5% of control group, non-significantly associated with stroke cases (p>0.05).

Cases and controls had comparable age of beginning of RA complaints respectively 60.00(±12.52) vs 51.65 (±15.41), (p=0.118).

About 50% of cases were smokers vs 40% in control group. Smoking history and duration of smoking did not differ statistically significantly Pearson Chi-Square test (p=0.737) between cases (29.60±10.16) and controls (22.97±12.08).

Observing seropositivity of the patients, there were 80% of cases seropositive vs control 88%. The difference was not statistically significant (p=0.609), respectively for anticitrullinated protein (ACPA) antibodies (p=0.362) and for rheumatoid factor (RF) (p=0.526).

X rays of small joints of hands and feet, revealed erosions in small joints in 50% of stroke patients (p=1.000) vs control patient 46%. In total 46.7% of RA patients had erosive disease; 10.5% needed total joint replacement surgery, respectively 9.1% of stroke patients vs control 10.5% (Fisher's exact test p=1.000)

Interestingly, 90.0% of RA cases with stroke and 96.0% of non-stroke controls had detectable synovitis in musculosceletal ultrasound Fisher's exact test (p=0.609). RA disease activity (DAS28) mean in case group was 4.41(±1.55) .In control group it was 4.06 (±1.46); (p= 0.475), DAS28 above 4.17 was observed in 60% of patients with stroke *vs* 49% of control group (p=0.741).

Health Assessment Questionnaire (HAQ) for functional status assessment was done. Median HAQ in case group was 1.5(1.0-2.0) vs control 1.38(0.5-2.0); (p=0.585).

After performing neurosonological examinations no statistically significant difference in CIMT(carotid artery intima-media thickness) *dx et sin* between cases IMT sin mean 0.94mm (±0.18); IMT dx mean 0.91 mm(±1.75) and controls IMT sin mean 0.88mm(±0.21); IMT dx mean 0.86mm (±0.21) could be found respectively CIMT sin (p=0.41) vs CIMT dx (p=0.49).

Duration of RA, disease activity (DAS28), health assessment questionnaire (HAQ), seropositivity, smoking history per years, the beginning of menarche and menopause for female patients, as well as AIP did not have any association with CIMT.

CIMT of the RA patients had correlation with one more traditional risk factor as hypertension IMT sin (p<0.001); IMT dx (p=0.004). For the patients who had HTN the median of IMT sin was 1.00(0.80-1.10) and IMT dx 0.9(0.76-1.10) vs patients without hypertensive disease IMT sin median 0.78(0.62-0.92), IMT dx median 0.78(0.62-0.94).

IMT of our patients had correlation with atherosclerotic lesions of brachiocephalic vessels, respectively IMT sin (p<0.001), IMT dx (p=0.01). The median of IMT sin 0.79(0.64-0.92); IMT dx 0.78(0.63-0.91) vs patients with atherosclerotic lesions median of IMT sin 1.00(0.79-1.10); IMT dx 0.90(0.76-1.10).

Furthermore, atherosclerotic lesions were more pronounced in RA patients with versus without stroke (p=0.041). Altogether 90% patients with stroke (p=0.041) had atherosclerotic

plaques in brachiocephalic vessels resulting in <50% luminal stenosis, while 33% of stroke patients (vs 10% of control group) had plaques causing >50% lumen obstruction (p=0.09).

Non-stenosing atherosclerotic plaques were age dependent (p=0.047), had correlation with BMI (p=0.003) and age of RA initial presentation (p=0.033) and age of RA diagnosis determined (p=0.027) as well as hypertension (p=0.001). Neither disease duration, nor seropositivity, erosive findings in joints, gender, smoking history, joint replacement surgery, disease activity and atherogenic index (AIP) had some association with atherosclerotic plaques. Except for atherosclerotic plaques stenosing lumen more than 50%, DAS 28 was of importance, (p=0.032). A difference in Das 28 score was found between patients with and without severe atherosclerotic changes of vessels. According to our data, the median of Das 28 5.19 (IQR 4.31-6.17) was higher in patients with severe stenosing plaques than in patients with non-stenosing plaques which do not protrude lumen for more than 50%, the median DAS 28 3.89 (IQR 2.86-5.21)

Discussion

Patients with established rheumatoid arthritis (RA) are at well-documented increased risk of subclinical and clinical cardiovascular diseases, including cerebrovascular diseases. Although the relative risks reported have varied across studies, partly due to differences in patient with RA characteristics, the relative risk of stroke was 1.5 (1.2-1.8) compared to general population after data from the Swedish National Patient Register, cohort of 37 245 prevalent patients with RA (Eriksson, 2017). For stroke, they noted higher relative risk estimates for women than for men. In the present study, patients with stroke were mostly females (80%), but it did not correlate with higher relative risk.

In contrast with risks of myocardial infarction in RA, there is little data on when, in relation to RA diagnosis, the risk of cerebrovascular disease is increased. Based on Swedish large cohort studies of RA, the risk of stroke in RA evolves more slowly, counting from RA diagnosis and is detectable a decade after diagnosis of RA, although an increased risk earlier in the course of the disease cannot formally be ruled out (Holmqvist 2013). It is similar to our study, where the mean disease duration was 6.135(±8.85) years.

Evidence to date suggests (Hollan 2015) that RA disease activity as well as the number and duration of flares over time do contribute to the risk of stroke events. Disease activity was calculated by Das 28 score, physical disability (Pincus 1983) was evaluated by HAQ, but it did not reveal any significance between case and control groups.

What is interesting, the high inflammatory activity described by mean Das 28 5.19 (IQR 4.31-6.17) was associated with severe stenosing plaques in brachiocephalic vessels. It coincides with Semb A. study results, where disease activity has been shown to be associated with plaque size in patients with RA (Semb 2013).

Disease severity (joint replacement surgery, multiple erosions) according to the results of the present study was not found to have a positive relationship with stroke cases ($p>0.05$).

Another disease-related factor that may mediate atherosclerosis is the presence of autoimmunity or immune dysregulation. It is believed that patients with rheumatoid arthritis (RA) who are seropositive for RF (rheumatoid factor) have a higher risk of CV events and mortality than seronegative patients with AR (Godson 2002). Nowadays the presence of RF in RA associates with an increased overall mortality rate, but anticitrullinated protein (ACPA) antibodies associates with increased cardiovascular death (Ajeganova 2016). In this cohort we could not find predisposition to stroke in seropositive patients.

Despite that, more classical risk factors as age as well as primary arterial hypertension were proved to be associated with increased cerebrovascular events like stroke in our study. Although recent meta-analysis of hypertension in RA (Boyer 2011) failed to detect any difference in the prevalence of hypertension in RA and the general population, inflammation-induced accelerated atherosclerosis including arterial hypertension increased arterial stiffness might explain the evolvement of stroke.

Smoking is a well-established risk factor for RA (Kalberg 2011). Smoking and inflammatory activity (Tsiara 2003) has also been demonstrated to increase levels of fibrinogen, a known risk factor for thromboembolic events, such as ischaemic stroke. Half of our study cases were smokers, but interestingly, smoking status was not associated with stroke cases.

The presence of carotid artery plaques (CP) in the general population (Hellings 2010) is closely related to future cerebrovascular outcome. Patients with RA have 2-3 times more atherosclerotic plaques in the carotid artery (Roman 2006) compared with the general population. The results of the present study confirm that patients with RA and stroke had a larger burden of carotid as well as rest of brachiocephalic vessel atherosclerotic changes. Altogether 90% patients with stroke had atherosclerotic plaques in brachiocephalic vessels resulting in <50% luminal stenosis ($p=0.04$) vs control 54%.

Conclusion

To sum up the results of this study non-fatal stroke was observed in older individuals, suffering from arterial hypertension and having non-significant, non stenosing arterial atherosclerotic plaques, protruding lumen less than 50%. Disease activity, seropositivity, severity were not associated with CV events in RA patients in our study.

We emphasize EULAR guidelines according for asymptomatic atherosclerotic plaque screening by use of carotid arteries could be considered as a part of good cerebral artery disease risk evaluator as well as a predictor of future cerebral events in RA population.

The preliminary results indicate that additional research is necessary to further investigate the relationship between RA patients and CV risk.

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EFFECT OF PATIENT'S WEIGHT, BODY MASS INDEX AND POSITION ON THE DIAMETER OF THE RIGHT INTERNAL JUGULAR VEIN

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Abstract

Effect of patient's weight, body mass index and position on the diameter of the right internal jugular vein

Key words: *Central venous catheterization, jugular vein, ultrasound*

Right internal jugular vein (RIJV) is the most common choice for obtaining central venous access. Lesser complications during cannulation arise if puncture succeeds on first attempt and size of RIJV's diameter is significant for that. Several methods are known to obtain better filling of central veins and accordingly expand their diameter, though not all of them are studied in patients undergoing general anaesthesia (GA). Body mass index (BMI) also might affect the diameter.

The aim was to evaluate how BMI correlates with the diameter of RIJV before and after induction of GA, and specify which of already known manoeuvres for cannulation of RIJV provides the largest diameter of it during GA.

We conducted prospective observational study, 30 consenting patients undergoing GA were enrolled. All patients were over 18 years (56,5±16,6), BMI 28,1±4,9 kg/m^2. We visualised RIJV at level of cricoid cartilage with high-resolution ultrasound using linear probe and minimal pressure on the neck. We measured the diameter (0,84±0,32cm) and area (1,03±0,64cm^2) of the vein before induction of GA and during following manoeuvres after GA: head in neutral position (P1), head rotation 30^o to the left (P2), elevation of patient's head using 5cm high cushion (P3), using pressure on the contralateral jugular vein (P4) and using PEEP 5cmH_2O (P5).

There was a correlation among BMI and the diameter of RIJV (r=0,47; p=0,01), and RIJV's area (r=0,43; p=0,02). There was no difference in the area of RIJV before and after GA in P1. After GA the area of RIJV in P5 is significantly larger than in P4. The area of the vein was larger in P5 than before induction of GA. None of the manoeuvres affected anterioposterior (AP) diameter of RIJV predictably.

Patient's weight and BMI predictably correlates with the diameter of RIJV- patient with a higher BMI has a larger diameter of the vein. In patients under GA the best manoeuvre of positioning for RIJV cannulation is P5, whereas P4 tends to reduce its area.

Kopsavilkums

Pacienta svara, ķermeņa masas un pozīcijas ietekme uz labās iekšējās jūga vēnas diametru

Atslēgvārdi: *centrālās vēnas kateterizācija, jūga vēna, ultrasonogrāfija*

Labā iekšējā jūga vēna ir biežākā izvēle centrālās venozās pieejas nodrošināšanai. Komplikācijas attīstās retāk, ja punkcija izdodas ar pirmo mēģinājumu. Svarīgs nosacījums ir vēnas diametra izmērs. Ir aprakstītas vairākas metodes, kas palielina vēnu pildījumu un attiecīgi diametru, bet ne visas šīs metodes ir pētītas pacientiem vispārējā anestēzijā (VA).

Pētījuma mērķis bija noskaidrot, kā ĶMI korelē ar labās iekšējās jūga vēnas diametru pirms un pēc VA, un precizēt, kurš no jau zināmiem manevriem nodrošina vislielāko vēnas diametru pacientiem VA.

Mēs veicām prospektīvu novērošanas pētījumu ar 30 konsekutīviem pieaugušiem pacientiem VA, vidējais vecums 56,5±16,6 gadi, ĶMI 28,1±4,9 kg/m^2. Vēna tika vizualizēta gredzenskrimšļa līmenī ar augstas izšķirtspējas ultrasonogrāfa lineāru zondi, pielietojot minimālu spiedienu uz kakla. Tika izmērīts vēnas diametrs (0,84±0,32cm) un laukums (1,03±0,64cm^2) pirms VA un veicot sekojošus manevrus VA laikā: galva neitrālā pozīcijā (P1), galvas rotācija 30^o pa kreisi (P2), 5cm galvas elevācija (P3), spiediens uz kontralaterālās jūga vēnas (P4) un PEEP 5cmH_2O (P5).

Tika atrasta pozitīva korelācija starp ĶMI un vēnas diametru (r=0,47; p=0,01), un laukumu (r=0,43; p=0,02). Salīdzinot šķērsgriezuma laukumu neitrālā pozīcijā pirms un pēc VA, netika atrasta nozīmīga atšķirība. VA laikā vēnas laukums P5 ir nozīmīgi lielāks nekā P4. Vēnas laukums palielinās P5, salīdzinot to ar P1. Neviens no manevriem neietekmēja vēnas sagitālo diametru paredzami.

Pacienta svars un ĶMI pozitīvi korelē ar vēnas laukumu un diametru – pacientiem ar lielāku ĶMI ir lielāks iekšējās jūga vēnas diametrs. Pacientiem VA labākais manevrs labās iekšējās jūga vēnas punkcijai ir P5, savukārt P4 ir tendence vēnas laukumu samazināt.

Introduction

During complicated surgery it can be necessary to obtain central venous access and central venous cannulation is frequently performed procedure – USA alone inserts more than 5 million central venous catheters each year (Heffner 2016). Right internal jugular vein (RIJV) is the most common choice for obtaining central venous access because this location is easily accessible and usually it does not interfere with the operation. It usually has a lower risk to complications due to its anatomy. Complications during cannulation can arise, and they do even in 15% of cases **(**Lorchirachoonkul 2012), but their incidence is less if puncture of the vein succeeds on first attempt and largeness of the diameter of right internal jugular vein is significant for that. The larger the diameter of the vein during the puncture, the easier it is to puncture it on first attempt. Several methods are known to obtain better filling of central veins and accordingly expand their diameter, such as Trendelenburg position, changing the extent of patient's head rotation, positive end expiratory pressure (PEEP) etc., though not all of them are studied in patients undergoing general anaesthesia (GA). The efficiency of Trendelenburg position for providing larger diameter of the vein has been proven in several studies (Armstrong 1994, Frykholm 2014, Parry 2004), but as it has its risks and contraindications, for example, neurosurgery, glaucoma patients and other patients at risk of high intracranial and/or intraocular pressure, the priority of this study was to find an alternative method which provides the largest diameter of right internal jugular vein during general anaesthesia.

The aim of this prospective observational study was to evaluate how body mass index correlates with the diameter of right internal jugular before and after induction of general anaesthesia, and specify which of already known manoeuvres for cannulation of right internal jugular vein provides the largest diameter of it during general anaesthesia.

Materials and Methods

We conducted prospective observational study between 1st October 2016 and 23rd January 2017 in Hospital of Traumatology and Orthopedics (Riga). 30 consenting patients (18 female (60%), 12 male (40%)) undergoing GA for elective spine surgery were enrolled. All patients were over 18 years (56,5 ± 16,6), BMI 28,1 ± 4,9 kg/m^2. Exclusion criteria were age under 18 years, neoplasms, wounds or scar tissue in the studied area of the neck, known right carotid artery stenosis above 70% or right subclavian vein thrombosis and hemodynamic compromise. For all patients GA was induced using fentanyl, propofol and atracurium, followed by tracheal intubation. For maintenance of anaesthesia sevoflurane was used. Dosage was evaluated and adapted to individual patient's needs based on their age, constitution and comorbidities. Before procedure we explained the study to each patient and acquired written consent. Due to ethical considerations none of the patients had their RIJV punctured because the operation did not require this manipulation.

We visualised RIJV at level of cricoid cartilage with high-resolution ultrasound (5 – 10 MHz) using linear probe (SonoSite M-Turbo portable ultrasound machine, Bothell, USA) and minimal pressure on the neck (Fig.1). We measured the anterioposterior (AP) diameter (0,84 ± 0,32cm) and cross-sectional area (1,03 ± 0,64cm^2) of the vein before induction of GA and during following manoeuvres after GA: head in neutral position, head rotation 30^o to the left, elevation of patient's head using 5cm high cushion, using pressure on the contralateral jugular vein and using PEEP 5cmH_2O. All measurements were made at the end of expiration to standardize the variables. We registered the following data: patient's age, gender, height, weight and RIJV's cross-sectional area and anterioposterior diameter during previously mentioned manoeuvres. We calculated patient's body mass index (BMI) and body surface area (BSA). Data are shown in Table 1.

Table 1. **Patient's demographical data and antropometric measurements**

		Mean	**SD**
Age, years		56,53	16,6
Gender, number, (%)	**Female**	18 (60%)	-
	Male	12 (40%)	
Weight, kg		82,53	18,5
Height, cm		171,13	10,1
BMI, kg/m^2		28,06	4,9
BSA, m^2		1,97	0,3

Data was statistically analysed using computer program IBM SPSS version 22.0. We used Shapiro-Wilk test, fixed effects model and linear regression. Results were described using mean and standard deviation (SD). P value < 0,05 was considered statistically significant.

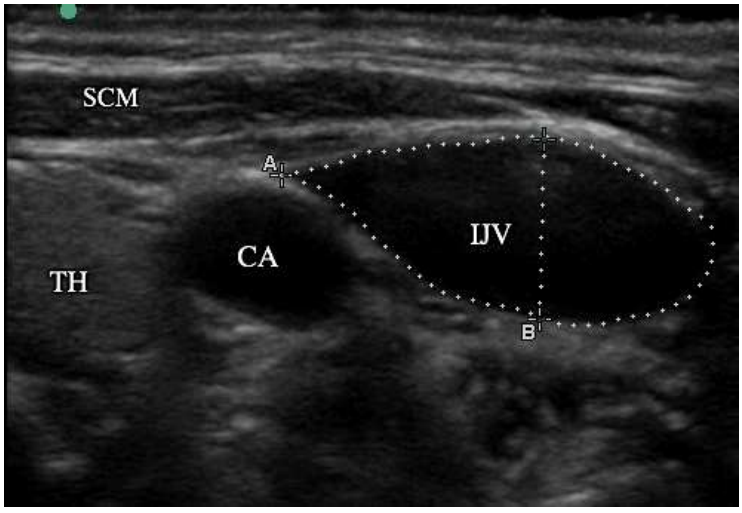

Figure 1. **Ultrasound visualisation of *vena jugularis interna dextra* and carotid artery** (Ševčuka, S. Anonymous patient. TOS. 23.11.2016.)

SCM – sternocleidomastoid muscle;
IJV – right internal jugular vein;
CA – carotid artery;
TH – thyroid gland.

Results

There was a positive correlation among body mass index and the anterioposterior diameter of right internal jugular vein (r= 0,47; p=0,01), and the cross-sectional area of right internal jugular vein (r=0,43; p=0,02). Correlations among right internal jugular vein's diameter and cross-sectional area before induction of general anaesthesia and other antropometric measurements (weight, height, BSA) were not statistically significant.

Right internal jugular vein's mean cross-sectional area was 1,03 ± 0,64 cm^2 and mean anterioposterior diameter was 0,84 ± 0,3 cm before induction of general anaesthesia, and in neutral position after induction of general anaesthesia they did not change significantly. Right internal jugular vein's average cross-sectional areas and anterioposterior diameters while using other manoeuvres are shown in Table 2 and Table 3.

After induction of general anaesthesia the cross-sectional area of right internal jugular vein while using PEEP 5 cmH_2O is significantly larger than while using contralateral neck pressure (1.29±0.91cm^2 vs. 0.98±0.72cm^2; mean difference 0.31cm^2 (CI 0.03-0.59); p=0.02). There was a tendency to a larger area of the vein while using PEEP 5 cmH_2O when compared before induction of general anaesthesia (mean difference 0,25 cm^2 (CI – 0,03-0,54); p=0,10) (Fig.2). None of the manoeuvres affected anterioposterior diameter of RIJV predictably (Fig.3).

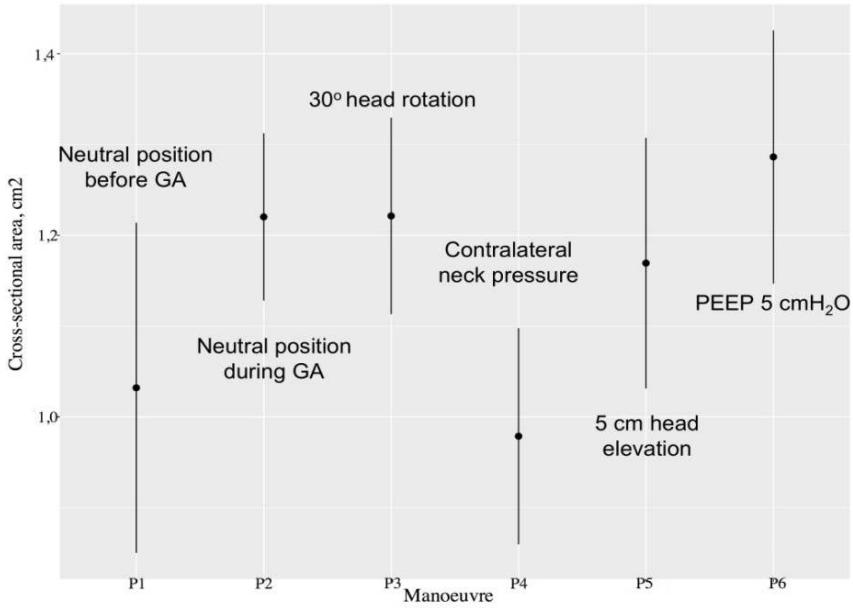

Figure 2. **Comparison of right internal jugular vein's cross-sectional area during several positioning manoeuvres**

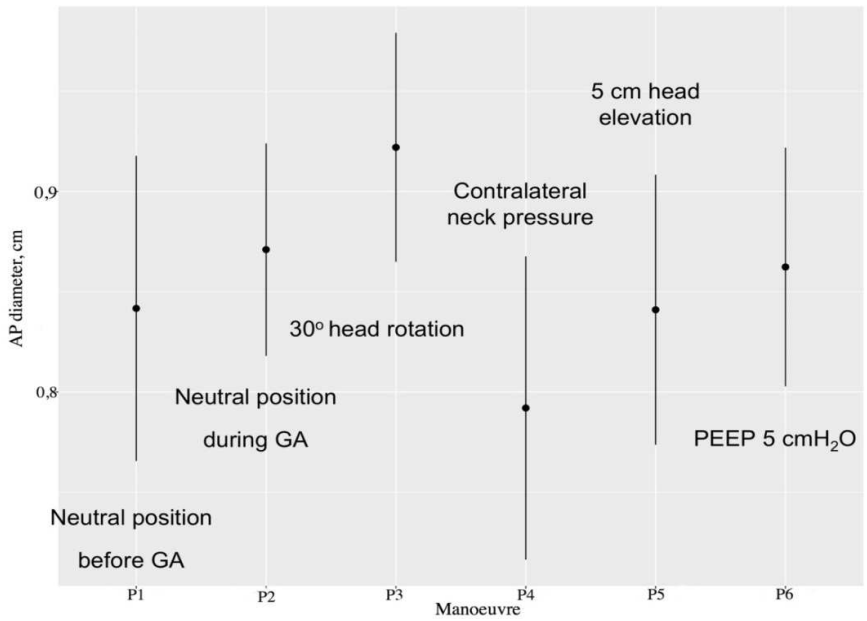

Figure 3. **Comparison of right internal jugular vein's diameter during several positioning manoeuvres**

36,7% of patients in neutral position both - before and after induction of general anaesthesia had right internal jugular vein's diameter < 0,7 cm, but 33,3% of patients had it above 1 cm.

Table 2. ***Vena jugularis interna dextra*** **diameter's mean values during different manoeuvres**

Manoeuvre	Mean (cm)	Standard deviation (SD)
Neutral position before GA	0,84	0,3
Neutral position during GA	0,87	0,4
30° head rotation	0,92	0,4
Contralateral neck pressure	0,79	0,4
5 cm head elevation	0,84	0,4
PEEP 5cmH_2O	0,86	0,4

Table 3**.** ***Vena jugularis interna dextra*** **cross-sectional area's mean values during different manoeuvres**

Manoeuvre	Mean (cm^2)	Standard deviation (SD)
Neutral position before GA	1,03	0,6
Neutral position during GA	1,22	0,8
30° head rotation	1,22	0,7
Contralateral neck pressure	0,98	0,7
5 cm head elevation	1,17	0,9
PEEP 5 cmH_2O	1,29	0,9

Cross-sectional area of the RIJV was modelled as individual anatomical specialities and positioning (using previously mentioned manoeuvres) function using mixed effect linear model. Patient's position affected *vena jugularis interna dextra* cross-sectional area significantly, $\chi 2(5) = 14,07$, $p = 0,015$. Results of this model are shown in Table 4.

Table 4. **Fixed effects model for predicting RIJV cross-sectional area**

Fixed effects: area ~ position	**Coefficient ± SE**
Neutral position before GA	1,03 ± 0,14
Neutral position during GA	0,19 ± 0,1 *
30^o head rotation	0,19 ± 0,1 *
Contralateral neck pressure	-0,05 ± 0,1
5 cm head elevation	0,14 ± 0,1
PEEP 5 cmH_2O	0,25 ± 0,1 ^{X}
Random effects:	
Variability among patients (standard deviation)	0,67
Variability among positions/manoeuvres (standard deviation)	0,34 ^{X}

* $p<0.10$; ^{X} $p<0.05$

Post hoc tests showed that cross-sectional area while using PEEP 5cmH_2O, comparing it to the cross-sectional area before induction of GA, increases by 25 (95% CI -0,03 – 0,54) cm^2, p=0,10, but comparing it to the cross-sectional area while using contralateral neck pressure - by 0,31 (95% CI 0,03 – 0,59) cm^2, p=0,02. Other manoeuvres did not affect cross-sectional area of right internal jugular vein significantly.

Modelling *vena jugularis interna dextra* anterioposterior diameter as positioning manoeuvres function we did not find any statistical significance, $\chi 2(5) = 1,49$, $p = 0,2$.

Discussion

In this prospective observational study we visualised right internal jugular vein of 30 consenting patients before elective spine surgery using high-resolution ultrasound. We measured the AP diameter (0,84 ± 0,32cm) and cross-sectional area (1,03 ± 0,64cm^2) of the vein before induction of GA and during following manoeuvres after GA: head in neutral position, head rotation 30^o to the left, elevation of patient's head using 5cm high cushion, using pressure on the contralateral jugular vein and using PEEP 5cmH_2O. All measurements were made at the end of expiration to standardize the variables.

Our study showed that right internal jugular vein's cross-sectional area is affected by patient's position and used manoeuvre significantly.

We obtained the smallest cross-sectional area or right internal jugular vein while using contralateral neck pressure, but the largest – while using positive end expiratory pressure. We did not find statistical significance between patient's position/manoeuvre and right internal jugular vein's anterioposterior diameter. We assume that these manoeuvres might affect vein's lateral diameter more.

Increase in vein's cross-sectional area and diameter while using PEEP has been described in several articles before (Bannon 2011, Marcus 2010). In this study, vein's cross-sectional area increases by 25,4% comparing it to the one before induction of general anaesthesia. That is more than previously described in study conducted by *Marcus et al*, where the cross-sectional area increased by 15,9%.

Based on the data in scientific literature, head elevation tends to increase the anterioposterior diameter of right internal jugular vein (Parry 2004), but this manoeuvre did not make significant changes in diameter in our study.

36,7% of patients in neutral position both - before and after induction of general anaesthesia had anterioposterior diameter of right internal jugular vein < 0,7 cm, which is described as a sign for predictably complicated cannulation and higher risk to mechanic complications. (Blanco 2016, Lorchirachoonkul 2012, Mey 2003). In 2003 *Mey et al* conducted a study in Europe with 493 patients and found that 12,1% of patients had RIJV's diameter ≤ 7. Other studies made in Western populations shows similar results. Only 33,3% of patients in previously described positions had the anterioposterior diameter of the vein above 1 cm, that is described as the normal or even lowest normal size of right internal jugular vein, sometimes even used as a distinction criteria from carotid artery (Bannon 2011).

We believe that differences from data in scientific literature might be due to included population's specifity – all patients were prepared for elective surgery (empty stomach, premedication etc.), and that might have affected filling of central veins. We also observed that patients with lower BMI had smaller size of the vein. It should be noted that shape and size of the right internal jugular vein was very variable among induviduals.

None of the manoevres affected anterioposterior diameter of the vein predictably, therefore it is advisable to use real-time ultrasound visualisation during venipuncture of right internal jugular vein, especially in patients with low BMI.

We could avoid deficiencies of this study by expanding the range of patients included. It is possible, that results could be differend from those described in this study if we repeated the study in a wider range of population. This study does not provide data about right internal jugular vein's anterioposterior diameter and cross-sectional area of patients in acute medical conditions; all patients were stable and prepared for spinal surgery. We consider that right internal jugular vein's lateral (LL) diameter and the relationship between right carotid artery and right internal jugular vein would have been valuable measurements that could represent significant information before cannulation of the vein, for example, vein-artery overlap, non-classical localisation of the vein etc. We did not measure and register all these variables, but two of included patients had vein-artery overlap, which is a great risk for accidental carotid artery cannulation if venipuncture is done (Rajinikanth 2008).

Filling of central veins and size of right internal jugular vein's anterioposterior diameter, also patient's individual anatomical differences have an impact on development of mechanic complications, especially if venipuncture is made only by using surface anatomical markers, and studied manoeuvres could not provide optimal conditions for cannulation of right internal jugular

vein for all patients. Therefore real-time ultrasound visualisation is significant for providing successful cannulation and reducing risk to mechanic complications.

Conclusions

Patient's weight and BMI predictably correlates with the diameter and cross-sectional area of right internal jugular vein - patient with a higher BMI has a larger cross-sectional area and diameter of the vein.

In neutral head position before general anaesthesia right internal jugular vein's average cross-sectional area is 1,03 cm^2 and anterioposterior diameter 8 mm, and after induction of general anaesthesia it does not change significantly. Change in position after general anaesthesia does not affect right internal jugular vein's anterioposterior diameter significantly.

In patients undergoing general anaesthesia the best maneouvre for right internal jugular vein's cannulation is application of PEEP 5cmH_2O as it increases cross-sectional area, whereas application of contralateral neck pressure tends to reduce its area.

None of the manoevres affected anterioposterior diameter of the vein predictably, therefore it is advisable to use real-time ultrasound visualisation during venipuncture of right internal jugular vein in patients undergoing general anaesthesia.

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LATE RADIOLOGICAL OUTCOMES AFTER ARTHROSCOPICALLY ASSISTED AND TRADITIONAL SURGICAL TREATMENT OF COMPLETE ARTICULAR DISTAL RADIUS FRACTURES

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Abstract

Late radiological outcomes after arthroscopically assisted and traditional surgical treatment of complete articular distal radius fractures

Key words: *Radiology, arthroscopy, radius, fracture, surgery*

Introduction: In twenty first century traditional surgical treatment of complete articular DRF is combined with intraoperative arthroscopical management of the entire articular surface and structures. Postoperative radiological assessment of the joint is mandatory in evaluation of surgical outcomes.
The aim of this study was to compare late radiological outcomes between traditional surgical (TS) and arthroscopically assisted (AA) approach of complete articular DRF.
Materials and methods: In this retrospective study we included 37 patients from 2009-2014 with DRF (AO 23-C) who were treated with either TS or AA approach. Data included patients sex, age, injured and dominant hand, high or low velocity trauma, surgical approach and technique and late radiological outcomes ≥1 year after surgery (radial inclination (RI), radial height (RH), volar tilt, articular surface). Collected statistical data were analyzed with SPSS v.20.0 software.
Results: Research included 25 women, 12 men, average age of both groups was 48 ± 2,6yrs. Left hand injuries were in 22 cases, right hand- 15, 18 patients had trauma in their dominant hand, 30 patients were with low velocity trauma, 7 - high. There were 23 patients with AA and 14 with TS treatment. Volar locking plate was used in 85% AA and 52% TS patients, K-wires and external fixation devices were used in 25% and 48%, respectively. Smooth articular surface was present in 64% AA and 57% TS patients. Analyzing independent sample test, RI was significantly smaller in AA group (AA=19,5±0,7 vs. TS=24,0±0,9, P=0,02), RH also was smaller in AA group (AA=10,7±0,7 vs. TS=12,4±0,5, P=0,042). Although visual analog scale showed AA=1 point, TS=2 points, it was not significant.
Conclusion: Late radiological outcomes after complete articular DRF have better outcomes in TS group than in AA group. However, further longitudinal research for evaluation of functional and radiological outcomes of AA is needed.

Kopsavilkums

Vēlīnie radioloģiskie rezultāti pēc artroskopiski asistētām un tradicionāli veiktām osteosintēzēm pilnīga artikulāra spieķa kaula distālā gala lūzuma gadījumos

Atslēgas vārdi: *Radioloģija, artroskopija, spieķa kauls, lūzums, ķirurģija*

Ievads: Divdesmit pirmajā gadsimtā tradicionālā osteosintēze pilnīgu artikulāru spieķa kaula distālā gala lūzuma (DRF) gadījumos tiek kombinēta ar intraoperatīvu artroskopisku pieeju locītavu virsmai un struktūrām. Radioloģiskais locītavas novērtējums pēcoperācijas periodā ir obligāts, lai izvērtētu ķirurģiskos rezultātus.
Mērķis: Salīdzināt vēlīnos radioloģiskos rezultātus pēc tradicionālas osteosintēzes (TS) un pēc artroskopiski asistētas osteosintēzes (AA) pilnīgu artikulāru DRF gadījumā.
Materiāli un metodes: Šajā retrospektīvajā pētījumā tika iekļauti 37 pacienti laikā no 2009. līdz 2014. gadam ar pilnīgiem artikulāriem DRF (AO klasifikācija 23-C), kuriem veikta TS vai AA. Tika iekļauti šādi dati: pacientu dzimums, vecums, ievainotā un dominējošā roka, augstas vai zemas enerģijas trauma, ķirurģiskā tehnika, kā arī vēlīnie radioloģiskie rezultāti ≥1 gadu pēc operācijas (radiālā inklinācija (RI), radiālais augstums (RH), volārās virsmas liekums, locītavas virsma). Dati tika analizēti ar SPSS v.20.0 palīdzību.
Rezultāti: Pētījumā tika iekļauti 25 sievietes un 12 vīrieši, vidējais vecums abās grupās bija 48 ± 2,6 gadi. Kreisās rokas ievainojumi bija 22 gadījumos, labās rokas – 15 gadījumos. Astoņpadsmit pacienti bija ievainojuši dominanto roku, 30 pacientiem bija zemas enerģijas trauma, bet 7 – augstas enerģijas trauma. AA grupā tika iekļauti 23 pacienti, bet TS grupā – 14 pacienti. Bloķējošās volārās konstrukcijas plātnes tika izmantotas 85 % gadījumu AA grupā, bet tikai 52 % gadījumu TS grupā. Kiršnera stieples un ārējās fiksācijas aparāti tika izmantoti 25% un 48% gadījumu, attiecīgi. Gluda artikulāra virsma bija 64% gadījumu AA grupā and 57% gadījumu TS grupā. Neatkarīgo izlašu testu neparametriskais tests AA pacientu grupā uzrādīja ievērojami mazāku RI (AA=19,5±0,7 vs. TS=24,0±0,9, P=0,02), mazāku RH (AA=10,7±0,7 vs. TS=12,4±0,5, P=0,042). Lai arī vizuālo analogu skala uzrādījā 1 punktu AA grupā un 2 punktus TS grupā, šie rādījumi nebija statistiski ticami.
Secinājumi: Vēlīnie radioloģiskie rezultāti pilnīgu artikulāru DRF gadījumā ir labāki TS grupā nekā AA grupā. Tomēr ir nepieciešami turpmāki pētījumi, lai izvērtētu funkcionālos un radioloģiskos rezultātus pēc artroskopiski asistētām osteosintēzēm.

Introduction

Distal radius fractures (DRF) are one of the most common fracture types worldwide (25% of fractures in the paediatric patients and up to 18% in elderly patients). DRF has an increasing incidence amongst boys and girls under the age of 20 due to sports-related traumas. (Nellans et al. 2012)

Surgical treatment nowadays is the first-line treatment option for DRF. Fractures can be fixated externally or internally (osteosynthesis with plates). External fixation is used in cases, when fracture is multifragmentar but in recent years the rate of internal fixation for DRF has increased. Internal fixation with volar locking plates for DRF provides an overall decreased incidence of complications, significantly less radial shortening, and significantly greater postoperative wrist motion when compared to external fixation. (Bales et al. 2012; Richard et al. 2010)

Nowadays, arthroscopic assistance has gained more popularity than traditional surgery. Main idea of arthroscopic assistance is to achieve a better anatomical reduction of the articular fragments. Main advantages of arthroscopic assistance are minimally invasive procedure with good view of the articular surface and assessment of soft tissue injuries (ligaments and triangular fibrocartilage complex). Arthroscopy increases the quality of the intra-articular reduction and at follow-up patients who undergo arthroscopically assisted surgery have a greater degree of motion range in joint (supination, flexion, and extension) than patients undergoing traditional surgery. (Abe Yukio et al., 2011; Ruch et al. 2004)

It has been established also in other studies that better functional outcomes, shorter recovery time and lower number of adverse effects can be achieved after arthroscopically assisted surgery more frequently than after traditional surgery. (Smeraglia et al, 2016).

Radiological assessment after internal fixation is mandatory despite surgical approach. Assessment is done by fluoroscopy. Frequently used parameters and their reference intervals are shown in Table 1. (Hodgson 2009, AO foundation)

Table 1. **Radiological parameters and reference intervals of distal radius**

Radiological parameter	Reference interval
Radial height	12 millimetres
Radial inclination	average 23^{o}
Scapholunate angle	30^{o} - 80^{o}
Volar tilt	11^{o} - 12^{o}
Ulnar variance	-2 till 0
Palmar inclination	average 12^{o}

In recent study radiological parameters that were evaluated on average 26 months after arthroscopically assisted surgery showed 21° of radial inclination, 2° of volar tilt and 0.7 mm of ulnar variance. These results were better than in patients after TS. (Khanchandani et al. 2013; Varitimidis et al 2008)

However, there have also been discussions that functional outcomes in patients with DRF do not correlate with radiological outcomes after surgery despite the approach and therefore could not be used to as surrogates for successful treatment. (Plant 2017)

We aimed to assess late radiological outcomes in patients with complete articular DRF in two groups – arthroscopically assisted and traditional surgery and to see if these outcomes are better in arthroscopic assistance group just as they are when considering functional outcomes.

Materials and methods

Patients form Centre of Plastic and Reconstructive Microsurgery of Latvia were drew in research. Inclusion criteria were distal radius intra-articular fracture, traditional surgery or arthroscopically assisted surgery, volar locking plate or external fixation techniques, ergotherapy. Excluded were patients with extra-articular fractures, complex trauma (polytrauma, Bennett's fracture, carpal bone fractures, both hand injuries, etc.).

Data from patients in year 2009 to 2014 were collected. Data consisted of patient age, gender, injured hand, injury according to AO classification, co-injuries and dominant hand. Also styloid fracture of ulna was detected. Mechanism of trauma (velocity) was included too. Data of pain measurement according to visual analogue scale was collected (pain year after surgery). X-ray images (dorsopalmar and lateral projections), which were made a year or more after surgery were described and used in study. It included information of articular surface (smooth, fibrosis, sclerosis, arthrosis), radial inclination, radial height, volar tilt and ulnar variance.

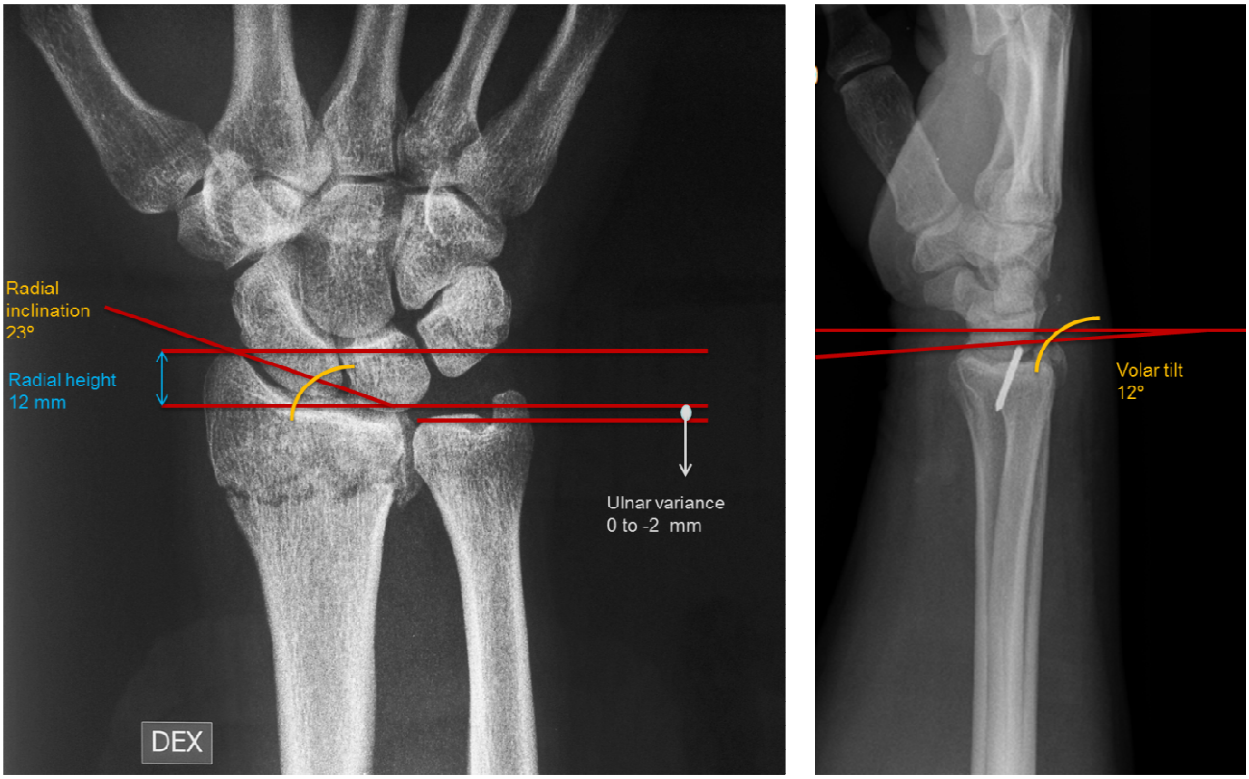

Figure 1 and 2. **Radiological parameters in dorsopalmar and lateral view**

The radial height was measured between two parallel lines: horizontal line from the top radial styloid and horizontal line from lunate fossa. Radial inclination is an angle between horizonlat line from lunate fossa and oblique line from radial styloid to medial corner of radius. Ulnar variance is distance between two parallel lines: horizontal line from lunate fossa and horizontal line from ulnar surface. Previously mentioned were established in dorsopalmar projection (Figure 1). In lateral view volar tilt was assessed. It is an angle between two lines: connection of lips of radius articular surface and a perpendicular line to long axis (Figure 2).

Patients were labelled with numbers during analysis of data. Statistical analysis was performed using *Microsoft Excel 2010* and *IBM SPSS Statistics v. 22.0*. Descriptive statistics (mean, standard deviation, minimum, maximum) and frequencies were used to describe researched groups. To find out differences between frequencies (condition of articular surface) of both groups, Chi-Square test was performed. Shapiro-Wilk test was used to identify normality of data. Parametric data were compared using independent sample T test (visual analogue pain scale) and nonparametric data was compared through independent sample nonparametric test (radial inclination, radial height, ulna variance and volar tilt). Level of statistical significance was accepted at p value less than 0,05.

Results

From 37 patients 23 (62%) over went traditional surgery and 14 (38%) had arthroscopically assisted osteosynthesis. Gender distribution was 74% women and 26% men in arthroscopically assisted method and 57% women and 43% men in traditional surgical technique. Mean age of patients was 48 ± 2,6 (19-79) years. The incidence of right hand injury was 43,5% in traditional surgery group and 35,7% in arthroscopically assisted group, but left hand – 56,5% and 64,3%, respectively. 18 patients had injured their dominant hand. More frequently low velocity trauma has caused fracture – 82,6% of traditional surgery and 78,6% of arthroscopically assisted cases, but high velocity trauma was present at 17,4% and 21,4% cases, respectively. Styloid fracture had 78,3% of traditionally treated patients and 64,3% of with arthroscopical assistance treated patients. Distribution of fractures according to AO classification in traditional surgery was – C1: 56,5%; C2: 17,4%; C3: 26,1%, but in arthroscopically assisted technique – C1: 42,9%; C2: 42,9%; C3: 14,3% (Figure 2). Volar locking plate was used in 64,9% of cases: 52,2% of traditional surgeries and 85,7% in arthroscopically assisted surgeries, but external fixation and K-wires as a method was selected in 65,1% of all cases: 47,8% of traditional surgeries and 14,3% of arthroscopically assisted surgeries.

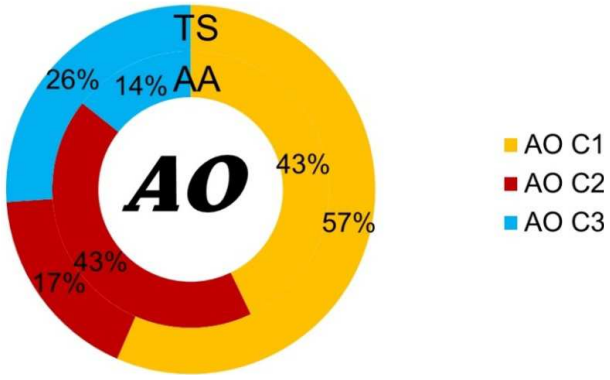

Figure 3. **Distribution of AO classification between traditional surgery and arthroscopicallu assisted surgery groups**

Late radiological outcomes of articular surface are following: in traditional surgery group 68,4% of patients have smooth articular surface, 21,1% have sclerosis, 5,3% have arthritis and 5,3% have arthrosis. In arthroscopically assisted group 90,0% have smooth articular surface and 10,0% have sclerosis. Analyzing Chi-Square test the groups had no significant difference between late radiological outcomes of articular surface (p = 0,589).

In Shapiro-Wilk test normality was not present analysing radiological parameters (p > 0,05). Independent sample nonparametric test revealed statistically significant difference between traditional surgery group (TS) and arthroscopically assisted surgery (AA) group in radial inclination (RI) (RI_{TS} = 24,0 ± 0,9 vs. RI_{AA} = 19,5 ± 0,7 mm; p = 0,02) and radial height (RH) (RH_{TS} = 12,4 ± 0,5 vs. RH_{AA} = 10,7 ± 0,7 mm, p = 0,042). No statistical significance was found between groups in volar tilt (p = 0,377) and ulnar variance (p = 0,257) (Table 2).

Table 2. **Comparison of late radiological outcomes in traditional surgery and in arthroscopically assisted surgery**

	TS	**AA**	
Radial inclination, mm	24,0	19,5	p = 0,02
Radial height, ^{0}	12,4	10,7	p = 0,042
Volar tilt, ^{0}	5,3	3,7	NS
Ulanr variance	-1,1	-1,6	NS

Visual analogue pain scale results showed mean score of 2,2 ± 0,5 points in traditional surgery group and 1,6 ± 0,6 points in arthroscopically assisted group. According to Shapiro-Wilk test, the distribution of data was parametric (p = 0,002). The independent sample T test was applied to indicate differences between arthroscopically assisted surgery results and traditional surgery results: no significance was found (p = 0,532).

Discussion

Our results suggest that traditional surgery have better late radiological outcomes than arthroscopically assisted surgery. Results controvert with our proposed aim. We expected to find

better radiological outcomes in arthroscopically assisted surgeries like it is with functional outcomes.

The arthroscopically assisted method in Latvia is relatively new. It is used since 2009 in Centre of Plastic and Reconstructive Microsurgery of Latvia (Plastikos 2012). The worlds experience with wrist arthroscopies is greater – it was applied as a diagnostic tool since 1980's (Geissler, 2005). Possibly, Latvia should gain larger experience and analyse the newest cases.

The radiological outcomes should be compared and correlated with functional outcomes and activity outcomes. As it was mentioned before – radiological outcomes do not correlate with function. Longitudinal research with active and intensive ergotherapy could bring out the main results. Also post-operative x-ray should be compared with later x-rays. The stability of external fixation and volar locking plate is also debatable.

Conclusions

- Most frequent is injury in non-dominant hand.
- Radial inclination and radial height is significantly closer to anatomical values in traditional surgery than in arthroscopically assisted surgery.
- No difference between methods was found in pain measurement year after surgery.

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POLYPHARMACY AND QUALITY OF LIFE IN SENIOR POPULATION

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Abstract

Polypharmacy and quality of life in senior population

Key words: *Geriatrics, polypharmacy, quality of life, health*

Introduction: As the population gets older and medicine develops, the consumption of medication raises. According to CDC/NCHS 2008, the percentage of 2 and more prescription drugs reach 76% over the age 60 monthly. When a new complaint appears, another drug is added to the therapy.

Aim is to find significant relation between amount of drugs patients use and health according to SF-36.

Materials and methods: A cross-sectional study was conducted with 107 seniors (age > 65 years). Questionnaire and SF-36® Health Survey were completed. Collected statistical data were analysed by SPSS V20.0 software. Impairments in physical functioning, physical pain, social functioning, emotional health, vitality and general health were compared between two groups – seniors who use 1 or less medication (non-polypharmacy; NP) and seniors who use 2 or more medications (polypharmacy; P).

Results: The average age of seniors was 71.6 years. 37% of respondents do not use any medication, 36% use 1 drug, 27% use 2 and more drugs. Analysing Spearman's correlation coefficient, there was found statistically valid correlation between age and physical health ($r = -0.240$; $p = 0.013$) and more significant in seniors affected by P ($r = -0.402$; $p = 0.031$), but unconvincing in NP group ($p > 0.05$).

ANOVA test brought out significant differences between P and NP groups in physical functioning (76.7 ± 3.7 vs. 88.0 ± 1.7; $p = 0.002$), physical pain (72.2 ± 5.5 vs. 84.4 ± 2.6; $p = 0.026$), social functioning (74.8 ± 5.1 vs. 88.6 ± 2.7; $p = 0.012$). Independent sample test was used for nonparametric data and revealed differences between P and NP groups in emotional health (80.1 ± 2.3 vs. 85.2 ± 1.3; $p = 0.035$), vitality (73.3 ± 2.3 vs. 80.9 ± 1.3; $p = 0.004$) and general health (44.5 ± 2.8 vs. 56.1 ± 2.2; $p = 0.004$).

Conclusion: Our results suggest that multiple drug therapy is an indicator of decreased quality of life in seniors in all scales of SF-36 Health Survey.

Kopsavilkums

Polifarmācija un dzīves kvalitāte senioru populācijā

Atslēgvārdi: *Geriatrija, polifarmācija, veselība, dzīves kvalitāte*

Ievads: Medikamentu patēriņš ir pieaudzis līdz ar populācijas novecošanu un medicīnas nozares attīstību. CDC/NCHS 2008 datos uzrādīts, ka virs 60 gadu vecuma 76% lieto 2 un vairāk medikamentus. Lietošana netiek kontrolēta – jaunam simptoma nozīmē jaunu medikamentu.

Mērķis ir noskaidrot lietoto medikamentu skaita saistību ar veselības kvalitāti pēc SF-36 anketas.

Materiāli un metodes: Šķērsgriezuma pētījumā anketēja 107 seniorus (> 65 gadiem) ar aptauju un Short Form Survey 36 (SF-36). Datus analizēja ar MS Excel 2010 un SPSS v.22.0. Traucējumi fiziskajā funkcijā un tās ierobežojumos, sāpēs, vispārējā veselībā emocionālajā un funkcijā un tās ierobežojumos, vitalitātē un sociālajā funkcijā tika salīdzināti starp senioriem, kuri lieto 1 un mazāk medikamentus (nav polifarmācija, NP) un kuri lieto 2 un vairāk medikamentus (polifarmācija, P).

Rezultāti: Dalībniekiem bija vidēji 71.6 gadi. 37% nelieto ikdienā medikamentus, 36% lieto 1 un 27% lieto 2 un vairāk. Spīrmana korelācijas koeficenta analīzē atklājas statistiski nozīmīga saistība starp vecumu un fizisko veselību ($r = -0.240$; $p = 0.013$), kas ir vēl izteiktāka P senioriem ($r = -0.402$; $p = 0.031$).

Dispersijas analīzē atklājās atšķirība starp P un NP grupām fiziskajā funkcijā (76.7 ± 3.7 vs. 88.0 ± 1.7; $p = 0.002$), sāpēs (72.2 ± 5.5 vs. 84.4 ± 2.6; $p = 0.026$), sociālajā funkcijā (74.8 ± 5.1 vs. 88.6 ± 2.7; $p = 0.012$). Neparametriskajā testā atšķirība starp P un NP grupām bija emocionālajā veselībā (80.1 ± 2.3 vs. 85.2 ± 1.3; $p = 0.035$), vitalitātē (73.3 ± 2.3 vs. 80.9 ± 1.3; $p = 0.004$) un vispārējā veselībā (44.5 ± 2.8 vs. 56.1 ± 2.2; $p = 0.004$).

Secinājumi: Multipla medikamentoza terapija ir indikators pasliktinātai dzīves kvalitātei visas SF-36 skalās.

Introduction

Nowadays general tendency in world is population ageing. Life expectancy at birth in developed countries varies from 76 to 80 years. It is expected, that from year 2000 till year 2030 number of individuals at age 65 and more will increase sharply: in Europe proportion of seniors will

raise from 15.5% to 24.3%, but in Asia it will double: 6% to 12% (Barrett 2016). With growing age, medicine has new challenge – polymorbidity and polypharmacy. Prescription drug consumption has increased: use of two and more drugs since 1999 have raised from 25,4% to 31,2% in United States, but five and more – from 6,3% to 10,7% (CDC 2008). The last researches in Latvia show that 31.6% of seniors use 5 and more drugs daily (Serzante 2017).

Polypharmacy still do not have ultimate definition and threshold. Some authors suggest 5 and more drugs as polypharmacy, but the range varies from 5 to 25 (Rohrer 2013). Risk groups are women and seniors (Corio 2017). Polypharmacy is caused by multimorbidity, population ageing, hospitalizations, more than one attending physician and lack of patient education (Rambhade 2012).In United Kingdom the average number of drugs senior consume is eight (Cantlay 2016) but in United States – 14 (Helth Reserch Funding 2014). Other authors suggest, that monthly individuals after 60 years use 1 drug – 12,0%; 2 drugs – 12,4%; 3-4 drugs – 27,3%, 5 and more – 36,7%, but more than 2 drugs use 76% of seniors (CDC 2008).

Common conditions associated with polypharmacy are osteoporosis, arthritis, cardiovascular diseases, cancers, type 2 diabetes and arterial hypertension. Visiting doctor, patients expect new medication in therapy (Barrett 2016). Because of fear of judgement doctors prescribe additional drug: phenomenon is described as “defensive medicine” (Garfinkel 2015). Physicians, clinical pharmacists and patients are responsible of polypharmacy. It is associated with higher risk of adverse drug reactions – 7% of population and 12% of hospitalised patients experience adverse drug reactions (Rambhade 2012). Drugs interact with patient, other drugs and food (Geriatrics Interprofessional Inerorganizational Collaboration). Drug to drug interactions are present in 2,39% of cases (Rambhade 2012). Prescribing 5-7 drugs, adverse drug events are 4 times more likely than using one drug (Barret 2016). The most affected are frail seniors – they are more vulnerable and more frequently experience adverse effects (Rosted 2016). Frailty is related to decrease in total body volume of water (increased drug concentration), adiposity (drug accumulation), increased liver metabolism and kidney clearance. Adverse drug events in seniors include falls, cognitive dysfunction, bowel and bladder symptoms, gastrointestinal problems, bleeding, postural hypotension and cardiac abnormalities (Geriatrics Interprofessional Inerorganizational Collaboration). Polypharmacy is also associated with higher mortality in men (Wimmer 2015).

Polypharmacy is under-recognised (Garfinkel 2015) and preventable problem (Rambhade 2012). In 76% of cases patients believe that consultation on their therapy and polypharmacy would be beneficial (Jameson 2001). Assessment of total pharmacological therapy is the start point. The doctor should revise the diagnoses and related medications. Drugs without clear clinical indication should be discharged. Beers criteria (1993) include list of potentially inappropriate medication list (Griebling 2016). For example, ketorolac and myorelaxants are potential drugs without clear

clinical significance in seniors. Also therapeutic duplication should be excluded (Corio 2017). Non-pharmacological therapy, alternative therapy, priority establishment and dosage are advised. (Corio 2017, Rambhade 2012). 44% of seniors admit at least one discharged medication (Rohrer 2013). New medication for seniors should be appointed according to principle "start low and go slow" – low dosage, which is increased gradually (Griebling 2016).

The aim of our study is to recognise potential seniors affected by polypharmacy and to evaluate their health status according to SF-36 questionnaire. The study aims to find out, how dramatically quality of life is decreased in seniors who consume more than 1 medication daily.

Materials and Methods

A case-control cross-sectional was performed. Participants were found in senior groups of interests as dancing, folk dancing, choirs, Society "Riga Active Seniors Alliance" and Pauls Stradiņš Clinical University Hospital (PSCUH) Departments of Arithmology, General Cardiology, Pulmonology and Urology. The study had previously been agreed with the group managers, department heads and PSCUH Education and Science Department. Participants were selected according to the criteria as age 65 and more years, the willingness to participate in the study, the ability to fill out questionnaires. Excluded from the study were all those respondents who were younger than 65 years and did not want to participate in the study. After selection of the criteria, the study included 107 seniors.

Seniors completed the questionnaire themselves or were interviewed, according to their will. Clarifying questions were allowed during the completion of the questionnaire. Filling of the questionnaire was provided in a confidential environment.

The questionnaire consisted of two parts. The first part included general questions about senior age, sex, occupation, education level, also prescription medications they use (count and purpose). Participants who were exposed to 2 and more prescription drugs daily were presumed as polypharmacy affected. Polypharmacy threshold was low, because of population – predominantly active seniors.

The second part was Short Form Survey 36 (SF-36) questionnaire. It is used as a convenient and internationally validated tool for assessment of quality of life. It is widely available and easily interpreted. For the first time a similar questionnaire was developed by the insurance company. Nowadays widely applied version is created by the John E. Ware et al in 1985 and modified in 1992. It consists of 36 questions: 11 main and 25 minor. The questionnaire divides in 8 health scales (physical function, role of physical functions, physical pain, general health, vitality, social function, emotional functioning and role of emotional functioning), which can be divided into two large - physical health (physical function, role of physical functions, physical pain, general health) and mental health (vitality, social function, emotional functioning and role of emotional

functioning). Each scales' value is expressed as a percentage, 100% means excellent health in particular scale.

Questionnaires during data analysis were numbered, ensuring confidentiality. Microsoft Excel 2010 and IBM SPSS Statistics v.22.0 were used for data analysis. There was used descriptive statistics (mean values, standard deviation (SD), minimum and maximum values, the percentage distribution of respondents). Polypharmacy affected seniors (case) were compared with non-polypharmacy seniors (control). Spearman's correlation analysis was used to find coincidence in age and health, and polypharmacy or non-polypharmacy. Shapiro-Wilk test represented normality of data. For parametric data Analysis of variance (ANOVA) was used to compare cases and controls, but non parametric data were compared using independent sample nonparametric test. Statistical significance was accepted at p value less than 0.05.

Results

The mean age of participants was 71,6 ± 0,51 (65 - 86) years. In non-polypharmacy group it was 70,9 ± 4,8 years and 73,3 ± 6,1 in polypharmacy group. Distribution between men and women was 47 and 31 in non-polypharmacy group and 24 and 5 in non-polypharmacy group. 6,5% of respondents are occupied, 31,8% are retired and occupied and 61,7% are retired. Elementary education have 7,5% of respondents, high school education – 14,0%, higher education – 58,9%, professional education – 19,6%. 37,4% of respondents do not use prescription drugs, 35,5% use one, 23,4% use two, 2,8% use three and 0,9% use more than 4 prescription drugs daily (Fig.1). From data, 27,1% of seniors use 2 and more drugs. The most frequently used drugs are anti-hypertensives (50,5% of cases) and other cardio-vascular drugs (29%), less often are consumed psychiatric and sleeping-pills (3,7% and 11,2%) and others.

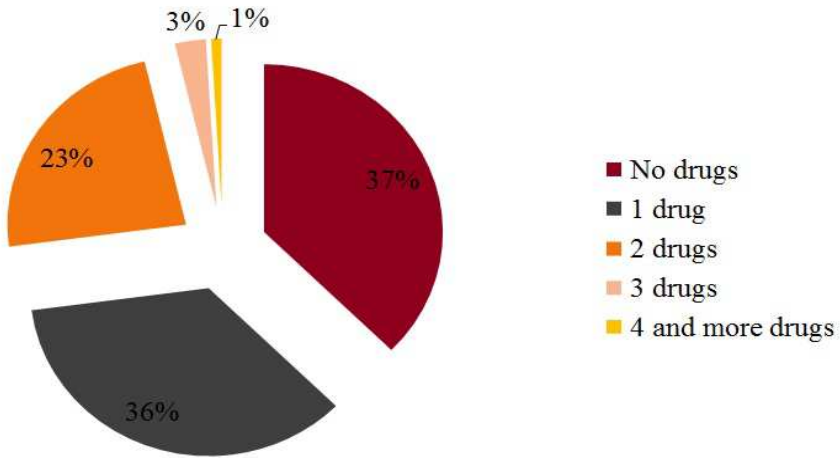

Figure 1. **Consumption of drugs in elderly**

SF-36 scores were compared between polypharmacy and non-polypharmacy groups. Analysis of variance (ANOVA) was used for parametric data according to Shapiro-Wilk test: physical

functioning (p = 0.004), role of physical functioning (p = 0.000), pain (p = 0.001), role of emotional functioning (p = 0.000), social functioning (p = 0.000); independent sample nonparametric test was used for mental health (p = 133), physical health (p = 0.103), emotional functioning (p = 0.133), vitality (p = 0.525) and general health (p = 0.693). Statistically valid difference was found in all scales of SF-36. Mean polypharmacy group and non-polypharmacy group scores in physical health were 65,8% and 79,2% (p = 0.000); physical functioning – 76,7% and 88,0% (p = 0.002); role of physical function – 62,1% and 83,2% (p = 0.003); pain – 72,2% and 84,4% (p = 0.024); general health – 44,5% and 56,1% (p = 0.004); mental health – 77,0% and 85,8% (p = 0.001); emotional function – 80,1% and 85,2% (p = 0.035); role of emotional function – 78,2% and 91,2% (p = 0.014); vitality – 73,3% and 80.9% (p = 0.004); social function – 74,8% and 88,6% (p = 0.012) (Table.1).

Table 1. **Difference between SF-36 scores in polypharmacy and non-polypharmacy groups**

	Polypharmacy	***Non-polypharmacy***	
Mental health	77%	85.8%	p = 0.001
Emotional function	80.1%	85.2%	p = 0.035
Role/emotional	78.2%	91.2%	p = 0.014
Vitality	73.3%	80.9%	p = 0.004
Social functioning	74.8%	88.6%	p = 0.012
Physical health	65.8%	79.2%	p = 0.000
Physical function	76.7%	88%	p = 0.002
Role/physical	62.1%	83.2%	p = 0.003
Pain	72.2%	84.4%	p = 0.024
General health	44.5%	56.1%	p = 0.004

Spearman's correlation coefficient is used in our study because of nonparametric data. In Shapiro-Wilk test normality is present in age of non-polypharmacy group (p= 0.000), physical health of non-polypharmacy seniors (p = 0.000) and were absent in physical health and of polypharmacy group (p_{group} = 0.103; p_{age} = 0.000). Correlating age and physical health, statistically valid association was found in all seniors (r = -0.240; p = 0.013). But separating participants into polyparmacy affected seniors and not affected, correlation between age and physical health was found only in affected ones (r = -0.402; p = 0.031). No correlation between age and physical health was found in drug non-users (r = -0,124; p = 0,281). Correlations in age and mental health were not found: p = 0.501 correlating all respondents; p = 0.264 and 0.314 correlating polypharmacy and non-polypharmacy group separately.

Discussion

The aim of research was to find difference in SF-36 score between seniors, who use multiple drugs daily and those who do not. The study also revealed mean health status of seniors in Latvia and tendency of multi drug therapy and most frequent purposes.

If drugs treat impairment in mental or physical health, why consumers do not have as good health as those, who do not have impairment? Do drugs treat diseases or decrease our health when

used in enormous amounts? Despite, there should be seniors, who do not use medications and have illness, therefore impaired health. Are there many side effects which influence senior well-being? Are doctors and patients informed about drug interactions? Does science knows, how multiple drugs interact and do they benefit? This study revealed many questions, which are not answered in this study, for that reason new research could define and resolve them.

Future studies should include data on patient diseases. To compare polypharmacy and non-polypharmacy groups objectively, information about senior health (diseases) should be included. Compared can be only seniors with equal diseases and excluded should be those, with dramatic illness. The questionnaire should be improved with questions: when the disease started, what was the health self-assessment then, and how it changed, after drug therapy. Side effects should be evaluated precisely.

A separate section that had not been studied was non-prescription medication in senior population. This is the main limitation of our study. Perhaps comparing patients with high prescription drug consumption, impairment in mental health scale might be discovered. The number of home held medications may indicate status of general health.

Conclusions

- One fourth of research seniors are affected by polypharmacy.
- Seniors, who do not use drugs, have better health in all scales of SF-36 questionnaire.
- Our study shows that multiple drug therapy is an indicator of decreased health.
- Ageing and decrease in physical health correlate. However, no correlation is found in seniors, who do not consume drugs; seniors' – consumers' health decrease with ageing.

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SENIOR AND PRE-SENIOR CAR DRIVING SKILLS AND HEALTH ASPECTS

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Abstract

Senior and pre-senior car driving skills and health aspects

Key words: *Geriatrics, car driving skills, health, quality of life*

Introduction: Older drivers is just as important risk group as beginner drivers. Because of decrease in physical and mental functions, the chance of getting into car accident is more likely. Senior age is essential factor in statistical data compared with pre-seniors.

Aim: To find out, if senior (S) and pre-senior (PS) driving skills differ; are driving skills related to state of health?

Materials and methods: A cross-sectional study was performed with 86 seniors (age > 65yrs) and 50 pre-seniors (age 55-64yrs). Participation was voluntary, respondents were interviewed in senior group activities. A questionnaire was used to evaluate general information about drivers, quality of life (SF-36), and driving performance (AAA Foundation for Traffic Safety: Driver 65 Plus). Collected data were analysed with SPSS *v.20.0* and *MS Excel 2010*.

Results: Respondents consisted of 61 women and 75 men. In S, 69% drive manual and 31% automatic transmission, in PS – 84% and 16%, respectively. 29% of S have good driving skills and 71% have doubtful skills and resemble with PS group. S use their car 4 times per week, PS – 5. Analysing independent sample T test, pre-seniors had better results in general health (S=62.2±2.2 vs. PS=57.8±1.8, p=0.013) and in role of limitations due to physical functioning (S=83.7±3.1 vs. PS=91.2±2.6, p=0.018). Driving performance did not differ in groups (p>0.05). Chi-Square test was used to compere age groups with driving assessment (p>0.05).

Conclusion: Although pre-seniors have better health, it is not a predictor of driving performance in senior population.

Kopsavilkums

Senioru un pre-senioru automašīnas vadīšanas spējas un veselība stāvoklis

Atslēgvārdi: *Geriatrija, automašīnas vadīšanas spējas, veselība, dzīves kvalitāte*

Ievads: Vecāka gadagājuma autovadītāji ir tikpat nozīmīga riska grupa kā iesācēji. Novecojot pasliktinās fiziskā un mentālā funkcija, līdz ar to pastāv lielāka varbūtība iekļūt ceļu satiksmes negadījumā. Par to liecina statistikas datos redzamā tendence senioru un pre-senioru vecumā.

Mērķis: Noskaidrot, vai senioru (S) un pre-senioru (PS) autovadīšanas spējas atšķiras; vai tās ir saistītas ar veselības stāvokli?

Materiāli un metodes: Transversālā pētījumā piedalījās 86 seniori (virs 65 gadiem) un 50 pre-seniori (55-64 gadi). Dalība bija brīvprātīga, respondenti tika organizēti no interešu pulciņiem. Pētījumā izmantoja anketu, kas sastāvēja no jautājumiem par braukšanas apstākļiem, SF-36 anketas un braukšanas pašnovērtējuma (AAA Foundation for Traffic Safety: Driver 65 Plus). Datu analīzei izmantoja *MS Excel 201*0 un *SPSS v.22.0*.

Rezultāti: No pētāmajiem 61 bija sievietes un 75 - vīrieši. S grupā 69% brauc ar manuālo ātrumkārbu un 31% izmanto automātisko ātrumkārbu, savukārt PS grupā - 84% un 16%. Labas braukšanas spējas spējas S grupā ir 29%, bet nepietiekamas - 71%, līdzīga tendence ir PS grupā. S izmanto automašīnu 4 reizes nedēļā, bet PS - 5. Neatkarīgu izlašu T testā atklājās, ka PS ir labāka vispārējā veselība (S=62.2±2.2 vs. PS=57.8±1.8, p=0.013) un ierobežojumu fiziskās veselības dēļ (S=83.7±3.1 vs. PS=91.2±2.6, p=0.018). Braukšanas spējas starp grupām neatšķirās. Hī kvadrāta testu izmantoja braukšanas novērtēšanai starp grupām (p>0.05).

Secinājumi: Lai gan pre-senioru veselības stāvoklis ir labāks, tas neliecina par autvadīšanas spējām.

Introduction

With development of modern medicine global trend is population ageing. At Millennium, senior proportion in population was 15,5% in developed countries, and by 2030 it is expected to increase to 24,3% (Barrett 2016). Also proportion of senior car drivers is increasing. In United States it has increased by 50% since 1999 (CDC 2016). Senior car drivers are one of the risk groups on road after beginner drivers. Seniors are involved in more accidents and the consequences are more fatal than in pre-seniors. In Latvia the tendency is not appearing yet because of decreased life

expectancy - seniors in 2015 were involved in 302 accidents per 100 000 drivers (comparing with beginners – 893, and pre-seniors 314 per 100 000 drivers). However, road injuries and deaths are raising with age – seniors drivers last year had 120 injuries and 8 road deaths, pre-seniors – 116 and 7, but age group 45 – 54 years had 113 and 4 per 100 000 drivers (CDDD 2016). In Europe the tendency is alike. 25% of all road fatalities are in seniors (European Commission. Road safety in the European Union 2015). In average, fatalities of seniors after 75 years are five times higher than in whole population (European Union's Horizon 2020 research 2016).

The term “senior” is related to persons aged 65 and older, but pre-senior age is considered form 55 to 64 years (Rudman 2006). During natural ageing process, the body becomes more fragile in average at 65 years, but it might happen as early as at 60 years (Berardelli 2012). In ageing many health related problems may appear, which can influence performance of driving.

Almost all of systems are included in ageing and are related to possibly decreased function and driving performance. One of the main senses is vision, for example, cataracts and decrease of accommodation directly influence vision. Also motor skills and coordination is important in driving. Seniors have decreased functional range of motions in neck and lower limb joins. The neck flexibility is responsible for appropriate side to side and mirror checking. Coordination skill impairment becomes manifest when multiple tasks are done, for example, steering and operating with additional gadgets (European Union's Horizon 2020 research 2016). Impairment of hearing is important on road too, like oncoming ambulance, train or other cars (AAA Senior Driving). The most important is cerebral activity and cognitive function – with ageing decrease of neurons influence not only decisions making and cogitation, but also visual perception and interpretation (European Union's Horizon 2020 research 2016). Dementia is also an important road safety issue, and potentially endangers society (Odenheimer 1993).

Impairments of functions starts before senior age, however pre-seniors manage to compensate and regulate body changes. As the age increases, also self-regulation by individuals is increased, especially after age of 70 years. The older driver gets, the less enjoyable becomes driving process. Decrease of enjoying driving decreases self-regulation (Donorfio 2008). In youth women are better drivers than men because of self-regulation, however at senior age – self-regulation is equal and women have worse performance due to low confidence (Donorfio 2008, D'Ambrosio 2008).

We brought forward hypothesis, that due to decrease of senior health, pre-senior driving skills might be better than senior. In this research the senior and pre-senior health status will be detected and the driving skills will be assessed.

Materials and Methods

Seniors (age after 65 years) and pre-seniors (age 55-65 years) were included in this study. Inclusion criteria also were present car driving skills. Exclusion criteria were driving cessation,

younger than 55 years, inability to fill the questionnaire and unwilling to participate in this study. Participants were found in senior group activities, dances, choirs, etc., agreed by organiser before. Participation was voluntary and confirmed with signature according to Declaration of Helsinki. From 157 respondents 136 were included - 86 of them seniors and 50 pre-seniors.

Three part questionnaire was used in this study. First part included socio-demographic data (age, sex, education level, occupation), impairment of sensations (hearing, vision, balance) and questions about the driver and driving conditions (transmission of the car, days per week using car, driving skill assessment, sense of safety on road).

Second part was Short Form 36 (SF-36) questionnaire. The type of questionnaires was created in late 90's by assurance companies, for fast evaluation on clients' health and prognosis of decline in health and health related costs. Modification and simplification of questionnaires followed afterwards. SF-36 was developed in 1985 by John E. Ware et al. Last modification was in 1992. It consists of 11 basic questions and 25 extended questions. Results are interpreted into 8 health concepts – physical functioning, role functioning, physical pain, general health, vitality, social functioning, emotional health and role emotional. According to answers, every concept is expressed in per cents - 100% is excellent health and 0% is completely impaired health.

Third part was self-rating tool Driver 65 Plus: Check Your Performance (AAA Foundation for Traffic Safety). It consists of 15 questions (signalling, seat belt wearing, intersections, busy traffic, reaction time, thoughts while driving, tolerance of traffic situations, eye examination, consumed drug information, interest about health and wellness, family member concerns, road accidents, warnings and tickets). The possible answers are: always, sometimes, never or none, one to two and three and more. According to risks in each question, the answers are equalized to 0, 3 or 5 points. Larger sum of points indicates to poorer driving skills. 0-15 points is interpreted as good skills, 16-34 points – watchful skills and 35 and more points – hazardous skills.

Statistical data were analysed using Microsoft Excel 2010 and IBM SPSS Statistics v.22.0. Descriptive statistics was expressed as mean ± standard deviation (SD), minimum and maximum value and percentage distribution. Seniors and pre-seniors were compared using independent sample T test or independent sample nonparametric test (according to Shapiro-Wilk test of normality result). Chi square test was used to find differences between distribution of senior and pre-senior driving skills. Statistical importance was accepted at p value 0,05 and less.

Results

Analysing first part of questionnaire, in pre-seniors 52% were women and 48% were men, but in senior group – 40% women and 60% men (Fig.1). Mean age of pre-seniors was 59,3 ± 3,1 years, but average age of seniors was 71,1 ± 5,0 years. Education level in senior and pre-senior groups were almost equal: elementary education – 4,7% vs. 4,1%, high school - 15,1% vs. 18,4%, higher

education – 59,3% vs. 57,1% and professional education – 20,9% vs. 20,4%. The following data represents distribution between senior and pre-senior occupation – 8% are employed, 59% retired and 33% of seniors are retired and employed, but in pre-seniors - 76% are employed, 10% retired and 14% are retired and employed.

In average, pre-senior drive 5,6 ± 1,9 days per week, but seniors – 4,8 ± 2,1 days. Only 2% of pre-seniors feel unsafe while driving themselves, but seniors twice more – 4,7%. 16% of pre-seniors consider their driving skills in moderate level; however 27% of seniors have average and bad self-assessment. Manual transmission car drive 84% of pre-seniors and 68% of seniors. But automatic transmission vehicle use 16% of pre-seniors and 38% of seniors.

Impaired vision admits 40% of pre-seniors and 45% of seniors, impaired hearing – 4% and 24%; impaired balance and vertigo – equal in both groups – 6% (Table 1).

Table 1. **Comparison of senior and pre-senior car drivers**

	Pre-Seniors		**Seniors**	
Gender	Women: 52%	Men 48%	Women: 40%	Men: 60%
Manual transmision	84%		68%	
Impaired hearing	4%		24%	
Impaired vision	40%		45%	
Imbalance	6%		6%	
Do they feel safe on road?	98%		95%	

Analysing SF-36 answers in second part of questionnaire, physical functioning in seniors and pre-seniors was 88,7% vs. 92,4% and role of limitations due to physical functioning – 83,9% vs. 90,5%. Results in physical pain were almost equal – 86% in seniors vs. 88% in pre-seniors. Pre-seniors' general health reach 62,0%, but seniors' – 57,3%. In mental health concepts, emotional functioning was better in senior than pre-senior group – 83,5% vs. 80,9%, but limitations due to emotional functioning were alike – 88,6% vs. 89,9%. Vitality in seniors and pre-seniors was 79,4% and 78,5%. Social functioning in both – seniors and pre-seniors were identical – 89,6%.

According to Shapiro-Wilk test, parametric data are physical functioning, limitations due to physical functioning, physical pain, social functioning, vitality and limitations due to emotional functioning ($p = 0,000 – 0,024$). Emotional functioning and general health are calculated as nonparametric data ($p > 0,05$). In independent sample T test, limitations due to physical functioning were significantly better in pre-seniors than in seniors ($p = 0,018$). Physical functioning ($p = 0,343$), physical pain ($p = 0,115$), social functioning ($p = 0,405$), vitality ($p = 0,576$) and limitations due to emotional health ($p = 593$) had no significant difference between groups. Independent sample nonparametric test brought out better pre-seniors' results in general health ($p = 0,013$), but no difference between groups in emotional health ($p = 0,093$) (fig.1).

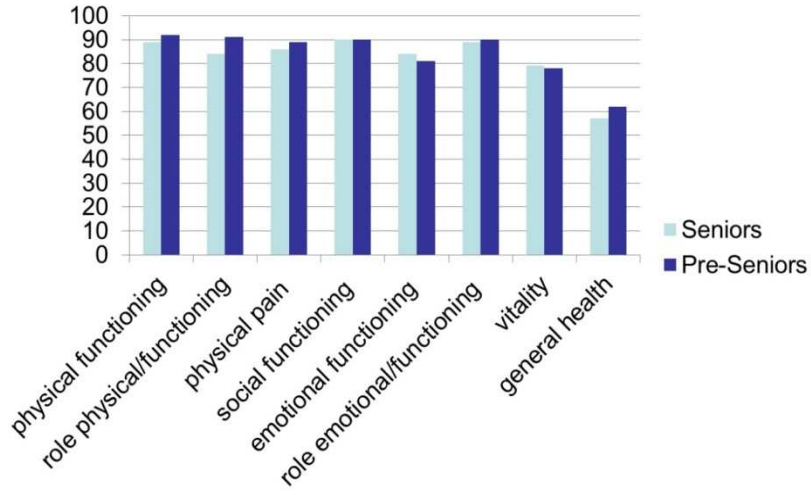

Figure 1. **Senior and pre-senior health status according to SF-36**

Results in self-rating tool are following – good driving skills have 23% of pre-seniors and 29% of seniors. Watchful skills have 67% of pre-seniors and 65% of seniors, and according to answers, hazardous skills have 10% of pre-seniors and 6% of seniors. Mean result in senior group was 19 ± 0,9 points and 21 ± 1,4 points – in pre-senior group (Shapiro-Wilk test of normality; p = 0,792). However, 2 point difference was not significant in independent sample nonparametric test (p = 0,502). Also in Chi-Square test there were not found relationship between age group and driving skills (p = 0,504; degree of freedom = 2) (Table 2).

Table 2. **Chi-Square test results in driving skill assessment**

	Pre-Seniors		**Seniors**		**Chi-square test**
0-15 points	23%	Mean: 21 points	29%	Mean: 19 points	NS
16-34 points	67%		65%		
More than 36	10%		6%		

Discussion

Despite senior health is worse than pre-senior, driving skills do not differ between age groups and our hypothesis is not approved. The aim was realised and summary of senior and pre-senior health status was assessed. Also driving self-checking score was detected.

Probably hypothesis was denied because of senior marked self-regulation. Senior group included active seniors from folk dances and choirs. Active seniors have better cognitive skills and coordination. Research senior group do not represent whole senior population in Latvia, it might be with significantly decreased health scales. If research included hospitalised, less socials seniors, their driving skills more likely would differ from pre-senior skills.

Further researches should evaluate presence of self-regulation. Objective and complex health assessment (vision tests, hearing test, range of motion/ flexibility assessment, medications,

coordination tests, arterial blood pressure, reaction time, depression test), dementia screening (Clock drawing test, Mini-Mental test) and driving on road performance with theoretical tests would bring out the real situation.

Medical certificate renewal data could also become a material for further researches. Renewal process is repeated not longer than after every ten years. Check-up frequency increase with impairment of health. The data would also reveal the most frequent causes of prohibitions to participate in traffic.

Conclusions

- Pre-seniors have fewer complaints about limitations due to physical functioning than seniors.
- Pre-seniors have better general health than seniors.
- Seniors - car drivers have more often impaired hearing than pre-seniors.
- Seniors more frequently feel unsafe in traffic than pre-seniors.
- Seniors and pre-seniors have equal driving skills.
- Seniors use their car less days per week than pre-seniors.

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CONGENITAL COMPLETE ATRIOVENTRICULAR BLOCK ETIOLOGY AND TREATMENT PRINCIPLES

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Abstract
Key words: *Pediatric Cardiology. Congenital complete atrioventricular block*
Introduction: Incidence of congenital complete atrioventricular block (CAVB) is 1 per 20 000 live births. Mostly it is caused by maternal anti-Ro/La antibodies but can be associated with congenital heart diseases or sporadic in caused by gene mutations.
Aim: Aim is to identify the most common etiology for congenital CAVB and treatment principles.
Materials and methods: In this retrospective study medical histories of 13 patients with CAVB were collected and analysed. Collected data included age at diagnosis, gender, presence of maternal anti-Ro/La antibodies, ventricular rhythm at birth, type and time of treatment, and outcome. Diagnosis was compared in two groups of patients- neonatal lupus patients and non-immune patients.
Results: Of all 13 patients maternal anti-Ro/La antibodies were found in 10 cases and in 3 cases, maternal anti-Ro/La antibodies were absent. Eleven patients were diagnosed prenatally with a mean age at diagnosis 24,82 ± 6,9 gestational weeks and postnatal were diagnosed 2 patients with a mean age at diagnosis 97 ± 134,3 months. Prenatally diagnosed patient mean ventricular rate at birth was 62 ± 11.6 beats per minute. Of all patients with congenital CAVB 10 underwent pacemaker implantation but 3 had no indications for pacing so far. Of the prenatally diagnosed patients who underwent pacemaker implantation 6 had urgent pacemaker implantation whith mean age at implantation 8,3 ± 4 days but 3 had delayed pacemaker implantation with mean age at implantation 21.02 ± 17.76 months. One (7,7%) patient from the total died.
Conclusions: Maternal lupus antibodies are the most common cause of congenital CAVB. Non- immune congenital CAVB was mostly diagnosed postnatally, when compared to neonatal lupus patients. Due to the small number of patients there is insignificant data showing the difference between groups and time of pacemaker implantation. Ventricular rate <60 bpm is main predictive factor for urgent pacemaker implantation.

Kopsavilkums
Atslēgvārdi: *Bēnu kardioloģija. Iedzimta pilna atrioventrikulāra blokāde*
Ievads: Iedzimtas pilnas atrioventrikulāras (AV) blokādes sastopamība ir 1 uz 20 000 dzīvi dzimušo. Visbiežāk tā ir mātes anti-Ro/La antivielu izraisīta, bet tā var būt arī asociēta ar iedzimtiem strukturāliem sirds defektiem vai sporādiska ģenētisku mutāciju dēļ.
Mērķis: Mērķis bija noskaidrot galvenos etioloģiskos faktorus un ārstēšanas iespējas bērniem ar iedzimtu pilnu AV blokādi.
Materiāli un metodes: Šis bija retrospektīvs pētījums kurā tika apkopotas un izanalizētas 13 pacientu slimības vēstures pacientiem ar iedzimtu pilnu AV blokādi. Tika analizēti dati iekļaujot: pacientu vecumu diagnostikas brīdī, mātes anti-Ro/La antivielas mātes vai bērna asins plazmā, ventrikulāro ritmu dzimšanas brīdī, ārstēšanu un iznākumu. Pacienti tieka iedalīti divās grupās, tas ir, pacienti ar neonatālo lupus un pacienti ar neimunoloģisku pilnu AV blokādi.
Rezultāti: No visiem 13 pacientiem, 10 gadījumos tika atrastas mātes anti-Ro/La antivielas, bet 3 gadījumos tās netika konstatētas. Prenatāli pilna AV blokāde tika diagnosticēta 11 gadījumos 24,82 ± 6,9 gestācijas nedēļā. Postnatāli pilna AV blokāde tika diagnosticēta 2 gadījumos 97 ± 134,3 mēnešu vecumā. Prenatāli diagnosticētiem pacientiem ventrīkulu frekvence dzimšanas brīdī bija 62 ± 11.6 reizes minūtē. No visiem 13 pacientiem, 10 tika implantēts elektrokardiostimulators (EKS), bet 3 pacientiem līdz šim nav bijušas indikācijas EKS implantācijai. No visiem prenatāli diagnosticētajiem pacientiem, 6 tika veikta steidzama EKS implantācija ar vecumu implantācijas brīdī 8,3 ± 4 dienas, 3 pacintiem tika veikta atlikta EKS implantācija ar vecumu implantācijas brīdī 21.02 ± 17.76 mēneši, bet 2 pacientiem līdz šim EKS implantācija nav bijusi nepieciešama. Viens no 13 pacientiem ir miris.

Introduction

Congenital complete atrioventricular block (CAVB) is a rare atriovenricular (AV) node disorder characterized by absent supraventricular impulse conduction to ventricles, causing significant bradycardia (Park 2008: 546). Incidence of CAVB is 1 per 20 000 live births. Congenital

CAVB mostly manifests prenatally, but it can occur at any time up to 50 years of life. Majority of congenital CAVB is diagnosed by the gynecologist in routine fetal sonography (Baruteau 2016).

Most common cause of congenital CAVB is maternal anti-Ro/La antibodies, called neonatal lupus. Less frequently it has been associated with stuctural congenital heart diseases (CHD) or sporadic CAVB caused by gene mutations (Baruteau 2016). Congenital CAVB is irreversible.

CAVB in case of neonatal lupus is passively acquired autoimmune disease in which maternal anti-Ro/La antibodies cross the placental barrier affecting cardiomyocytes in AV node (Friedman 2003). Women with positive serum titres of anti-Ro/La antibodies carry 1% to 3% risk of having a child with CAVB (Friedman 2003, Jaeggi 2004). Usually it develops between 18 to 24 gestational weeks but it can occur up to the 36th gestational week (Hutter 2010). Reccurency rate in subsequent pregnancies are 18% (Friedman 2003).

There are three hypotheses how maternal anti-Ro la antibodies cause complete AV block. First mechanism is when maternal antibodies enter fetal circulation, significantly but reversibly binding to L-type calcium channel receptors and inhibiting their activity, causing inability to transfer electrical impulses in AV node. Second hypothesis is when maternal antibodies bind to myocytes promoting apoptosis and creating an immune complex which activates tumor necrosis factor alpha, macrophages and other inflammation factors followed by fibrosis. Third mechanism is based on a cross-reaction between anti-Ro/La antibodies and serotoninergic 5-hydroxytryptamine receptors. Autoantibodies bind with α_1C and α_1D Ca channel subunits which are located on the surface of AV node myocytes, causing inhibition of L-type and T-type Ca. Therefore, signal transmission of the AV node is interrupted (Ambrosi 2012, Karnabi 2010).

Recent research shows that 10% of patients with structural congenital heart defect (CHD) associated complete AV block has *de novo* mutations *NKX2.5 and Tbx5* genes. Most commonly it has been associated with transposition of the great arteries, atrioventricular septal defects and right or left atrium isomerism (Baruteau 2016, Hunter 2015, Khairy 2009)

In case of congenital isolated non-immune CAVB mutations has been observed in *TRPM4, KCNK17, SCN5A, SCN1B* and *SCN10A* genes (Baruteau 2016).

Postnatally, for diagnostics of CAVB golden standard is 12 lead electrocardiogram (ECG). It cannot be applied in prenatal diagnostics because of multiple limitations such as distance between fetus and mothers skin, low voltage, fetus movenemts, maternal abdominal muscle contractions and others. The main method for prenatal diagnostics of CAVB is echocardiography with M mode (Hunter 2015).

Main treatment for CAVB is pacemaker implantation, although in patients with hemodynamically significant bradycardia recommended treatment is with atropine, epinephrine, dopamine or isoproterenol with or without transcutaneous pacing (Baruteau 2016, Brignole 2013).

Several recent research has demonstrated efficient prenatal (transplacental) treatment with glucocorticoids (GK) and β- adrenergic receptor agonists (β-mimetics). This therapy is indicated in case fetus heart rate is <55 beats per minute (bpm). Prenatal therapy with GK and β-mimetics reduce prenatal fetal complication and prenatal mortality rate (Donofrio 2014, Jaeggi 2004).

Materials and methods

This was retrospective research. It was done at the Children's Clinical University Hospital in Riga from December 2016 to March 2017. In this study 27 patient medical histories diagnosed with CAVB were collected and analyzed during the period from 1 January 2003 to 31 December 2016.

Inclusion criteria were patients younger than 18 years of age, patients that had congenital CAVB, diagnosis confirmed after January 2003. Exclusion criteria were patients older than 18 years of age, patients that had acquired CAVB and diagnosis confirmed before January 2003.

Collected data included age at diagnosis, gender, presence maternal or newborn anti-Ro/La antibodies, structural heart defects, ventricular rate at birth, presence of fetal complications, medical treatment, urgent or delayed pacemaker implantation, age at pacemaker implantation and outcome.

Diagnosis was compared in two groups of patients- neonatal lupus patients and non-immune patients. Neonatal lupus patients were defined if maternal anti-Ro/La antibodies were found and non-immune patients were defined if anti-Ro/LA antibodies were absent.

Patients with urgent implantation of pacemaker were defined by an implantation at first admission to hospital and delayed implantation was defined by indications later in life.

Data was compiled in Microsoft Office Word, Microsoft Office Excel and Statistical Package for the Social Sciences (SPSS® 21.0).

Results

From all 13 patients included in this study, 38,5% (N=5) were boys and 61.5% (N=8) were girls. Maternal anti-Ro/La antibodies were found in 92,3 % (N=10) of cases and in 23.1% (N=3) of cases, maternal anti-Ro/La antibodies were absent. Out of three patients whom autoantibodies were not detected, one had CHD associated CAVB but two had non-immune sporadic congenital CAVB (see fig.1).

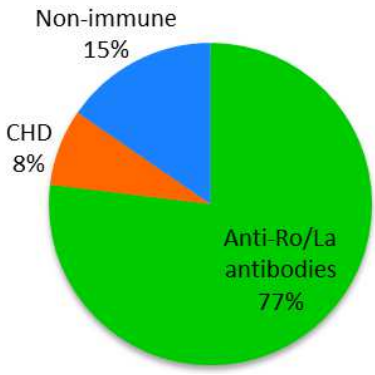

Figure 1. **Etiology of congenital complete atrioventricular block**

Prenatally were diagnosed 11 (84,6%) but postnatally 2 (15,4%) patients (see fig.2). Of 11 prenatally diagnosed patients 10 were with neonatal lupus and one patient with CHD associated CAVB. The one patient with CHD associated CAVB had left atrium isomerism, abnormal vein drainage and additional superior vena cava. Of all 10 patients with neonatal lupus, in two cases autoantibodies were found at 22 gestational weeks in the mothers plasma, four patient mothers had symptomatic and previously confirmed systemic disease and in four cases maternal anti-Ro/La antibodies were confirmed in patients plasma postnatally up to 15 day of life. Prenatally CAVB was diagnosed at the age of 24,82 ± 6,9 gestational weeks. Of two postnatally diagnosed patients, one patient was diagnosed at two months of age. This patient developed second degree AV block at the age of 1 month 2 weeks that rapidly progressed to CAVB. In his case CHD and maternal anti-Ro/La antibodies were absent. Other patients developed CAVB at the age of 12 years. It is known that this patient in previous ECG's had sinus rhythm and it is known that this patients mother developed CAVB in adolescence.

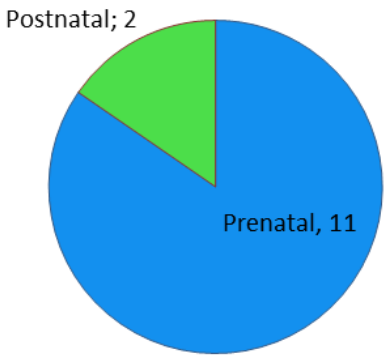

Figure 2. **Time of diagnosis**

Of all patients with congenital CAVB 10 (76.9%) underwent implantation of pacemaker and 3 (23.1%) had no indications for pacing so far. Pacemaker implantation has been performed in eight patients with neonatal lupus, in only one patient with CHD associated CAVB and in one patient with non-immune CAVB (see tab.1)

Table 1. **Pacemaker implantation in patients with congenital CAVB**

	Implanted	**Not implanted**
Neonatal lupus	8	2
CHD associated CAVB	1	-
Non-Immune CAVB	1	1

Of all 11 prenatally diagnosed patients, six underwent urgent pacemaker implantation with age at the time of implatation 8,3 ± 4 day of life. One of six patients who underwent an urgent pacemaker implantation had prenatally diagnosed fetal *hydrops* with pericardial effusion and

significant bradycardia. Another had dilated cardiomyopathy with decreased left ventricle ejection fraction and also significant bradycardia. The remaining four out of six patients who underwent urgent pacemaker implantation had hemodynamically significant bradycardia.

Delayed pacemaker implantation was performed in three out of 11 prenatally diagnosed patients. In these cases patients age of implantation was 21.02 ± 17.76 months.

Two out of 11 prenatally diagnosed patients had no indications for pacemaker implantation so far (see fig.3.)

One out of two postnatally diagnosed patients underwent pacemaker implantation at age of six months and three weeks, but other had no indications for implantation.

Figure 3. **Pacemaker implantation in children with prenatally diagnosed CAVB**

Ventricular rate at the birth of all six patients that underwent urgent pacemaker implantation was 3,67 ± 2,07 bpm. Patients who got a delayed pacemaker implantation or patients that had not received pacemaker implantation, ventricular rate at the birth was 72 ± 8,16 bpm.

There is a statistically significant correlation between patients ventricular rate at birth and necessity for urgent pacemaker implantation (p = 0.047) (see fig.4).

None out of all 11 prenatally diagnosed patients had received prenatal medical therapy.

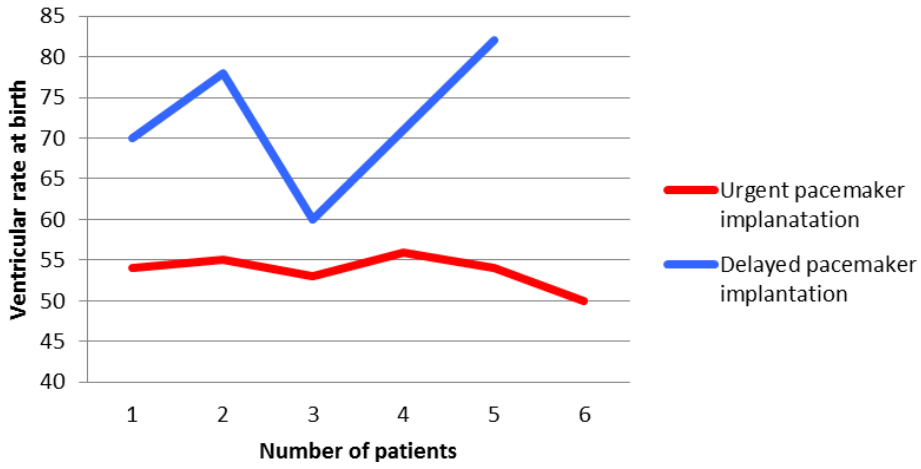

Figure 4**. Comparison of ventricular frequency at birth of patients with or without urgent pacemaker implantation**

One out of 13 patients died (see fig.5.). This patient had neonatal lupus that was diagnosed at 34th gestational week. Ventricular rate at the birth was 54 bpm and urgent pacemaker implantation was performed at the 13th day of life. Despite all treatment the patient died.

Discussion

In Latvia incidence of congenital CAVB is 1 per 24 000 new borns, which is slightly less than incidence in the world. It can be explained by the possibility that some of neonatal dead patients have not been diagnosed with CAVB or death has been registered under another pathology.

Baruteau, et. al. suggests fetal ventricular rate <55 bpm causes prenatal and postnatal complications. In our research all patients who underwent urgent pacemaker implantation ventricular rate at the birth was <56 bpm. All of these patients had hemodynamically significant bradycardia which can be evaluated as an important postnatal complication. We suggest that ventricular rate at the birth <56 bpm in patients with prenatally diagnosed CAVB is a significant predictive factor for urgent pacemaker implantation.

Jaeggi, et.al. research data shows that prenatal medical therapy with GK and β-mimetics significantly decreases prenatal and postnatal complication risk and prenatal mortality rate. So far in Latvia prenatal medical therapy has not been used. We suggest that the usage of prenatal thearapy in Latvia would decrease prenatal and postnatal complication rate and decrease prenatal mortality rate.

Conclusions

Maternal lupus antibodies are the most common cause of congenital CAVB. Non- immune congenital CAVB was mostly diagnosed postnatally, when compared to neonatal lupus patients. Due to the small number of patients there is insignificant data showing the difference between groups and time of pacemaker implantation. Ventricular rate <60 bpm is the main predictive factor for urgent pacemaker implantation.

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PARENTS' TRUST IN GENERAL PRACTITIONER COMPARED TO TRUST IN EMERGENCY DEPARTMENT OBSERVATION UNIT (EDOU) IN CHILDREN'S CLINICAL UNIVERSITY HOSPITAL

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Abstract
Key words: *Parents, children, trust, communication, general practitioner (GP), emergency department (ED)*
Introduction: Many parents seek help at the EDOU due to their children's minor health issues. Only in about 20% of cases patients actually need hospital treatment, for others help of a GP would be enough.
Aim: To determine reasons why parents go to EDOU not GP, and parents' trust and communication quality with their GP.
Materials and methods: A prospective study was carried out in 2017 by a random survey of parents (n=300 patients), who received a lower priority in the sorting process of EDOU. Statistical analysis was performed using MS Excel, IMB SPSS Statistics 22 software.
Results: 53% (157) of parents came to the hospital without any referral from a GP or ambulance.
41% (123) had not contacted their GP during this particular illness, and 64% (192) had not seen the GP prior to coming to the hospital.
On a scale of 1 to 10 (1-lowest, 10- highest) parents rated their trust in GP as an average of 7.8 (median 8, min 1, max 10), trust in the hospital as 8.7 (median 9, min 1, max 10) and the communication with their GP as 8.3 (median 9, min1, max 10).
46% (135) of parents rate their trust to the hospital higher than their GP; 42% (125) rate their trust the same for both and 12% (34) rate trust to the hospital worse.
Only 19% (57) of all patients were hospitalized,
Conclusions: Children's primary health care system needs improvements. Parent cooperation with GP should be promoted to prevent unnecessary visits to the EDOU.

Kopsavilkums
Atslēgvārdi: *Vecāki, bērni, uzticība, komunikācija, ģimenes ārsts (ĢĀ), neatliekamā palīdzība*
Ievads: Bērnu Klīniskās Universitātes slimnīcas Neatliekamās medicīniskās palīdzības un observācijas nodaļā (NMPON) pēc palīdzības vēršas daudz vecāku sakarā ar maznozīmīgiem bērnu veselības traucējumiem.Tikai 20% gadījumu pacientiem tiešām nepieciešama slimnīcas palīdzība, pārējiem pietiktu ar ĢĀ palīdzību.
Mērķis: Noskaidrot iemeslus, kāpēc vecāki vēršas uz NMPON nevis pie ĢĀ, kā arī vecāku uzticēšanos un komunikāciju ar ĢĀ.
Materiāli un metodes: Prospektīvais pētījums veikts 2017.gadā kā randomizēta to bērnu vecāku aptauja, kuri saņēmuši zemākas prioritātes vērtējumu NMPON šķirošanas procesā (n=300 pacienti). Statistikas analīze veikta, izmantojot MS Excel, IMB SPSS Statistics 22 programmu.
Rezultāti:
53% (157) vecāku ieradās slimnīcā bez ĢĀ vai NMP nosūtījuma.
41% (123) vecāku nebija sazinājušies ar ĢĀ konkrētās saslimšanas laikā un 64% (192) nebija apmeklējuši ĢĀ pirms došanās uz slimnīcu.
Skalā no 1 līdz 10 (1- zemākais, 10-augstākais) vecāki vērtēja savu uzticību ĢĀ ar vidējo vērtējumu 7.8 (mediāna 8, min 1, max 10), uzticību slimnīcai ar 8.7 (mediāna 9, min 1, max 10) un komunikāciju ar savu ĢĀ ar 8.3 (mediāna 9, min 1, max 10).
46% (135) vecāku vērtē uzticību slimnīcai augstāk nekā ĢĀ; 42% (125) vecāku to vērtē vienlīdzīgi slimnīcai un ĢĀ un 12% (34) vērtē uzticību slimnīcai zemāk.
Tikai 19% (57) no visiem pacientiem tika hospitalizēti,
Secinājumi: Bērnu primārajā veselības aprūpes sistēmā ir vajadzīgi uzlabojumi. Jāveicina vecāku sadarbība ar ģimenes ārstu, lai novērstu nevajadzīgu NMPON apmeklējumu.

Introduction

Approximately 200 children with parents admit to the Emergency department and Observation unit (EDOU) in Children's Clinical University hospital every day. As having a referral

from a general practitioner (GP) or ambulance is not compulsory to receive a consultation at the hospital, as soon as a child's health problem appears, many parents decide to go to CCUH independently, via their own transport, at any time of the day. Such system is convenient for both patients and their parents (especially for those living in or nearby Riga) for many reasons. First, the child can be seen by a physician early during the onset of illness, there is no need to adjust to GP's working schedule and parents do not need to miss work to take their child to the physician.

At the admission department, there are two physician-assistants performing the triage (process of patient sorting), two receptionists and a junior nurse assistant that escorts patients further, where a physician will see them in a while. During the triage, the patient is briefly examined (history obtained, temperature, pulse measured, etc.) and sorted by color, depending on urgency of the situation and patient's condition. These health situations are often not urgent at all and the patients are sorted into white, green or yellow priority and wait in a queue for a pediatrician's consult for several hours (Tab.1)

Table 1. **Process of triage** (CCUH Guidelines, 2017)

Colour	Possible waiting time	Comment
Red	Immediate physician consult	Life in danger
Orange	15 minutes	Life-threatening condition
Yellow	60 minutes	No danger to life right now, but possible complications
Green	240 minutes	Life not in danger, not an emergency
White	Unlimited time	No need for an emergent help

In several western countries patients' use of Emergency Departments (EDs) is increasing. A substantial number of patients are self-referred, but do not need emergency care. (Kraaijvanger 2016) Variability in the proportion of non-urgent ER visits was found to range from 5 to 90 % (median 32 %). Non-urgent emergency visits are considered an inappropriate and inefficient use of the health-care system because they may lead to higher expenses, crowding, treatment delays, and loss of continuity of healthcare provided by a general practitioner. (Ruud 2016)

Previous statistics from CCUH show that 4% of all patients' state is critical, but 70% matches green or white category and could be treated by a general practitioner (according to information available on CCUH homepage). A small piece of paper explaining color codes and waiting times is given to the parents, but - as this study and everyday practice shows – parents pay no or little attention to these explanations. This causes frustration among parents, as they do not understand why they must wait for so long.

Such situation causes overcrowding at the ED and frustration among personnel as well. Personnel is busy consulting lower priority patients and this overworking can shift the focus from

patients that need help more, and whose general status is more severe. If this focus does not shift, the lower priority patients' parents are frustrated for the long waiting. This provokes dissatisfaction with the situation in the EDOU, which is laid on the personnel, and anger that is directed to the Health Care system in Latvia as a whole.

In many such cases with minor illnesses, a help of a GP or parents' own knowledge received from a GP could be enough to help the children and avoid needless visits to the hospital, especially during influenza epidemic season, not to mention the overcrowding situation at the EDOU. This study was specifically aimed at the lower priority patients to clarify some reasons of not contacting or seeing their GP in the first place.

Materials and methods

In the study 300 cases of patients (age 0-18 years) and their parents questionnaires were documented. On random days and at random times authors gave out questionnaires to parents of patients that were evaluated as "white", "green" and "yellow" priority on admission to EDOU and were awaiting a pediatrician's consultation. Patients admitted with acute trauma or suspected surgical illness were not included in this study. For the parents the participation was voluntary.

The questionnaire involved both open questions about patient information, several multiple choice questions and questions, where parents were asked to evaluate quality of communication as well as their trust in both GP and CCUH. After the questionnaire was filled in by parents, authors used the patient database to determine whether or not the patient was transferred to any other department for further treatment at the hospital.

Statistical analysis was performed using MS Excel, IMB SPSS Statistics 22 software and $p < 0.05$ was considered statistically significant. Cross tabulation with χ^2 test and Fischer's exact test were used.

Of the 300 patients included in the study, 74% were sorted green, 25% yellow and 1% white.

Results

After summing up and analyzing all answers from the questionnaire, the authors found out that most of the children – 99,7% (299) - admitted to EDOU had been living in Latvia. 86,1% (254) live in a city. 63,3% (186) live in Riga. Only 13,9% (41) answered that they live on the countryside, but sometimes this meant they live just outside/near Riga, seldom it meant rural regions.

Almost all children (about 99%) had an assigned general practitioner, only 3 of them did not have a GP.

The average length of the particular illness for a child at the moment of admission was 1.33 days (min – 1 day, max – 90 days). Both very long or very short periods of a mild to moderate illness usually means that it is not the case to go to the hospital. In addition to that, in 47,3% (140) cases the child's body temperature on admission was normal. Sometimes parents argued that the

temperature was higher at home, or that they felt that the child was feverish. Often, parents use unreliable thermometers or measure the temperature incorrectly.

Only 9,7% (29) parents took child's vaccination passport to the hospital. Bringing the vaccination passport to EDOU is not mandatory, but in cases with suspicion of an infectious disease it provides valuable information.

57 patients of 300 (19%) were hospitalized for further treatment, 29 of those were "yellow" and 28 – "green". So only about 12% of all "green" and 39% of all "yellow" patients were hospitalized. Others – examined by the physician, some received intravenous fluids, some – fever medication, and then sent back home. This shows that significant number of patients (81%) are needlessly admitted to the EDOU.

53% (157) of parents came to the hospital without any referral from a GP or ambulance, 39% (116) arrived with an ambulance referral and only 8% (25) came with a GP referral (Fig.1)

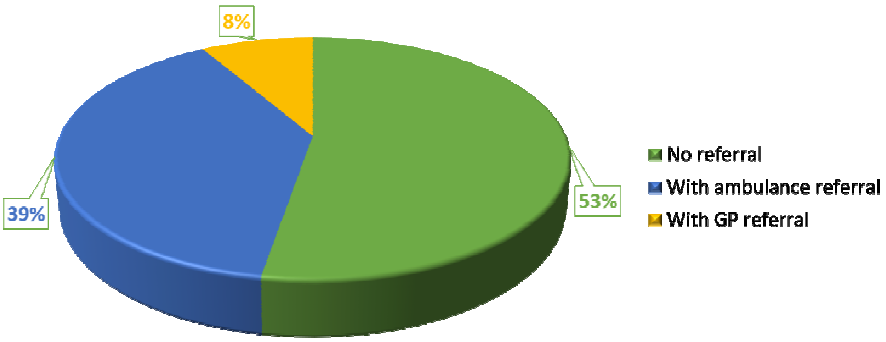

Figure 1. **Arrival at the hospital**

64% (192) had not visited their GP (in person) prior to coming to the hospital – 41% (123) of them had not contacted their GP at all during this particular illness, and 23% (69) had contacted GP through telephone. Only 36% (108) of the parents had visited the GP. (Fig.2).

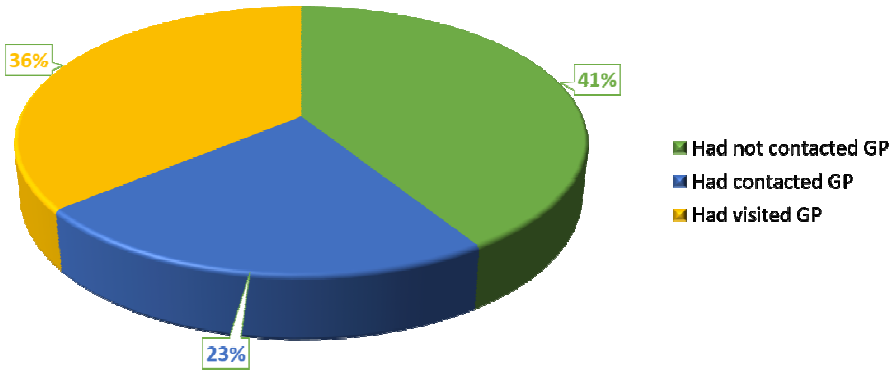

Figure 2. **Contact with the GP before coming to the hospital**

The most common reasons for not going to the GP were:

1) 45% (85) – GP does not work at this hour/date. This is debatable, as most patients/parents were interviewed on workdays and during morning/early afternoon time.
2) 46% (87) of parents answered “other” reasons - GP is on a sick leave, GP is not a pediatrician, GP not competent in particular case (a specialist’s consultation is necessary, GP not experienced enough), GP advised to go to ED, GP is too far, not possible to contact GP, want a different opinion, other physician/nurse advised to go straight to the hospital etc.
3) 13.8% (26) - parents prior to admission had thought they could handle the situation on their own and thus did not visit the GP. When child’s health condition worsened, they went to CCUH directly.
4) 13,2% (25) answered that there is a long queue at the general practitioner.

The most common reasons for coming to the EDOU:

1) 45,4% (134) - sudden deterioration of a child’s condition
2) 35,3% (104) - hospital provides more examinations, analysis and specialist consultations within a shorter time period. This is also discutable, because the statement is true, but it may or may have not been a direct reason for making the particular decision. The authors suppose that this answer was popular because it was offered as an option on the multiple choice question.
3) 19,3% (57) - no improvement following GP recommendations.
4) 32,9% (97) ”other reasons” – did not know what to do, a need for the intravenous fluids, GP or ambulance advised to go to the ED, more trust in the ED, medication does not help, awful previous experience, fear for a bad outcome, a child does not drink/eat, bad laboratory results.

When asked to rate their trust on a scale of 1 to 10 (1- the lowest, 10-the highest) parents rated their trust in GP as an average of 7.8 (median 8, min 1, max 10), trust to the hospital as 8.7 (median 9, min 1, max 10) and the communication with their GP as 8.3 (median 9, min1, max 10) (Fig.3).

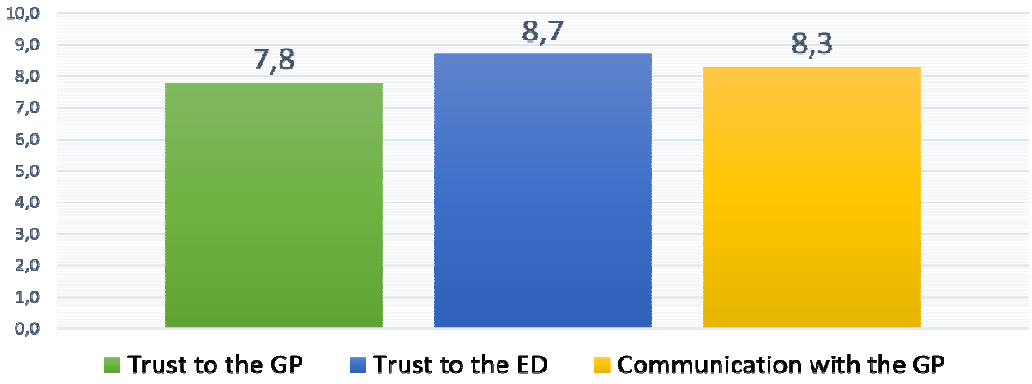

Figure 3. **Parents’ evaluation on a scale from 1 to 10 (average values)**

Those parents who rated their trust in GP less (on average 7.8), came to the hospital without referral more often. Those who came with a referral from a GP, trusted their GP more (on average 8.7, p = 0.04).

Those parents, who live outside Riga (64,4%), go to their GP less often before coming to the hospital than those, who live in Riga (48,8%, p=0.1, in Fisher's exact test between -2 and +2 à statistically significant).

46% (135) of the surveyed parents rate their trust to the hospital higher than to their GP; 42% (125) rate their trust the same for hospital and for GP and 12% (34) rate trust to the hospital worse (Fig.4).

There were as well some statistically insignificant results:

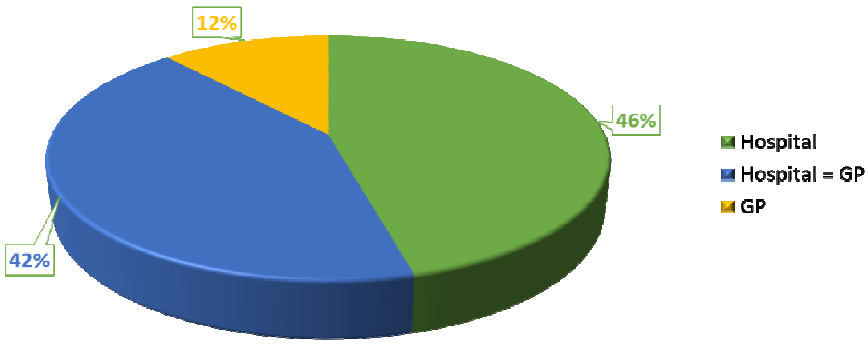

Figure 4. **Parents' preferences**

There were no significant differences in parent trust to GPs from different age groups.

Parents living in and outside Riga trust the hospital approximately the same.

Discussion

Providing care in the emergency department is significantly affected by non-emergent patients, as the emergency department is a place for critically ill patients; thus awareness training program is recommended. (Mirhaghi et al. 2016)

Parents assess their child's condition more critically and think that their child requires urgent medical aid more frequently than healthcare professionals. (Burokienė et al. 2017)

This study shows that many reasons given by parents coming to the EDOU are not reasonable or are debatable (such as saying that a GP is not competent in the particular case when not contacting the GP at all).

It seems that parents have little knowledge about children's health care and first aid. Many do not know how to give antipyretic medication to a child. Several parents come to the Emergency department asking for an otorhinolaryngologist consultation. Often it seems that parents do not know how the Emergency department works and what its primary concern is.

Currently CCUH is posting several informative posts on social media (twitter, facebook). The authors of this study have personally held several lectures for young parents about children's first aid and are currently posting short articles about first aid to children in a patient oriented newsletter in Latvia. But a much more effective way for educating parents would be an effort made by general practitioners themselves.

As CCUH has a specific pediatric emergency department, it seems logical that parents seek help here. Also, since most of Latvia's population is situated around or nearby Riga, CCUH is the closest children's healthcare center for many. The situation might be different in other regions of Latvia, which would be interesting to explore. Emergency departments in hospitals outside Riga are not specifically designed for pediatric healthcare. It is possible that parents in distal regions choose to turn to their GP and not to the regional hospital ED.

Recently an article has been published in Doctus magazine (April 2017), where CCUH EDOU chief physician Zanda Pučuka is sharing what she has observed in children's hospitals in Finland and Sweden. The healthcare system is quite different. For example, in Helsinki, there are primary healthcare centres where parents can get pediatrician's consultation in case of minor healthcare problems – this way they do not overcrowd the EDs.

There is still much to learn and improve in children's primary healthcare.

Conclusions

The study concluded that 46% of patients prefer to seek help at the CCUH EDOU because they trust CCUH EDOU more than they trust their GP (although their trust in GP is rated as 8). Average trust for the CCUH EDOU is higher than for the GP.

42% of patients rate their trust to the GP the same as for the EDOU, but still prefer to seek help at the CCUH EDOU.

According to the results of the study, many aspects of the children's primary health care system need improvements. Parent cooperation with GP should be promoted. Parents need to be encouraged to contact their GP more often and to only turn to CCUH EDOU in case of a real emergency. To do so, the parents need to be educated on how to recognize a medical emergency.

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SINGLE DOSE INTRAVENOUS PARACETAMOL IN PATIENTS AFTER HIP AND KNEE REPLACEMENT SURGERY

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Abstract

Single dose intravenous paracetamol in patients after hip and knee replacement surgery

Key words: *Paracetamol, haemodynamics, analgesia*

Introduction: Intravenous paracetamol is widely used drug in Hospital of Traumatology and Orthopaedics and is a part of standard post-operative analgesic protocol after major operations. But there are concerns about its haemodynamic effects in patients with cardiovascular risk factors.

Aim: To study incidence of clinically significant hypotension and changes in heart rate during intravenous paracetamol infusion and one hour after it.

Materials and methods: 96 patients (male 32(33%), age 64.9±9.7y, BMI 31.2±7.2 kg/m^2) that have undergone knee or hip replacement surgery were enrolled in this prospective observational study. Inclusion criteria: administration of intravenous paracetamol infusion for analgesia within 24 hours of surgery. Exclusion criteria: advanced cardiac failure (NYHA III-IV), previous myocardial infarction and significant aortic stenosis. Following characteristics were collected: age, gender, height, weight, ASA class, blood loss during surgery. Systolic, diastolic, mean blood pressure and heart rate were measured every 5 minutes during infusion and 15 minutes for an hour after. Data were analysed using linear mixed effects model and patients with change in haemodynamic parameters of 15% or more were obtained.

Results: Time from start of infusion significantly influenced systolic blood pressure (log likelihood 17.9, p=0.007). Systolic blood pressure was significantly reduced from baseline 30 minutes after end of infusion (difference 3.9 mm Hg (CI -7.3 -0.6); p=0.01). Heart rate did not significantly change during or after infusion. 6 of 89 patients had blood pressure drop under 90 mmHg.

Conclusion: Intravenous infusion of paracetamol causes statistically significant decrease of systolic blood pressure 30 minutes after end of infusion but its extent is not clinically relevant.

Kopsavilkums

Vienas devas intravenozais paracetamols pacientiem pēc ceļa un gūžas endoprotezēšanas operācijas

Atslēgvārdi: *paracetamols, hemodinamika, analgēzija*

Ievads: Intravenozais paracetamols ir plaši izmantots pretsāpju medikaments Latvijā. VSIA "Traumatoloģijas un ortopēdijas slimnīcā" tas ir iekļauts standarta pēcoperācijas atsāpināšanas protokolā un tiek nozīmēts lielākajai daļai pacientu pirmajās 24 stundās pēc lielo locītavu operācijām. Medicīniskajā literatūrā ir atrodami pētījumu dati par to, ka intravenozais paracetamols izraisa nozīmīgu jatrogēnu hipotensiju, kas var būt nevēlams blakusefekts pacientiem ar kardiovaskulārām blakusslimībām.

Mērķis: Izpētīt hemodinamisko rādītāju pārmaiņas pacientiem pēc lielo locītavu endoprotezēšanas operācijām saistībā ar intravenozu paracetamola infūziju.

Materiāli un metodes: Tika veikts prospektīvs novērojuma pētījums, kurā tika monitorēti 96 pacienti (32 vīrieši (33%), vidējais vecums 64.9±9.7 gadi, vidējais ĶMI 31.2±7.2 kg/m^2), kuriem laikā no 2016.g. novembra līdz 2017.g. februārim veikta ceļa un gūžas endoprotezēšanas operācija VSIA "Traumatoloģijas un ortopēdijas slimnīca" un pirmajās 24 pēcoperācijas stundās atsāpināšanai nozīmēts paracetamols intravenozā infūzijā. No pētījuma tika izslēgti pacienti ar smagu sirds mazspēju (NYHA III-IV), nozīmīgu aortas stenozi, kā arī miokarda infarktu, perkutānu koronāri intervenci vai šuntēšanu anamnēzē. Demogrāfiskie dati (vecums, dzimums, augums, svars, operācijas veids, ASA klase, asins zudums operācijas laikā) tika ievākti no pacientu slimības vēsturēm. Pacientu hemodinamiskie rādītāji (sistoliskais, diastoliskais, vidējais asinsspiediens un sirdsdarbības frekvence) tika mērīti pirms infūzijas uzsākšanas, katras 5 minūtes infūzijas laikā un katras 15 minūtes vēl stundu pēc infūzijas beigām. Rādītāju izmaiņu tendences tika aprakstītas, izmantojot jauktu lineāro efektu modeli, kā arī iegūts rādītāju izmaiņu biežums. Par klīniski nozīmīgām izmaiņām tika pieņemts rādītāju izmaiņas vairāk pa 15% no sākotnējā.

Rezultāti: Statistiski nozīmīga sistoliskā asinsspiediena vērtības samazināšanās salīdzinājumā ar tā vērtību pirms infūzijas novērojama 30 minūtes pēc infūzijas beigām (starpība 3.9 mmHg (CI -7.3 -0.6); p=0.01). Netika novērotas nozīmīgas sirdsdarbības frekvences izmaiņas infūzijas laikā un pēc tās. 6 no 89 pacientiem novēroja asinsspiediena krišanos zem 90 mmHg vērtības.

Secinājumi: 30 minūtes pēc intravenozas paracetamola infūzijas novēro statistiski ticamu, bet klīniski maznozīmīgu sistoliskā un vidējā asinsspiediena krišanos.

Introduction

Intravenous paracetamol is widely used analgesic drug worldwide and in Latvia. It has proven its efficacy and safety when used in its therapeutic doses (Sinatra 2005). It is administered in cases when oral intake is not possible and that is a reason why most patients receiving paracetamol intravenously is surgical patients or critically ill.

It is administered in Hospital of Traumatology and Orthopaedics for nearly all patients in first postoperative day after knee and hip replacement surgery. However, in medical literature there are studies about haemodynamic effects associated with intravenous paracetamol infusion suggesting it causes significant iatrogenic hypotension (Chiam 2015).

Nonetheless, we lack data about paracetamol effects after major orthopaedic surgery when administered intravenously. It could be relevant for patients with additional cardiovascular risk factors for whom hypotension could be dangerous.

Materials and Methods

A prospective observational study of adult (>18 years) 96 patients (male 28 (31%), age 64.7±9.9 years, BMI 31.2±7.2 kg/m^2) that have undergone knee or hip replacement surgery in the previous 24 hours and received intravenous paracetamol infusion for analgesia was performed from November 2016 to February 2017.

Exclusion criteria: advanced cardiac failure (NYHA III-IV), significant aortic stenosis, previous myocardial infarction, percutaneous coronary intervention or coronary bypass grafting performed.

The following patient characteristics were collected from medical documentation: age, gender, height, weight, type of surgery, ASA class, blood loss during surgery. Haemodynamic values (systolic, diastolic, mean blood pressure and heart rate) were measured at predetermined time points – before the infusion, every 5 minutes during infusion and every 15 minutes for an hour after it.

Data were analysed to identify trends in haemodynamics during observation period using linear mixed effects model and obtain number of patients with change in haemodynamic parameters of 15% or more.

Results

Patient population description – 89 patient data was analysed

- Sex: 28 male (31%), 61 female (69%);
- Age: 64.7±9.9 years (min 32 years, max 83 years);
- Body mass index: average 31.2±7.2 kg/m^2; min BMI=18.7 kg/m^2, max BMI=51.1 kg/m^2;
- ASA class: ASA I - 1 patient (1%), ASA II – 47 (53%), ASA III – 41 patient (46%);
- Blood loss during surgery: ranges from 100 to 1200 ml;
- 7 of 96 patients were excluded due to exclusion criteria.

Haemodynamic changes

- SYSTOLIC BLOOD PRESSURE (SPB)

22 of 89 patients (24.7%) had decrease in SPB from baseline value by 15% or more in at least one time point during observation period.

6 of 89 patients (6.7%) had SPB decrease below 90mmHg.

When time function added to identify trends in pressure changes*: post hoc test* indicated that SPB was significantly reduced from baseline 30 minutes after end of infusion (difference 3.9 mmHg (CI -7.3 -0.6); p=0.01).

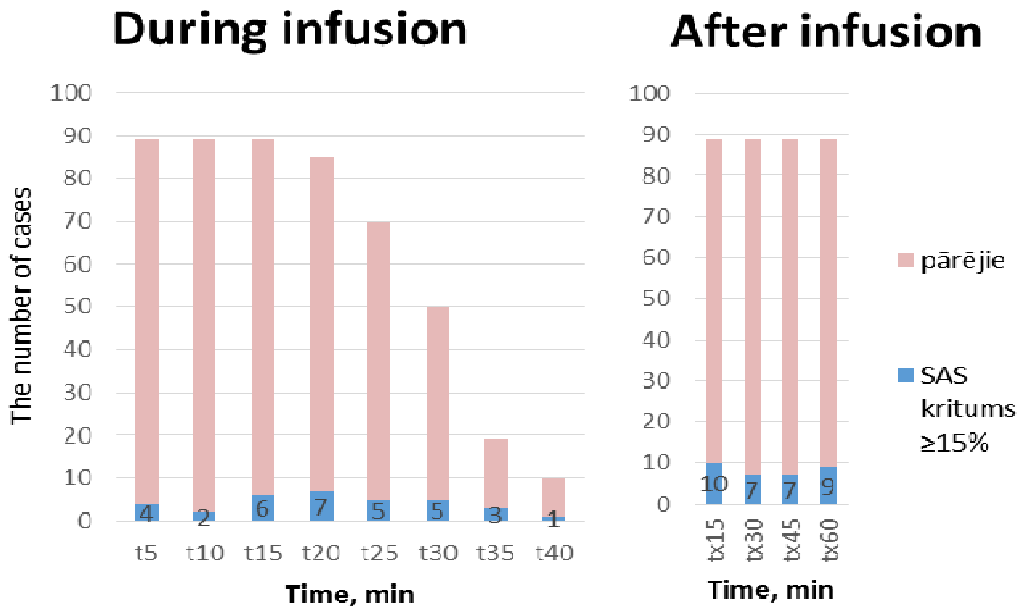

Figure 1. **Clinically significant (≥15%) SAS drop frequency from baseline at measurement time points, where t[n] – n-minutes from infusion start; tx[n] – n-minutes from infusion end**

- DIASTOLIC BLOOD PRESSURE (DBP)

39 of 89 patients (43.8%) had decrease in DPB from baseline value by 15% or more in at least one time point during observation period.

When trends in DBP changes observed*: post hoc test* indicated that there is no statistically significant decrease in DBP. $\chi 2(6) = 8.72$, $p = 0.19$.

- MEAN ARTERIAL PRESSURE (MAP)

26 of 89 patients (29.2%) had decrease in MAP from baseline value by 15% or more in at least one time point during observation period.

Post hoc test indicated that MAP decreased from baseline MAP by 2.5 mmHg (CI -5.2 0.2 mmHg; p=0.02) 30 minutes after the end of infusion.

- HEART RATE (HR)

29 of 89 patients (32.6%) had increase in HR from baseline value by 15% or more in at least one time point during observation period.

When trends in HR changes observed*: post hoc test* indicated that there is no statistically significant increase in HR. $\chi 2(6) = 6.12$, $p=0.41$.

- ASA CLASS, BMI AND BLOOD LOSS DURING SURGERY

No connection between SBP and HR change frequency and ASA class, body mass index and blood loss was observed. ($p>0.05$)

Discussion

Although systolic, diastolic and mean arterial pressure were reduced from baseline in at least one measurement point during observation period for 20-30% of patients, there were no systematic trends between those changes and time from infusion start. Also there was no connection between haemodynamic changes and factors (ASA class, blood loss and BMI) that could affect effect of paracetamol suggesting that there were other factors, unrelated to paracetamol that could influence these changes in arterial pressure and heart rate.

Although there were many patients who had changes in haemodynamic parameters for more than 15% from baseline, clinically significant systolic arterial pressure drop below 90 mmHg was observed only in 6 from 89 patients. Unfortunately, there is no information whether medical management of hypotension was necessary.

Research disadvantages:

- Infusion rate was different for patients and this troubled data processing. But in clinical practise intravenous drip system rate are hard to control. Maybe better choice option for this study would be perfusor.
- Patients are provided with standard postoperative care, so we can't exclude different confounding factors which could influence the outcome, for example, other drugs or intravenous fluid therapy before and after infusion of paracetamol.
- In this study only one paracetamol solution (B. Braun) was used. We cannot exclude the assumption that hypotension is caused not by paracetamol but excipients in solution. There is a chance that results would be different if other paracetamol solution was used.

Conclusions

1. 30 minutes after intravenous paracetamol infusion statistically but not clinically significant decrease in SPB (3.9 mmHg) and MAP (2.5 mmHg) was observed.
2. There was no statistically significant changes in heart rate.
3. There was no connection between haemodynamic changes during intravenous infusion of paracetamol and BMI, ASA class and blood loss during surgery.

Acknowledgement

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THE USABILITY STUDY OF THE INTERACTIVE EDUCATIONAL TOY

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Abstract

The usability study of the interactive educational toy

Key words: *usability, children, toy*

Introduction: Nowadays there is a rapid development of more advanced technologies, and toy manufacture is not an exception. “Cubies” toy is an interactive educational product invented by Latvian producers. Riga Stradins University Student scientific interest group of Rehabilitology has conducted a usability study of this toy. Testing of toys amongst children in the United States is a common practice. However, according to available information, usability study has never been carried out in Latvia.

The aim: was to assess the usability of the toy amongst children of different age and gender.

Methods: “task-based scenarios”, contextual interview, visual analogue scale, retrospective testing of video recordings were used for evaluation.

A sample of 109 children (51.4% males) from Latvian kindergartens were involved in the study. All the participants were divided into 3 age groups: 3, 4-5, 6-7 years old.

Descriptive statistics and nonparametric tests for comparison of groups were used for data analysis.

Results: More than a half of participants did not identify pictures of” badger”, “lizard”, “sparrow”, “lynx” and only 6.4% identified the picture of the “moss”on the cubes. The groups of children who did not identify the pictures of ‘lynx’ and ‘badger’ was statistically significantly associated with the younger age (p=0.00009, p=0.01, respectively); However, ability to identify said animals was not associated with average ‘free playing time’(p=0.82); There was no statistically significant difference in the average ‘free playing time’ between the gender groups (p=0.96) and between the mean ranks of three age groups (p=0.69); 93.6% evaluated the toy as an ‘interesting’ or ‘very interesting’ according to visual analogue scale, 92.7 % of participants would like to have similar toy for their private use.

Conclusion: The toy can be used amongst 3-7 years old healthy children, but at least 5 pictures on the cubes have to be improved for more successful usage. We are planning this research to be the basis for a number of subsequent studies related to the developmental and therapeutic effect of the “CUBIES” toy.

Conflict of interests: Scientific group did not receive any financial support for this study.

Kopsavilkums

Interaktīvās izglītojošās rotaļlietas lietojamības pētījums

Atslēgvārdi: *lietojamība, bērni, rotaļlieta*

Ievads: Mūsdienās ir vērojama ātra progresīvo tehnoloģiju attīstība un rotaļlietu rūpniecība nav izņēmums. "Cubies" rotaļlieta ir Latvijas ražotāju izgudrots interaktīvs izglītojošs produkts. Rīgas Stradiņa Universitātes rehabilitoloģijas studentu zinātniskais pulciņš organizēja šīs rotaļlietas lietojamības pētījumu. Rotaļlietu lietojamības pārbaude bērnu vidū, Amerikas Savienotajās valstīs ir izplatīta prakse. Bet, balstoties uz mums pieejamo informāciju, lietojamības pētījumi līdz šim nav īstenoti Latvijā.

Mērķis: novērtēt rotaļlietas lietojamību starp dažāda vecuma un dzimuma bērniem.

Metodes: novērtēšanai tika izmantoti “uz uzdevumiem balstīts scenārijs”, kontekstuālā intervija, vizuālā analogu skala, videoierakstu retrospektīvā pārbaude. Pētījumā tika iesaistīti 109 bērni (51.4% vīrieši) no Latvijas bērnudārziem. Visi dalībnieki tika sadalīti trijās grupās: 3, 4-5 un 6-7 gadus veci; Aprakstošās statistikas metodes un neparametriskie testi tika izmantoti datu analīzē.

Rezultāti: Vairāk kā puse no dalībniekiem neidentificēja attēlus uz kubiem ar “āpsi”, “ķirzaku”, “zvirbuli”, “lūsi” un tikai 6.4% identificēja attēlu ar “sūnām”. Bērnu grupa, kas neidentificēja attēlus ar “lūsi” un “āpsi” bija statistiski nozīmīgi saistīta ar jaunāku vecumu (p=0.00009, p=0.01, attiecīgi). Spēja identificēt minētos dzīvniekus nebija saistīta ar vidējo “brīvās spēlēšanās ilgumu” (p=0.82). Netika atrasta statistiski nozīmīga atšķirība vidējā “brīvās spēlēšanās” ilgumā starp dzimumiem (p=0.96) un starp trijām vecuma grupām (p=0.69); 93.6% novērtēja rotaļlietu kā “interesantu” vai “ļoti interesantu” balstoties uz vizuālo analogu skalu, 92.7% no dalībniekiem vēlētos līdzīgu rotaļlietu savā īpašumā.

Secinājumi: Rotaļlieta var būt lietojama veseliem bērniem vecumā no 3 līdz 7 gadiem, bet vismaz 5 attēlus uz kubiem vajag uzlabot veiksmīgākai lietošanai. Mēs plānojam šo pētījumu izmantot par pamatu vairākiem sekojošiem pētījumiem, kas būs saistīti ar "CUBIES" attīstošu un terapeitisko efektu.
Interešu konflikts: zinātniskā grupa nesaņēma nekādu finansiālu atbalstu šī pētījuma veikšanai.

Introduction

Interacting with toys plays a crucial role in child development and supports learning and cognitive processes, when toys are selected in accordance with developmental needs. Nowadays there is a rapid development of more advanced technologies, and toy manufacture is not an exception.

"Cubies" toy is an interactive educational product invented by Latvian producers. Inventors expect, that this toy, which is both physical and digital, can help to develop perception capacity in children and health or education workers to tutor children in an innovative and entertaining way. The first usability study of this toy has been conducted by Rīga Stradiņš University Student Scientific interest group of Rehabilitology in order to understand, if it can be successfully usable amongst healthy 3-7 years old children.

Usability Evaluation focuses on how well users can learn and use a product to achieve their goals. The aim of usability studies is a deep understanding of users, their needs, values, abilities and limitations. The object of use and usability study can be a book, website, toy or anything a human interacts with (Rubin 2008: 13). Testing of toys amongst children in the United States, Canada or Turkey, for example, is a common practice (Karaa 2014). However, according to available information, this kind of study has never been carried out in Latvia.

Materials and methods

The "Cubies" toy consists of the base platform and a set of three cubes (Fig. 1). To start playing child has to put one or several cubes on the base platform and listen to the story, which is played back via built-in loudspeakers. This is a "successful scenarios" of usage.

Figure 1. **Picture of the "Cubies" toy prototype**

"Cubes" can be placed on the base in thousands of combinations. And each combination creates a different entertaining short story. Several collections of cubes are possible. Each collection has 150-400 stories. We have used "*The wild animals*" collection in our study.

We have started with sending offers to take part in the study to 30 Riga kindergartens, which perform their educational programms in Latvian and four of them agreed to participate.

Further we have recieved permission to conduct the study from the Riga Stradins University Ethics commitee. All the parents of involved children also signed the permissions, which allowed us to take a video-recordings of the sessions with children.

Before starting direct work with children, we have organised three training sessions for the interviewers to develope a precise algorithm of interaction with children and reacting to extraordinary situations, in order to avoid information bias.

During the sessions, we have used several methods for data collection:

- **Contextual interviews:** During these interviews, researchers watch and listen as users work in the user's own environment: in our case - kindergartens.
- **The Task-Based Scenarios:** Combine watching users do their own work with asking them to try a few of tasks (Nielsen 1993). For example: *"Please, imagine, that your parents have bought you such a toy and did not explain how to play with it. Can you show me, how can you play with this toy?"*.
- **Visual analogue scale**: to assess the interest and satisfaction of the users (Fig. 2).

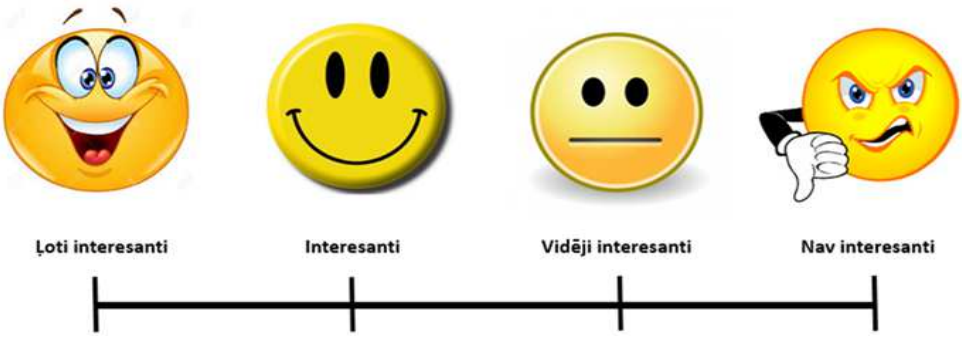

Figure 2. **Visual analogue scale for interest assessment**

During the sessions following aspects of usability for CUBIES toy prototype, collection "*The Wild animals"* were assessed:

- the time it takes for a child to understand how the toy functions and start playing with the toy;
- the number of attempts that is required to bind the cube on the base platform – further '*successful attempt*';
- attention span, while listening to one of the stories from the toy;

- ability to identify all the pictures on the cubes;
- the number of attempts needed to accomplish simple task with the toy;
- the satisfaction of children with the toy;
- One session with one child was approximately 20-25 minutes long**.**

Data analysis

All the data were checked for normality using *Kolmogorov- Smirnov* test and histograms. For data analysis, we used descriptive statistics and nonparametric tests: *Mann-Whitney* and *Kruskal-Wallis* tests. SPSS v23.0 software was used.

Sample

109 children (51.4% males) from 3 to 7 years old were involved in the study. Latvian language speakers, without mental, vision or movement disorders. All the participants were divided into three age groups: 3 years old (10.1 %), 4-5 years old (52.3 %) and 6-7 years old (37.6 %)

Results

For children to understand how to start playing took from 1.79 to 248.81 seconds, with median 71.88 seconds. There was no significant difference in the average time till the '*successful attempt'* between the: gender groups (p=0.44) and three age groups (p=0.59); 97.2 % of children needed only one attempt to place a cube on the platform correctly, which means that size and shape of cubes and platform are comfortable for usage; Most of the children (81.70%) listened to the end of the first story. Average time children were playing during their "free time" 4.5 minutes (Fig. 3).

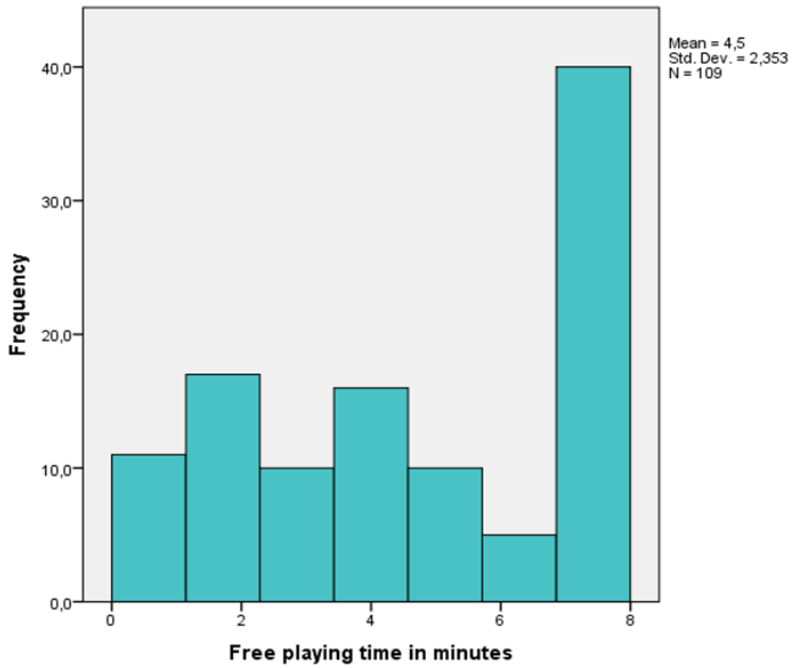

Figure 3. **Histogram "Free playing time in minutes"**

There was also no significant difference in the average ‘’free playing time’ between the gender groups (p=0.96) and three age groups (p=0.69) and 39 % of children played for maximally allowed by the protocol “free playing time”: 7 minutes, which is average length of attention for a sustained activity, such as viewing television, for all three age groups of participants (Herbert 2004) Unfortunately, 82.6% of participants did not identify the picture of: „badger” (Fig. 4), 56.9% did not identify the picture of “lizard” (Fig. 5), 53.2% did not identify the picture of “sparrow” (Fig. 6) and 63.3% of children did not identify the picture of “lynx” (Fig. 7). Only 6.4% identified the picture of the “moss” (Fig.8) on the cubes.

Figure 4. **“Badger”**

Figure 5. **“Lizard”**

Figure 6. **“Sparrow”**

Figure 7. **“Lynx”**

Figure 8. **“Moss”**

Only the groups of children who did not identify the pictures of ‘lynx’ and ‘badger’ were associated with the age, (p=0.00009, p=0.01, respectively) which can be related to the inadequate knowledge about this animals in younger children. However, the ability to identify said animals did not influenced average ‘free playing time’ (p=0.82);

92.7 % of participants would like to have similar toys at home and 93.6 % of children evaluated the toy as an ‘interesting’ or ‘very interesting’ according to our visual analogue scale;

Discussion

We have used ***convenience selection*** in our study, due to very low response rate. We have sent our offers to take part in the study to 30 Riga’s kindergartens, which perform their educational

programms in Latvian language. Responce rate was 13% and only four kindergartens agreed to participate in our study.

It was important, that influence of interviewer on child's behavior can affect results and create an information bias that way. ***Prophylaxis of possible information bias:*** We have organised three training sessions for all of the authors involved in direct work with children. The aim of this sessions was to develop a precise algorithm of interaction with children. Statistical analysis showed, that there is no significant difference in the average free playing time between the groups of children with different interviewers (p=0.1). It allows us to think, that training sessions were useful and we reduced the influence of interwievers.

Prophylaxis of possible measurement biases

All measurements carried out during the sessions were synchronously recorded by two students and then checked retrospectively on video recordings and validated by a third student in order to avoid measurement bias (Pannucci 2010: 619–625)

Conflict of interests

Scientific group did not receive any financial support for this study. The authors alone are responsible for the content and writing of the paper.

Conclusion

Children of both genders and all three age groups equally quickly intuitively understood how to play with the toy and needed only one attempt to bind the cube to the base platform and accomplish simple tasks: the size and shape of cubes and platform are comfortable for usage. More than a half of participants found the toy interesting and would like to have a similar toy for their private use, which allows us to conclude that the toy can be successfully used amongst healthy 3-7 years old children, but at least five pictures on the cubes have to be improved for more successful usage.

We are planning this research to be the first one in a number of subsequent studies related to the "CUBIES" toy. The various features of this toy will allow us to assess its developmental and therapeutic effect on healthy children and children with disabilities in the future. A complete program of children's usability testing is the essential component to creating products that are child-friendly and child-approved.

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THE ROLE OF COMPUTED TOMOGRAPHY IN DETECTION OF TUMOUR INVASION BEYOND THE BOWEL WALL OF COLON CARCINOMAS

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Abstract

The role of computed tomography in detection of tumour invasion beyond the bowel wall of colon carcinomas

Key words: *computed tomography, colon cancer, T staging*

Introduction: Colorectal cancer is the third most common tumour in men and the second in women. It is one of the leading causes of death related to cancer. The depth of tumour invasion beyond the bowel wall (T stage) is one of the factors that affect prognosis in colorectal tumours. With current discussion about the use of neoadjuvant chemotherapy for colon cancer patients, accurate evaluation of T stage is essential for the planning of optimal therapy.

Aim: To determine the accuracy of a preoperative computed tomography (CT) scan in detection of tumor invasion beyond the bowel wall of colon carcinomas.

Materials and methods: Data on the preoperative CT scans of 101 patients, who underwent resectional curative surgery for colon cancer at the Oncology Centre of Latvia in period of 01.12.2015.-30.11.2016. were reviewed retrospectively, evaluating the T stage of the TNM system. The histopathological findings served as the reference standard. Statistical analysis was performed with SPSS.

Results: For evaluating tumour invasion beyond the musculais propria (T3/T4 vs T≤2), CT imaging had 81,2% accuracy, 90% sensitivity, 64% specificity, and the positive and negative predictive values were 84% and 75%, respectively. The T stage determined by CT and pathology had moderate agreement with a kappa coefficient of 0,481, with statistical significance (p<0,0005).

Conclusions: This study shows that CT has an overall good sensitivity of 90% for detecting, whether the tumour had invaded beyond the MP. CT can be effectively used to identify high-risk colon cancer patients and could play a role in future treatment stratification.

Kopsavilkums

Datortomogrāfijas loma resnās zarnas vēža invāzijas caur zarnas sienu noteikšanā

Ievads: Kolorektālais vēzis ir trešais visbiežāk diagnosticētais audzējs vīriešiem un otrais biežāk diagnosticētais audzējs sievietēm. Tas ir viens no vadošajiem nāves cēloņiem, saistītiem ar onkoloģiju. Audzēja invāzijas caur zarnas sienu dziļums (T stadija) ir viens no faktoriem, kas ietekmē pacienta prognozi kolorektālā vēža gadījumā. Ņemot vērā pašreizējo diskusiju par neoadjuvantas ķīmijterapijas pielietojumu resnās zarnas vēža pacientiem, precīza T stadijas novērtēšana ir būtiska optimālas terapijas plānošanai.

Mērķis: Noteikt pirmsoperatīva datortomogrāfijas (CT) izmeklējuma precizitāti, nosakot audzēja invāziju caur zarnas sienu resnās zarnas vēža gadījumā.

Materiāli un metodes: Retrospektīvi tika apskatīti 101 pacienta pirmsoperatīvo CT izmeklējumu dati, kuriem tika veikta ārstnieciska resnās zarnas vēža operācija Latvijas Onkoloģijas centrā, laika periodā no 01.12.2015.-30.11.2016., novērtējot T stadiju pēc TNM sistēmas. Histoloģiskā atradne tika izmantota kā "zelta standarts". Statistiskā analīze tika veikta ar SPSS datorprogrammu.

Rezultāti: Audzēja invāzijas caur muskuļslāni atšķiršanā (T3/T4 no T≤2), CT izmeklējums uzrādīja 81,2% efektivitāti, 90% jutību, 64% specifiskumu, pozitīva un negatīva rezultāta vērtības prognozē bija 84% un 74%, attiecīgi. Tika iegūta mērena vienošanās starp CT un histopatoloģiju, nosakot T stadiju, ar kappa koeficientu 0,481 un statistisku ticamību (p<0,0005).

Secinājumi: Šis pētījums norāda, ka CT ir augsti jutīgs (90%) nosakot, vai audzējs ir izplatījies caur zarnas sienas muskuļslāni. CT var tikt efektīvi izmantots augsta riska zarnas vēža pacientu identificēšanā, un varētu būt klīniski nozīmīgs izmeklējums ārstēšanas metodes izvēlē.

Introduction

Colorectal cancer is the second most commonly diagnosed cancer in Europe and one of the leading causes of death worldwide. It is the third most common tumour in men and the second in women, accounting for about 10% of all tumour types (Labianca et al. 2013). The depth of tumour

invasion beyond the bowel wall is one of the factors that affect prognosis in colorectal tumours (Dighe et al.2010).

Colon (or large intestine) extends from the end of small intestine to the end of anus, and is 1 to 1,65 meters long, accounting for about one fifth of whole intestinal canal lenght. Large intestine forms an arch that covers the loops of small intestine (Žagare u.c. 2010). It can be divided into 5 segments, determined by the blood supply and extraperitoneal or retroperitoneal localisation:

1) Caecum with the appendix and ascending colon;
2) Transverse colon;
3) Descending colon;
4) Sigmoid colon;
5) Rectum. (De Vita 2015).

Although in literature colorectal cancer is described as one entity, anatomical and biological factors present colon and rectal cancer as two different units in terms of treatment and prognosis (Feng-ying 2009). Considering that, rectum is not included in this study, and colon is described only till rectosigmoid junction.

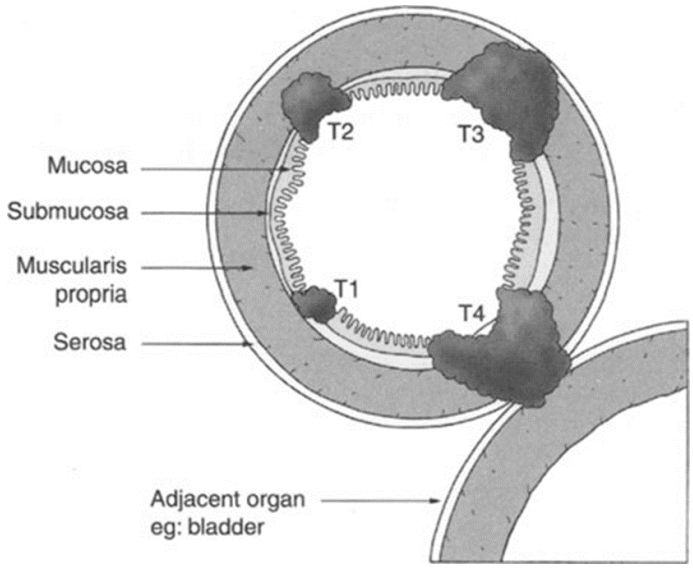
Throughout the lenght of colon, in direction from the intestinal lumen or cavity to the outside, there are four layers of wall:

1) **Mucosa** – in the cecum and colon, it is pale, smooth, destitute of villi, and raised into numerous crescentic folds which correspond to the intervals between the sacculi;
2) **Submucosa** – connects the muscular and mucous layers closely together;
3) **Muscularis propria** – consists of an external longitudinal, and an internal circular layer of non-striped muscular fibers.
4) **Serosa** – is derived from the peritoneum, and invests different portions of the large intestine to a variable extent. The cecum is completely covered by the serous membrane. The ascending, descending, and iliac parts of the colon are usually covered only in front and at the sides; a variable amount of the posterior surface is uncovered. The transverse colon is almost completely invested, the parts corresponding to the attachment of the greater omentum and transverse mesocolon being alone excepted. The sigmoid colon is entirely surrounded. The rectum is covered above on its anterior surface and sides; below, on its anterior aspect only; the anal canal is entirely devoid of any serous covering (Gray).

Radiological imaging has a role in tumour staging at the time of diagnosis, which allows to choose appropriate treatment. Colon cancer is staged with computed tomography (Tudyka et al. 2014). Tumour staging is based on the assumption that it reflects the prognosis. Staging system should identify the main prognostic features, so patients could be divided into categories with a similar outcome. This information can be further used to provide stage-specific treatment (Chapman

2004). TNM classification is being used for staging of colon carcinomas, developed by American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), in which the local invasion of tumour (T stage) is divided as follows:

- **Tx**- Primary tumor can not be assessed;
- **T0**- No evidence of primary tumor;
- **Tis**- Carcinoma in situ: intraepithelial or invasion of lamina propria;
- **T1**- Tumor invades submucosa;
- **T2**- Tumor invades muscularis propria;
- **T3**- Tumor invades through the muscularis propria into the pericolorectal tissues;
- **T4a**- Tumor penetrates to the surface of the visceral peritoneum;
- **T4b**- Tumor directly invades or is adherent to other organs or structures (Compton 2017).



Picture 1. **Cross-section of colon. Local tumor invasion (T stage) classification**

Source: Chapman, A.H., Radiology and Imaging of the Colon. In: Medical Radiology. Diagnostic Imaging and Radiation Oncology., Berlin–Heidelberg: Springer Verlag, 2004, p. 51-147.

A diagramm of local tumor invasion is shown on Picture 1. It shows that T1 and T2 stage tumors are limited by muscularis propria, T3 stage tumor has invaded through muscularis propria and T4 stage tumor has also invaded adjacent organ, in example, bladder.

Neoadjuvant drug therapy has the potential to reduce local and distant failure of treatment for high-risk colon cancer by preoperative downsizing of the primary tumour and allowing earlier action for undetected micrometastatic disease. It could also potentially reduce tumour cell shedding at the time of surgery, a process thought to contribute to dissemination of tumour cells (Nelson et al. 2001). Unlike in rectal cancer cases, neoadjuvant therapy is not usually done for colon cancer patients (Krūmiņš u.c. 2013), and the staging is performed mainly to determine operability on the

basis of tumour ingrowth into surrounding structures and the presence of distant metastases (Nerad et al. 2016). However, neoadjuvant treatment might be added in the guidelines for colon cancer treatment, as a large trial (FOxTROT) is currently evaluating the role of neoadjuvant therapy in CT-defined high-risk colon cancer patients, where tumour invasion beyond the muscularis propria (T3-T4 stage tumour) is considered as high-risk colon cancer. These patients could benefit from neoadjuvant chemotherapy (FoxTROT Protocol 25/11/2015), so accurate evaluation of T stage is essential for the planning of optimal therapy.

Aim

The aim of this study was to determine the accuracy of a preoperative computed tomography (CT) scan in detection of tumor invasion beyond the muscularis propria of colon carcinomas (T3-T4 stage of the TNM system).

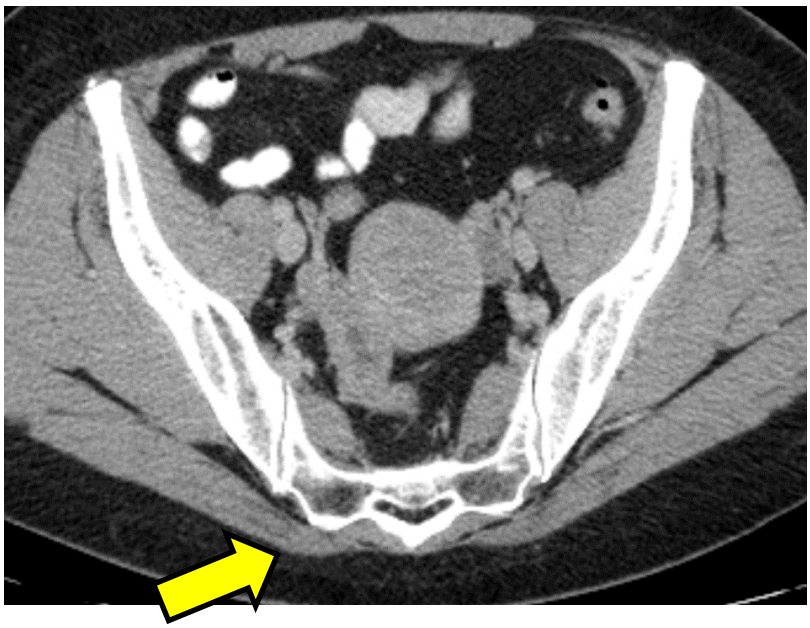
Materials and methods

Data on the preoperative computed tomography (CT) scans, performed at Riga East university hospital (RAKUS) stationary "Oncology Centre of Latvia" for patients with diagnosis of colon cancer (C18 after ICD-10 classification) and rectosigmoid junction (C19 after ICD-10), who underwent resectional curative surgery for colon cancer at the Oncology Centre of Latvia in period of 01.12.2015.-30.11.2016. were reviewed retrospectively. Presence and site of neoplasm were assessed, in addition to the depth of tumour invasion. Using certain CT criteria, tumour spread (T stage of the TNM system) was evaluated. The used CT criteria for T stage evaluation were following: adressing known limitations at CT in distinguishing between T1 and T2 lesions, they were combined to represent one T stage- T≤2. Tumours were staged as T≤2 in case of a thickened colon wall with smooth outer border and a clear surrounding fat plane, as T3 if there was a smooth or nodular extension of a discrete mass and disruption of the muscle coat with extension into pericolic fat, and as T4, if obliteration of fat planes between tumour and adjacent organs was seen (see Table 1).

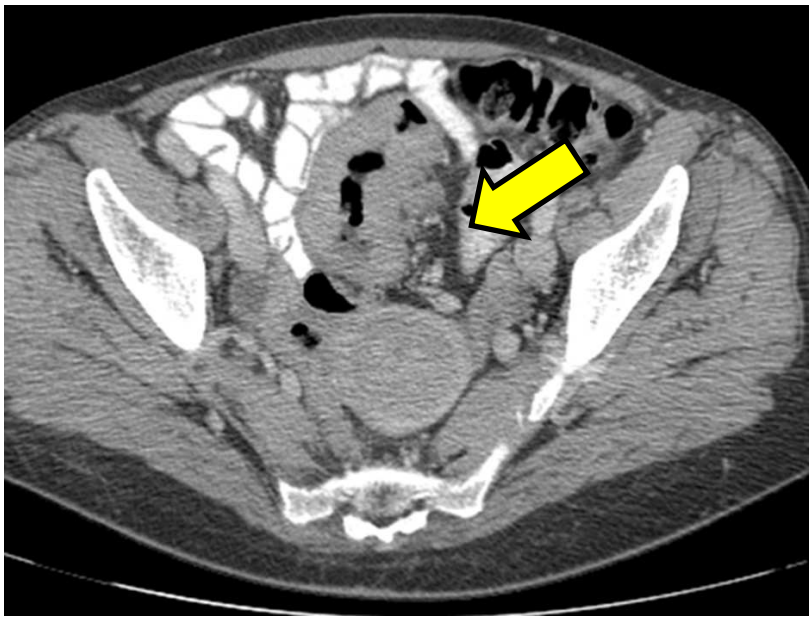
Table 6. **CT criteria used for each T stage evaluation**

Stage		CT criteria
T stage	T≤2	Thickened colon wall with smooth outer border and a clear surrounding fat plane
	T3	Smooth or nodular extension of a discrete mass and disruption of the muscle coat with extension into pericolic fat
	T4	Obliteration of fat planes between tumour and adjacent organs

This is how the used criteria looks on CT images, obtained from the study:



Picture 2. **T≤2 stage tumor on CT- tumor of rectosigmoid junction with smooth outer border and a clear surrounding fat plane**



Picture 3. **T3 stage tumor on CT- tumor of sigmoid colon with nodular outer margin and infiltration into pericolic fat**

T stage determined by CT was then compared with histopathological pT stage of the resected colon specimen, which was used as the reference standard. The findings were compiled, using Microsoft Office Excel software and statistical analysis was performed with IBM SPSS 22. True positive, true negative, false positive and false negative results were determined and sensitivity, specificity, accuracy, positive predictive values (PPV) and negative predictive values (NPV) were calculated. Agreement between CT and histopathology was assessed by Cohen's kappa coefficient, with k value of <0,81 defined as almost perfect agreement, and values of 0,61-0,80 and 0,41-0,60 defined as substantial and moderate agreement, respectively.

Results

A total of 101 patients were included in this study, aged 40 to 92 years old, with mean age of 68,4 (SD= 9,7). There were 59 (58,4%) male and 42 (41,6%) female patients. The greatest prevalence of the disease was found in age group of 60-79 years. In 56 (55,4%) cases tumour was localised in sigmoid colon and rectosigmoid junction, in 10 cases (9,9%)- in descending colon/splenic flexure, in 11 cases (10,9%)- in transverse colon/hepatic flexure and in 24 cases (23,8%) – in ascending colon/caecum tumour localisation (see Table 2).

Table 7. **Demographics of patients included in the study**

Age	Min – max	40-92
	Mean	68,4
Sex	Male	59 (58,4%)
	Female	42 (41,6%)
Tumor site	Sigmoid colon / rectosigmoid junction	56 (55,4%)
	Ascending colon/ caecum	24 (23,8%)
	Transverse colon / hepatic flexure	11 (10,9%)
	Dexcending colon / splenic flexure	10 (9,9%)

Out of 101 tumours, there were 68 T3-T4 stage tumours detected on histopathology, and 61 of them were correctly staged by CT. There were 61 true positive, 12 false positive, 7 false negative and 21 true negative cases (see Table 3).

Table 8. **Accuracy of CT in detection of local tumour invasion (T stage)**

		T stage determined by histopathology		Total
		pT≤2	**pT3-T4**	
T stage determined by CT	**T≤2**	21	7	28
	T3-T4	12	61	73
Total		33	68	101

CT and histopathology had a moderate agreement for T stage evaluation, with a kappa coefficient of 0,481, with statistical significance (p<0,005).

In results, for evaluating tumour invasion beyond the musculais propria (T3/T4 vs T≤2), CT imaging had 81,2% accuracy, 90% (95% CI, 80-96%) sensitivity, 64% (95% CI, 45-80%) specificity, and the positive and negative predictive values were 84% (95% CI, 76,3-89%) and 75% (95% CI, 59-86%), respectively (see Table 4).

Table 9. **Accuracy of CT in detection of tumour invasion beyond the MP (stage T3-T4)**

Parameter	**Stage T3-T4 (n=68)**
Sensitivity	90%
Specificity	64%
Accuracy	81%
Positive predictive value	84%
Negative predictive value	75%

Discussion

Study population consisted of 101 patients, of which 58,4% were males and 41,6%- females. It coincides with literature data, that claims greater colon cancer incidence in men. The greatest prevalence of disease was seen in age group of 60-79 years, which is a part of colorectal cancer screening population in Latvia. The frequency of tumour localisation in this study group corresponds to literature data- the most frequent tumour localisation was sigmoid colon and rectosigmoid junction, followed by caecum and ascending colon, trasnverse colon and hepatic flexure, descending colon and splenic flexure in descending order. For identifying tumour invasion beyond muscularis propria (stage (T3-T4), CT is highly sensitive (90%) but with lower specificity (64%). The obtained results is equivalent to 2016 meta-analysis, in which the acquired sensitivity was 90% and specificity of 69% (Nerad E., et al., 2016). The low value of specificity can be explained by inability of CT to distinguish benign desmoplastic reaction (T2 stage) from infiltration of fat planes (T3), which is a well known problem in colon cancer staging (Wegener O.H., 1992). However, the high values of sensitivity and positive predictive value (84%) are considered to be clinically useful and proves the significance of CT in selecting patients with high risk colon cancer, who could benefit from neoadjuvant chemotherapy.

Conclusions

- The greatest colon cancer prevalence is in age group of 60-79 years, and the incidence is higher ir men.
- The most frequent tumour site is sigmoid colon and rectosigmoid junction.
- This study shows that CT has an overall good sensitivity of 90% for detecting tumour invasion beyond the muscularis propria.
- This high value of sensitivity is considered clinically useful.
- CT enables accurate identification of high-risk colon cancer patients (stage T3-T4), who could benefit from neoadjuvant chemotherapy, if it would be added in guidelines for colon cancer management.

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DEPRESSION AND ANXIETY AMONG STUDENTS COMPARED NOT-STUDYING YOUNG PEOPLE

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Abstract
Key words: *Depression, anxiety, students, young people*
Introduction: Anxiety is the most common mental health diagnosis in students' population. But depression is a common mental disorder worldwide, with an estimated 350 million people affected (WHO, 2016). Depressive disorders reach its peak in people who are in their twenties to early thirties.
The aim of the study was to determine existence of depression and anxiety among students and compare it to the people in the same age who are not studying.
Methods and materials: In the study was used self-reported questionnaire. Depression was assessed by the Patient Health Questionnaire PHQ 9, but anxiety by the Taylor Manifest Anxiety Scale (Taylor, 1953). Statistical data was processed in MS Excel and IBM SPSS Statistics.
Results: 231 respondents took part in this study. 67,1% (n=155) of them were women and 32,9% (n=76) men. Mean age was 25,3 years (SD=3,5). Depressive symptoms were observed in 58% respondents. High level of anxiety were in 51,9% respondents, but 45,5% of respondents - moderate anxiety. 43,3% (n=100) of respondents were students, 56,7% (n=131) were non-students, but 75% were employees. 59% of students were working too.
There was no statistically significant correlation between students and prevalence of depression or anxiety ($p > 0,05$). Employees had a statistically significant correlation with a prevalence and severity of depression. Respondents who had an employment, they had significantly rarer depression symptoms than not-working young people ($p<0,05$). Students who were working had no statistically significant difference of prevalence of depression or anxiety compared to not-working students.
Conclusion: There was no significant difference between students and non-students. In both groups' anxiety and depression prevalence was high.

Kopsavilkums
Atslēgas vārdi: *Depresija, trauksme, studenti, jauni cilvēki*
Kopsavilkums: Trauksme ir viena no biežākajām psihiskām diagnozēm studentu vidū. Toties depresija ir plaši izplatīta garīga saslimšana visā pasaulē, kas skar aptuveni 350 miljonu cilvēku. (PVO,2016). Depresijas saslimstība sasniedz augstāko saslimšanas pīķi otrā un trešā dekādē.
Pētījuma mērķis ir noskaidrot depresijas un trauksmes izplatību jaunu cilvēku vidū un salīdzināt depresijas un trauksmes biežumu starp studentiem un nestudējošiem jauniem cilvēkiem vienā vecuma grupā.
Metodes un materiāli: Pētījumā tika izmantotas individuāli aizpildāmas jautājumu aptaujas anketas. Depresija tika novērtēta, izmantojot depresijas pašnovērtēšanas anketu, bet trauksme tika novērtēta, izmantojot Trauksmes izpausmju skalu. Statistiskā datu analīze tika veikta ar MS Excel and IBM SPSS Statistics.
Rezultāti: Pētījumā piedalījās 231 dalībnieks, no tiem 67,1% (n=155) bija sievietes, bet 32,9% (n=76) bija vīrieši. Vidējais vecums bija 25,3 gadi (SD=3,5). Depresijas simptomus novēroja 58% respondentu. Augsta līmeņa trauksme konstatēta 51,9% pētījuma dalībnieku, bet 45,5% respondentu – vidēja līmeņa trauksme. 100 respondentu jeb 43,3% bija studenti, 131 jeb 56,7% no aptaujātiem nebija studenti. 75% no visiem aptaujātiem dalībniekiem ir nodarbināti, toties studentu grupā nodarbināti un algotu darbu strādā 59%.
Pētījumā netiek konstatēta statistiski nozīmīga korelācija starp studentiem un trauksmi, un depresiju ($p>0,05$). Atrasta statistiski nozīmīga saistība starp algotu darbu un depresijas biežumu un smaguma pakāpi. Pētījuma dalībniekiem, kuri ir nodarbināti un strādā algotu darbu, retāk konstatēti depresijas simptomi kā nestrādājošiem aptaujātajiem ($p<0,05$). Toties studentiem, kuri paralēli arī strādā, nav novērota statistiski nozīmīga starpība trauksmes un depresijas izplatībā salīdzinot ar nestrādājošiem studentiem.
Secinājumi: Pētījumā netiek konstatēta nozīmīga atšķirība starp studentiem un nestudējošiem jauniem cilvēkiem vienā vecuma grupā. Abās grupās novērota augsta trauksmes un depresijas sastopamība.

Introduction

Young people go under a significant stress when they start to study in universities because of pressure on them: career, being on your own in a new environment in a different study place, relation changes with family, changes in social life and new friends. Because of the challenges

faced when adapting to these life changes, students are at risk of developing anxiety and depression (Sharma et al 2013). The American College Health Association– National College Health Assessment – a nationwide survey of college students at 2- and 4-year institutions – found that about 30% of college students reported feeling "so depressed that it was difficult to functioning" at some time in the past year. Depression could affect student's academic performance in the university. Many studies have shown sex differences in prevalence - more of depression, less of anxiety. Women report more symptoms of depression than males (Sharma et al 2013).

Depression is a common mental disorder worldwide, with an estimated 350 million people affected (WHO 2016). Mental health disorders are one of the leading causes of disability worldwide. At its worst, depression can lead to suicide. Suicide is the second leading cause of death in 15-29-year-olds (WHO 2017).

Anxiety is a physiological and psychological state characterized by emotional, cognitive, somatic and behavioral components. It combines to create an unpleasant feeling such as uneasiness, fear or worry (Wahed et al 2017). Anxiety is a generalized mood condition that occurs without an identifiable triggering stimulus, while many symptoms of depression include, persistent sad, anxious or "empty" feelings, feelings of hopelessness, feelings of guilt, worthlessness and/or helplessness, irritability, restlessness, and loss of interest in activities or hobbies once pleasurable (Wahed et al 2017).

Anxiety is the most common mental health diagnosis in college students (Brown 2016). American College Health Association (ACHA) 2015 National College Health Assessment survey reported that nearly one in six college students (15.8%) had been diagnosed with, or treated for anxiety. High rates of psychological morbidity among students, such as anxiety and depressive symptoms, have been reported in several studies from different western countries (Dahlin et al 2005). The 2010 Global Burden of Disease Study mentioned depressive disorders reaches its peak in people who are in their twenties to early thirties.

The prevalence of depression and anxiety in lifetime among adolescents and young adults worldwide is currently estimated from 5% to 70%. Some other studies have maintained that up to 25% of all young adults will experience a depressive episode by the age of 24 years. (Sahoo et al 2010) That is the highest prevalence of any adult age-group (Young et al 2001). Similarly, there had been with variations in prevalence of anxiety disorders reported (Sahoo et al 2010).

The aim of the present study was to determine prevalence of depression and anxiety among students and to compare prevalence of depression and anxiety to the people in the same age who are not studying.

Material and Methods

The target population included young people who are studying or not studying. A cross-sectional study conducted of 231 young people who answered to the self-reported questionnaire via internet. Of the total sample, 155 were women and 76 were men. The mean age was 25,3 years and SD of 3,5. Approval of the study was obtained from the Ethics Committee at Rīga Stradiņš University. Before questionnaire were explained a study and asked an informed consent. Depression was assessed by the Patient Health Questionnaire PHQ-9, but anxiety was assessed by Manifest Anxiety Scale. Patient Health Questionnaire PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression. It corporate DSM-V diagnostic criteria of depression and it is useful in clinical practice (PHQ-9 overview, 2001). Manifest Anxiety Scale a measure used to assess chronic, manifest anxiety in adults. Therefore, it used to assess common manifestations of anxiety found among individuals of different age groups (Lowe et al, 2007). Reliability of the two scales is considered adequate and test-retest reliability is likewise considered adequate with 0.81 for anxiety and 0.854 for depression (Zhang et al 2013).

Statistical data was processed in MS Excel, using Statistical Package for the Social Sciences (IBM SPSS Statistics). The data were scored and Descriptive statistics like mean and SD was calculated. Significances were calculated using Pearson's chi-squared test. A p value less than or equal to 0.05 was considered statistically significant.

Results

231 respondents participated in this study. 67,1% (n=155) of them were women and 32,9% (n=76) men. Mean age was 25,3 years (SD=3,5). Figure 1[i] shows the distribution of the participants who have shared in the study. 43,3% of participants were students, 56,7% were non-students, but 88,5% of non-student's group were employee. 59% (n=59) of all students also were working. A total respondents who had an employment were 75,8% or 175 participants. Table 1[ii] and table 2[iii] show data about participants' marital status and education level at the study performance moment.

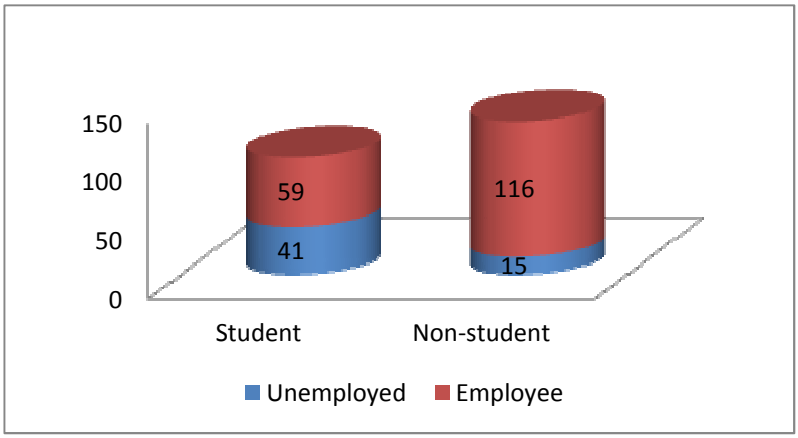

Figure 1. **Participants' occupation (n=231)**

Table. 1 **Marital status**

	Frequency	Percent
Married	40	17.3
Living common law	58	25.1
Single	130	56.3
Divorced	2	0.9
Widowed	1	0.4
Total	231	100.0

Table 2. **Levels of education (n=231)**

	Frequency	Percent
Proffesional degree	38	16.5
Bachelor degree/master degree	61	26.4
Other	2	0.9
Doctoral	1	0.4
Master	22	9.5
Incomplete higher education	40	17.3
Primary education	5	2.2
Secondary education	34	14.7
Secondary proffessional	28	12.1
Total	231	100.0

Depressive symptoms were observed in 58% of study participants. High and moderate levels of anxiety were in 97,4% respondents. (Show in figure 2[iv] and figure 3[v]).

There was no statistically significant correlation between students and prevalence of depression or anxiety ($p > 0,05$). Employees had a statistically significant correlation with a prevalence and severity of depression. Respondents who had an employment, they had significantly rarer depression symptoms than not-working young people ($p<0,05$). Students who were working had no statistically significant difference in prevalence of depression or anxiety compared to not-working students. Results of this study show no difference between women and men in prevalence of depression or anxiety.

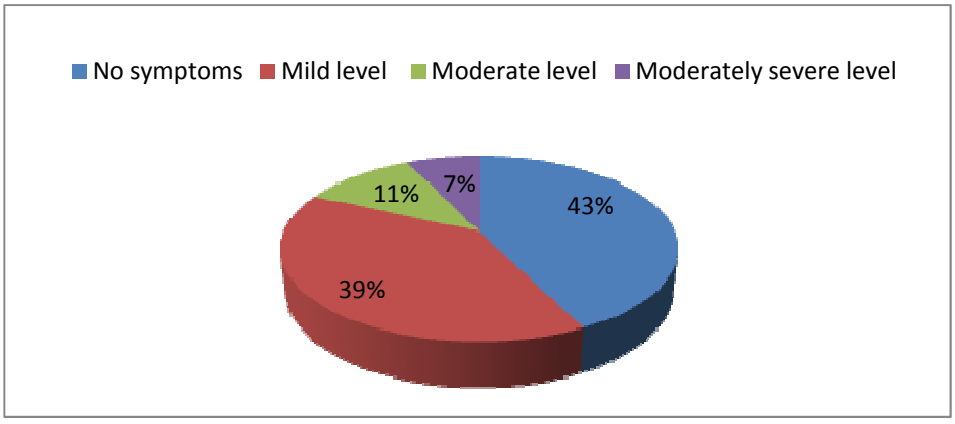

Figure 2. **Severity of depression (n=231)**

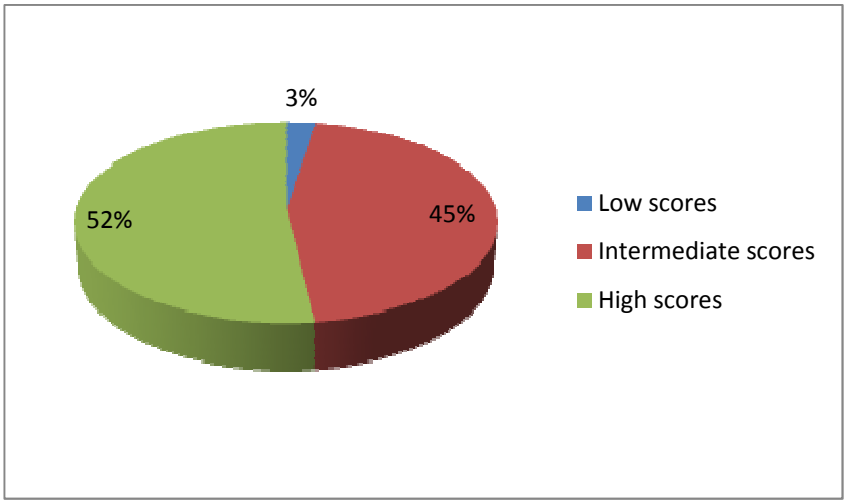

Figure 3. **Scores of anxiety (n=231)**

Discussion

In the study the prevalence of depression and anxiety was detected among 58% and 97,4%. It is higher than in the general population in Latvia: using data form survey Health Behavioral among Latvian adult population – depressive symptoms observed only 9,14%, but anxiety symptoms observed only 27%. Depression and anxiety in students' population is similar as in other studies. Therefore, might be that these results did not show a correlation between studying and depression and anxiety because of higher prevalence of depression and anxiety in a target population. As a risk factors of depression and anxiety disorder was described a certain personality traits, such as low self-esteem and being too dependent, self-critical or pessimistic which have more common occurrence in young people.

The correlation between students and depression or anxiety was conflicting. However, not all studies show similar findings. In this study there was no significant difference between students and young people non-students. In both groups the anxiety and depression prevalence were high. This justifies the need for more studies.

Besides, methodological issues (including sample size and target population, methods of the study) and confounding factors such as unrelated factor as a reason like trauma in childhood, hereditary, early life experiences etc. could also be the reason of inconsistent findings.

Conclusions

Findings of this study provide evidence that the current investigation revealed higher rate of depression and anxiety among young people comparing with general young people population. Depression and anxiety are present up to 50% of all young people without gender differences whether if they study in the university or college or not.

Acknowledgement

We thank Riga Stradiņš University Statistics Unit and people who shared in the study.

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[i] Data from study "Depression and anxiety among students compared not-studying young people", using descriptive statistics
[ii] Data from study "Depression and anxiety among students compared not-studying young people", using descriptive statistics
[iii] Data from study "Depression and anxiety among students compared not-studying young people", using descriptive statistics
[iv] Data from study "Depression and anxiety among students compared not-studying young people", using descriptive statistics
[v] Data from study "Depression and anxiety among students compared not-studying young people", using descriptive statistics

SUICIDE RISK AMONG PARANOID SCHIZOPHRENIA PATIENTS WITH DEPRESSION

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Abstract
Key words: *Paranoid schizophrenia, depression, suicide risk*
Introduction: Paranoid schizophrenia (PS) is one of the most severe mental disorders and approximately 1.1% of the population suffer from it worldwide. A significant problem is the high rate of committed suicides among persons with PS (Simeone et al. 2015). In the research, 25% of the patients have depression when the productive symptomatics of PS decrease. It is necessary to differentiate between negative symptoms and depression, because it is proved that the risk of committing suicide among people who suffer from depression is 6-15%, however in the case of PS – even up to 38% (Mensi et al. 2016).
Aim: To detect the association between the depression severity and suicide risk among PS patients.
Material and methods: The interview consists of sociodemographic information, Calgary Depression Scale for Schizophrenia (CDSS), Columbia – Suicide Severity Rating Scale
(C–SSRS). Data is statistically processed in Microsoft Excel and SPSS 20.
Results: 44 questionnaire respondents, 22 females (50%) and 22 males (50%). Minimal age is 24 years, maximal age - 68 years; median - 43 years. Spearman's rank correlation established statistically significant correlation between the depression severity according to the CDSS and suicide risk according to the C-SSRS (R=0.540, p=0.000). Depression was detected in 30 (63,3%) and the suicide risk in 19 (43%) of all the patients. Most of the patients - 33 (79.5%) suffer from the stable PS. The reminding 9 patients have episodic PS with increasing or stable residual symptoms. 8 of these 9 patients are females. During two independent sample T-tests it was established that the average score in accordance with the CDSS for males and females varies by 3.9 points. This difference is statistically significant (p=0.005), the level of depression is higher among females. Also the average score according to the C-SSRS for patients with a stable course and episodic course of PS varies by 1.14 points. This difference is statistically significant (p=0.038), and the suicide risk is higher among patients with episodic course of PS.
Conclusions: There is a high prevalence of depression among patients with PS, and the suicide risk among them is high. There is a strong correlation between the severity of depression and the suicide risk. Females with PS are more susceptible to depression and suffer more often also from episodic PS with residual symptoms; males are most likely to be susceptible to the stable form of PS and the risk of depression and suicide is lower. The rate of depression is undeniably important and attention should be paid to this aspect when treating the patients.

Kopsavilkums
***Atslēgas vārdi*:** *Paranoīda šizofrēnija, depresijas smagums, suicīda risks*
Ievads: Šizofrēnija ir viena no smagākajām psihiskajām slimībām, ar kuru slimo apmēram 1.1 % iedzīvotāju visā pasaulē. Nozīmīga sabiedriska un medicīniska problēma ir augstais pabeigtu pašnāvību skaits šizofrēnijas pacientiem (Simeone JC et al. 2015). Mazinoties šizofrēnijas produktīvai simptomātikai, pētījumos 25 % pacientu ir depresijas simptomi. Paranoīdās šizofrēnijas gadījumā ir svarīgi diferencēt negatīvo simptomātiku un depresiju, jo pierādīts, ka pašnāvības izdarīšanas risks dzīves laikā cilvēkiem, kuriem konstatēta depresija ir 6-15 %; šizofrēnijas gadījumā – līdz pat 38 %. (Mensi et al. 2016).
Mērķis: Noteikt korelāciju starp depresijas smagumu un suicīda risku paranoīdās šizofrēnijas pacientiem RPNC.
Materiāli un metodes: Pacientu intervijas, kurās ietilpst: sociodemogrāfiskie jautājumi, Calgary Depression Scale for Schizophrenia (CDSS), Columbia – Suicide Severity Rating Scale (C – SSRS). Dati statistiski apstrādāti EXCEL un SPSS 20. datorprogrammās, izmantojot aprakstošo statistiku un Spīrmena korelācijas koeficientu.
Rezultāti: 44 respondenti; 22 sievietes (50%) un 22 vīrieši (50%). Minimālais vecums ir 24 gadi, maksimālais - 68, mediāna - 43, biežākais sastopamais vecums – 27 gadi. Spīrmena korelācijas koeficienta aprēķins parādīja statistiski ticamu korelāciju starp depresijas smagumu pēc CDSS un suicīda risku pēc C-SSRS (R=0,540, p=0,000). Klīniski depresija pastāv 31 (70,5%) un no tiem suicīda risks - 20 (45,5%) pacientiem. Depresijas līmenis ir augstāks sievietēm: mode 12, mediāna 11,00, maksimums 22; vīriešiem mode 5, mediāna 6,00, maksimums 16. Lielākajai daļai pacientu (35 jeb 79,5%) ir nepārtraukta paranoīdā šizofrēnija, pārējiem 9 pacientiem ir epizodiska šizofrēnija ar pieaugošām vai stabilām reziduālām parādībām. 8 no šīm 9 pacientiem ir sievietes. Divu neatkarīgo izlašu t-testā konstatēja, ka vidējais punktu skaits pēc CDSS vīriešiem un sievietēm atšķiras par 3,9 punktiem, šī atšķirība ir statistiski ticama (p=0,005), depresijas līmenis ir augstāks sievietēm. Arī vidējais punktu skaits pēc C-SSRS pacientiem ar paranoīdas šizofrēnijas stabilu gaitu un epizodisku gaitu atšķiras par 1,14 punktiem, šī atšķirība ir statistiski ticama (p=0,038) un suicīda risks ir augstāks pacientiem ar šizofrēnijas epizodisko gaitu.

Secinājumi: Šizofrēnijas pacientiem depresija ir bieži sastopama un suicīda risks ir augsts. Depresijas smagums un suicīda risks pacientiem ar šizofrēniju ir cieši saistīts. Vairāk pakļautas depresijai ir sievietes ar šizofrēniju, kā arī sievietēm biežāk sastopama epizodiska šizofrēnija ar reziduālām parādībām; vīriešiem – pamatā nepārtrauktās šizofrēnijas forma un zemāks depresijas un suicīda risks. Depresijas rādītājs ir neapšaubāmi svarīgs un šim aspektam būtu jāpievērš uzmanība, aprūpējot pacientus.

Introduction

Schizophrenia is one of the severest psychic diseases affecting about 1% of word population (Sadock et al. 2009). According to the last epidemiologic data from Europe, 12-months prevalence of schizophrenia is 1.2% that means that each year in the European countries this disease affects up to 5 million people (Witchen et al. 2010).

Significant public and medical problem is high number of completed suicides in schizophrenia patients. Is has shown that the risk of suicide during one's life in people with diagnosed depression is 6-15%; in case of schizophrenia – 10% (even up to 38%) of mortality of schizophrenia patients (Semple et al. 2013). It is found that 30% of patients with paranoid schizophrenia have also depression syndrome that increases suicide risk (Hasan et al. 2012). While productive symptoms decrease 25% of patients have depression symptoms. In studies ~ 160 of 270 suicides is done in depressive state (Semple et al. 2013). In the case of paranoid schizophrenia, more attention should be paid to negative symptoms which are decrease in energy and activity, increase of anhedonia, social isolation, dysfunction. These symptoms are similar to depression, however Calgary Depression Scale for Schizophrenia (CDSS) allows specifying depression exactly in schizophrenia patients by specific, criteria of depression of exactly this diagnosis.

The most common mortality causes in schizophrenia patients are infectious diseases (4.3 %), diseases of the nervous system (4.2 %), urogenital system (3.7 %) and respiratory system (2.2 %) but the highest risk is to die from suicide (12.8 %). Especially increased suicide risk is during the first disease year (the longer is disease, the lesser risk of suicide) (Anthes et al. 2014); in case of early disease relapse: >30 % of repeated exacerbation is within the first 12-18 months after the first episode, 50% - within two years, 80% - within 5 years. Approximately in a quarter of the patients schizophrenia course with repeated exacerbation may be predicted. However people with schizophrenia of continuous course may have good functioning if appropriate support and help is given (NICE guidelines 2014).

Specific risk factors of suicide are the following: age up to 30-40 years, more often in male, more often in unemployed, frequently repeated exacerbation of the disease, previous attempts of suicide and autoaggression (for 75% increases risk of relapse), addiction, stress situations (Tērauds et al. 2014).

Paranoid schizophrenia F20.0 – most commonly diagnosed form of schizophrenia. Time criteria: duration of the symptoms – a month.

Clinical picture: positive symptoms: paranoid (relationship, persecution, influence) delirium, threatening, imperious verbal pseudohallucinations, psychic automatisms (expanded or as separate symptoms), less commonly – smell or taste hallucinations.

Primary negative symptomatology in case of paranoid schizophrenia is possible, however more often intensity of the negative symptomatology increases with each exacerbation. In case of schizophrenia of continuous paranoid schizophrenia, treatment results only in decrease in intensity of the positive symptoms but fails to achieve complete recovery characterized for patients with episodic disease course (The ICD-10 1993).

The aim of the work is to found correlation of depression and risk for suicide in patients with paranoid schizophrenia. Forehanded determination of suicidal tendencies and active psychological, social and pharmacologic help is an important aspect of their prevention.

Material and methods

The study was performed from 26.01.2017 till 26.03.2017 in acute psychiatric unit of Riga Psychiatry and Narcology center (RPNC). During this retrospective cohort study was interviewed 44 patients. Inclusion criteria for participation in the study were paranoid schizophrenia diagnosis (F20) according International Classification of Diseases, tenth edition (ICD-10); one or more hospitalizations due to schizophrenia in anamnesis; age 18 and over. Exclusion criteria were other co morbid diagnosed somatic or neurological diseases.

Patients with more than one hospitalization were included in order to avoid cases when the diagnosis of schizophrenia falsely could be made in the presence of extensive depressive symptoms unless it is clear that schizophrenic symptoms antedate the affective disturbance. Patients with other co morbid somatic or neurological diseases were excluded, because other diseases can enforce affective disturbances or cause it by themselves.

The presence of depression and suicide risk were evaluated with Calgary Depression Scale for Schizophrenia (CDSS) and Columbia-Suicide Severity Rating Scale (C-SSRS). Also patients were asked about their marital status, education, employment and drugs or alcohol using. The year of schizophrenia onset and numbers of hospitalizations due to schizophrenia were available in medical documentations.

The aim of CDSS is assessment of depressive symptoms separately from positive, negative and extrapyramidal symptoms in people with schizophrenia. It has 9 questions and all ratings of the items are defined according to operational criteria from 0-3 and time frame refers to last two weeks unless stipulated. The CDSS depression score is obtained by adding each of the item scores. All cases with score 6 or more according CDSS were defined as “depression”, less than 6 – “no depression”. A score above 6 has an 82% specificity and 85% sensitivity for predicting the presence

of a major depressive episode. C-SSRS has 6 questions; 3 answers of "yes" to any of the six questions indicate the presence of the suicide risk.

Data is statistically processed in SPSS 20 using Spearman's Rank Correlation Coefficient, Independent Samples t-test and descriptive statistics.

Descriptive statistics were used to describe socio-demographic variables for all population. The variables were gender, suicide risk, depression rate, the subtype of paranoid schizophrenia, marital status, employment, drugs/alcohols using.

The correlation between CDSS and C-SSRS was evaluated using Spearman's Correlation Coefficient to test the association between two ranked variables. Also was evaluated the correlation between the frequency of hospitalization and depression severity. Frequency of repeated hospitalizations was obtained based on the information about the year of the onset the total number of hospitalizations. In other words, the total number of hospitalizations is divided by the duration of the disease in months. The frequency of hospitalizations is important index that indicates the severity of disease course. Rejection of zero hypothesis and acceptation of alternative hypothesis was based on trustfulness level of the statistic hypothesis $p < 0.05$. T-test was used for comparison of mean values of two independent selections.

Then cases were divided into 2 groups based on the gender. The difference of suicide risk and depression severity between two groups was investigated using two independent samples T-Test. Further all cases were divided into "stable" and "unstable" schizophrenia's groups, the suicide risk and depression rate in them was also compared using two independent samples T-Test.

The depression level was also compared between alcohols/drug users and non-users groups. T-test measures a difference between means of two samples.

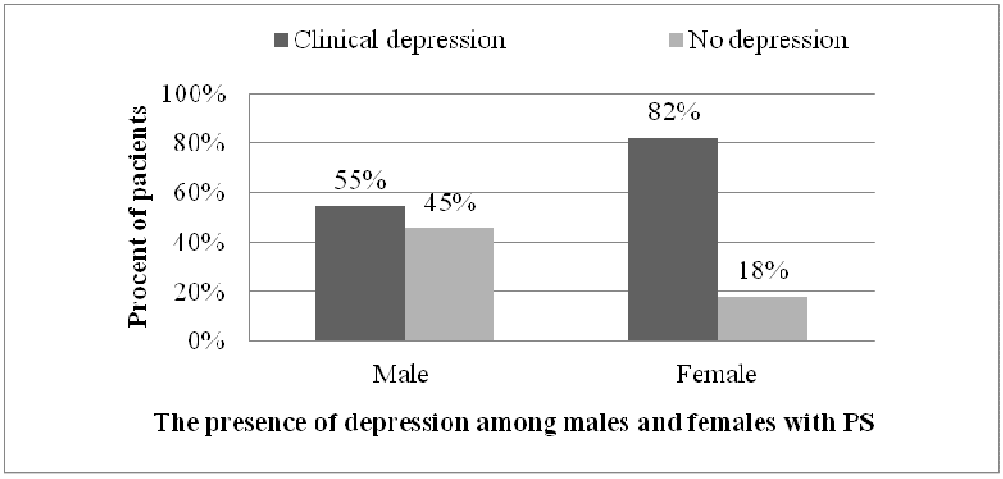
This work was carried out with the ethical approval of Riga P.Stradiņš university (RSU) Ethic committee. Researchers accessed processed and analyzed anonymized data. Identity and confidentiality of the patients were protected.

Results

44 questionnaire respondents, 22 females (50%) and 22 males (50%). Minimal age is 24 years, maximal age - 68 years; median - 43 years. 22 patients (50%) have primary education, 21 patients (45,5%) have secondary education, 1 patient (2,3%) have higher education. The average score of depression level in accordance with the CDSS for different educational level didn't compared due to lack of respondents with higher education. All patients are unemployed. 16 patients (36,4%) are single, 20 patients (45,5%) are divorced, 7 patients (15,9%) married, 1 patient (2,3%) is widow(er). 24 patients (54,5%) don't use alcohol or drugs, 20 patients (45,5%) regularly use alcohol or drugs.

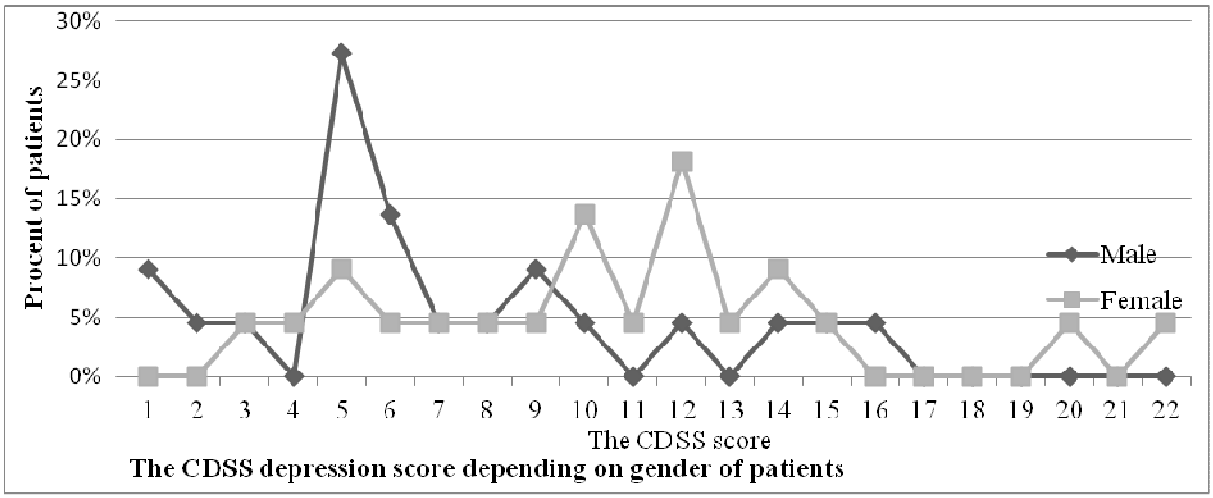
During two independent sample T-test it was established that the average score of depression severity in accordance with the CDSS for alcohol/drugs users and non-users is completely equal (9 points) and is statistically reliable (p=0,000). Drugs/substance using don't correlate with depression severity.

Spearman's rank correlation established statistically significant correlation between the depression severity according to the CDSS and suicide risk according to the C-SSRS (R=0.540, p=0.000). Depression was detected in 30 (63,3%) and the high suicide risk in 19 (43%) of the patients, Females with paranoid schizophrenia more likely have depression than men with paranoid schizophrenia. Only 12 (54,4%) males have clinical depression (6 or more points), among females clinical depression have 18 (81,8%) patients. The mean score for women is 10,95, for men – 7,05.



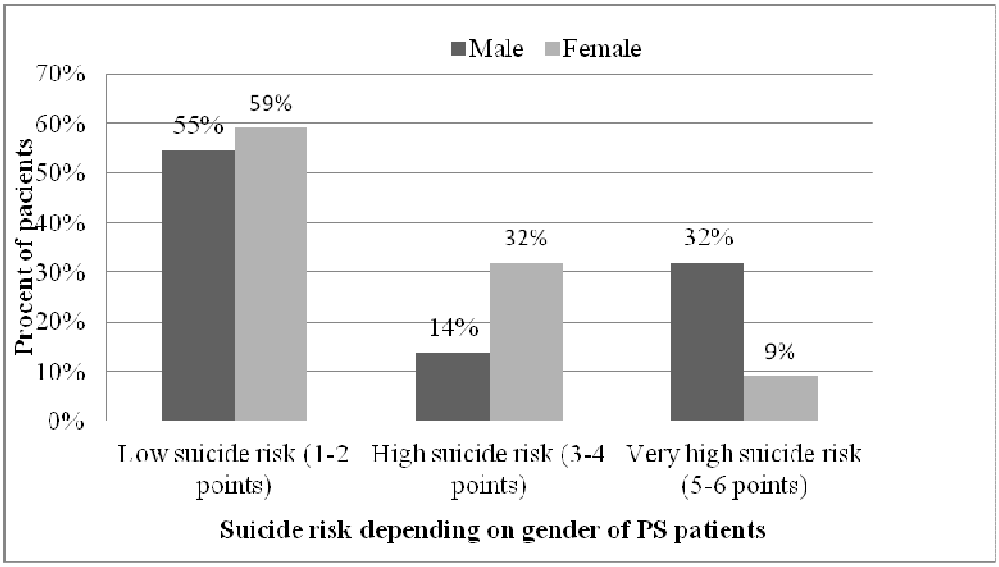
The presence of depression among males and females with PS

This graph shows the difference between the depression severity among female and male paranoid schizophrenia patients. Score 6 and more indicates clinically significant depression:

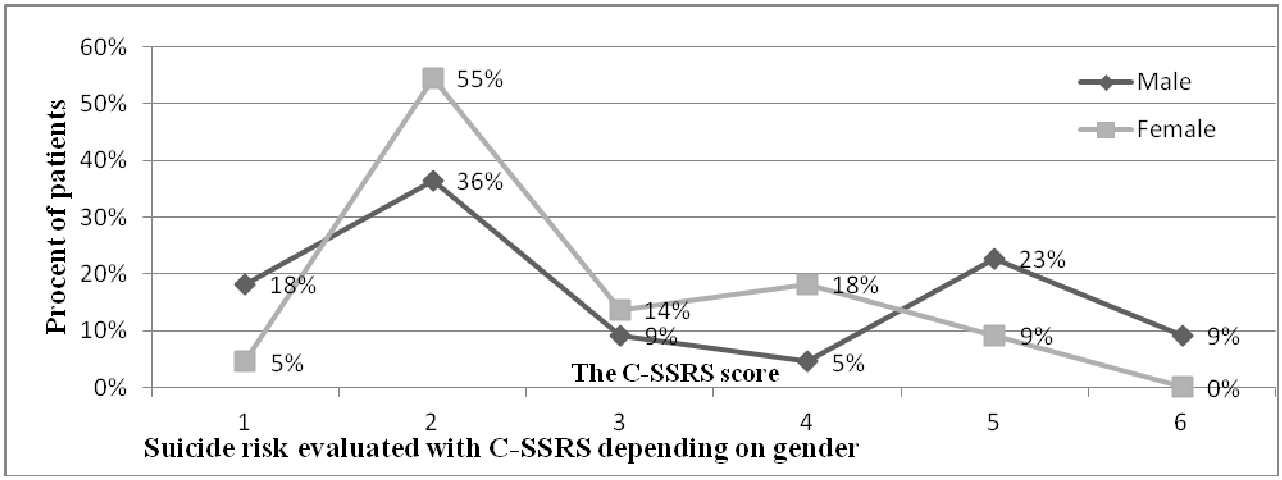


The CDSS depression score depending on gender of patients

Maximal values of suicide risk (5-6 points) are more likely for men, so many points (5-6 points) have 7 (31,8%) patients of male group and only 2 (9%) of female group, the medium risk. In women group more likely is medium risk of suicide (3-4 points), and only 3 (13,6%) men have the same score. 12 (54,5%) of men and 13 (59%) women have low suicide risk (less than 3 scores).

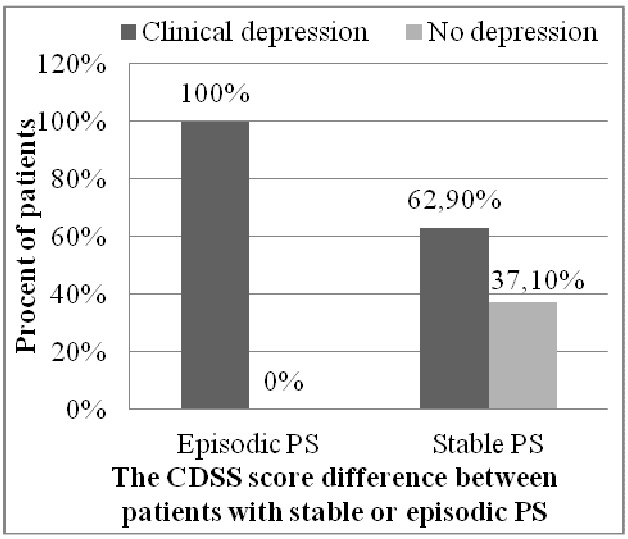


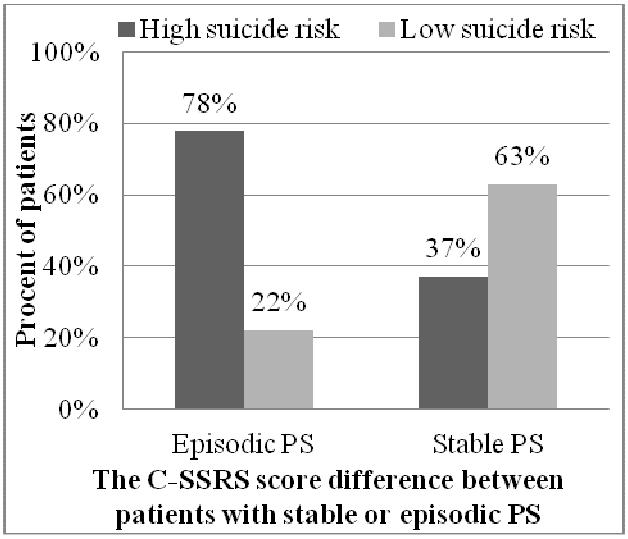
The next graph shows the difference between the suicide risk among female and male paranoid schizophrenia patients. Score 3 and more indicates clinically significant suicide risk:



Most of the patients - 35 (79.5%) suffer from the stable PS. The reminding 9 patients have episodic PS with increasing or stable residual symptoms. 8 of these 9 patients are females. All group (100%) of patients with episodic course of schizophrenia have clinical depression and 7 of 9 (77,8%) patients with episodic course of schizophrenia have suicide risk.

Next graphs show depression severity and suicide risk differences between stable and episodic PS:





During two independent sample T-tests it was established that the average score in accordance with the CDSS for males and females varies by 3.9 points. This difference is statistically reliable (p=0.005), the level of depression is higher among females. Also the average score according to the C-SSRS for patients with a stable course and episodic course of PS varies by 1.14 points. This difference is statistically significant (p=0.038), and the suicide risk is higher among patients with episodic course of PS.

Spearman's rank correlation didn't established statistically significant correlation between the duration of paranoid schizophrenia and depression severity according to CDSS (p=0,301, R=0,159). There are no correlations between frequency of repeated hospitalizations and severity of depression (p=0,544, R=-0,94) or suicide risk (p=0,292, R=-0,163).

Discussion

Generally the aim of the study was achieved and the association between the depression severity and suicide risk among PS patients was evaluated. This result does not contradict to those of previous studies and literatures, which assert that schizophrenia patients have an 8.5-fold greater risk of suicide, compared with the general population (Kasckow et al. 2011).

The prevalence of depression among schizophrenia patients varies from 10% and even up to 38% (Semple et al., 2013). In this study clinical depression have 70,5% patients, and it is more common among women than among men, whereas men show higher suicide risk than women, although in literature suicide attempt rates do not differ between the sexes (Harkavy-Friedman, J. M., 2007). One of explanations of this tendency could be attempts of suicide that may be motivated primarily by hallucinations or delusions, not only depression.

45,5% of all interviewed patients regularly use alcohol or drugs, but it does not correlate with depression severity. In literature co morbid drug or alcohol abuse is considered as predictor of dangerous behaviour such as suicide and violence.

The duration of PS and hospitalization frequency also was not associated with suicide risk and depression although this association was established in other studies (Chemerinski et al., 2008).

The factors that could affect the results are listed below.

1) In this study depression was evaluated by the use of CDSS, which specifically developed for the assessment of depression in schizophrenia patients. Anyway here might be a conceptual overlap between depressive and negative symptoms in a large sample of older medicated schizophrenia outpatients, because older medicated patients with schizophrenia often have impaired ability to recognize their symptoms and functional deficits (Chemerinski et al. 2008).
2) The using of antidepressants (AD) was not evaluated; AD may have a direct therapeutic effect on suicidal thoughts and behaviours as well as suicidal ideation as a side effect (Noschal et al. 2012).
3) Antipsychotics have a number of the side effects that can contribute to low mood and depression itself, for example, this are the sexual side effects (erectile dysfunction, loss of libido, inability to orgasm) that can be quite traumatic. The study also does not take into account the role of antipsychotics in depression development.
4) Some social factors such as marital status, employment, education, the quality of life, were not evaluated, too. The most of patients were single or divorced, without higher education and unemployed and all of these factors are risk factor for depression.
5) The statistics deserve a special attention. The comparison attempt of an episodic PS sample with stable PS sample could contain of a sampling error. Two samples have a large deviation in the structure. The group of episodic PS consists of only 9 patients but the group of stable PS – 35 patients. Almost all patients with episodic PS are females, but it was proved previously that the female gender is associated with a higher level of depression and male gender – with a higher suicide risk. A small amount of patients and an unequal distribution in gender structure make these results disputable and require furthers studies to evaluate the difference in depression severity and suicide risk between stable and episodic PS. In case, if the suicide risk and depression severity associate with a course of PS (stable or episodic) and they are different for episodic and stable PS, the comparison of suicide risk and depression severity between different genders of PS patients will be needed of a new revision. But it is necessary to add, that schizophrenia subtypes have been dumped in the DSM-5 because of their “limited diagnostic stability, low reliability, and poor validity,” according to the American Psychiatric Association (APA). This study was not based on DSM-5, but one of inclusion criteria was ICD-10 paranoid schizophrenia definition, that is used in clinical practice in EU.5) The difference in classifications, inclusion criteria and measure tools that are used in studies can directly affect results.

Conclusions

Study results align with data from several studies. There is a high prevalence of depression among patients with PS, and the suicide rate among them is high. There is a strong correlation between the severity of depression and the suicide rate. Females with PS are more susceptible to depression and suffer more often also from episodic PS with residual symptoms; males are most likely to be susceptible to the stable form of PS and the risk of depression and suicide is lower. The rate of depression is undeniably important and attention should be paid to this aspect when treating the patients. Results of the study are significant and clinically competent attention should be paid to this problem.

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