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Public health

ASSESSMENT OF THE EPIDEMIOLOGICAL SITUATION AND BURDEN OF COVID-19 ON GLOBAL, REGIONAL AND NATIONAL LEVEL

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Key words: COVID-19, SARS-CoV-2, assessment, epidemiological situation, burden

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Abstract

The current pandemic of corona virus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Global COVID-19 burden is characterized by a high variability in death rate across countries. Several possible explanations have been proposed, but it is not clear whether this variability is due to a single predominant factor or instead to multiple caus-es. The aim of this paper was to present and analyze the epidemiological situation and burden of the COVID-19 pandemic in Kosovo compared to other countries in Europe and the world. Material and methods: Public health approach and desk review were applied to present and analyze the trends over time of selected epidemiological indicators for COVID-19 based on multiple sources of data as well as WHO epidata and literature review. The assessment of the epidemiological situation in EU/EEA member states was done using the surveillance data routinely collected by ECDC. Official medical records from the National Institute of Public Health, other relevant health institutions; State Statistical Office and Ministry of Health in Kosovo were used. Results: According to ECDC as of 11 February 2021, 106,472,660 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been report-ed, including 2,323,103 deaths. COVID-19 cases have been reported from: Africa: 3,673,181 cases, Asia: 20,438,608 cases, Europe: 34,681,426 cases, America: 47,620,931 cases; Oceania: 57,809 cases, Others: 705 cases. Deaths have been reported from: Africa 95,128 deaths, Asia 343,886, America 1,107,066, Europe 775,883, Oceania 1,210 and Other 6 deaths. In Kosovo from 13 March 2020 until 15th February 2021 there have been 64,298 cases of COVID- 19 with 1534 deaths. Absolute values of the indi-cators remain high in all countries in Europe, including those with stable or decreasing trends in these indicators, suggesting that transmission is still wide spread. The epidemic trajectory over the next months will be deter-mined by the balance of four factors, with many different outcomes possi-ble: the continued scale-up of vaccination, declining seasonality, the spread of new variants and increased behaviors that favor COVID-19 transmis-sion.Conclusion: Findings from this paper can help to develop evidence-based policy interventions in Kosovo for risk assessment of COVID-19 and protection of general population and especially vulnerable groups with higher risk from COVID 19.

Јавно здравје

ПРОЦЕНКА НА ЕПИДЕМИОЛОШКАТА СОСТОЈБА И ОПТОВАРЕНОСТА СО COVID-19НА ГЛОБАЛНО, РЕГИОНАЛНО И НАЦИОНАЛНО НИВО

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Цитирање:Курти-Карамета А, Тозија Ф.Проценка на епидемиолошката состојба и оптовареност со COVID-19 на глобално, регионално и национално ниво. Арх Ј Здравје 2021;13(2) 5-16.

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Клучни зборови:COVID-19, SARS-CoV-2, проценка, епидемиолошка состојба, оптовареност

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Печатарски права: ©2021 2021Афердита Курти-Карамета, Фимка Тозија. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитират оригиналниот(ите) автор(и) и изворот.

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Извадок

Тековната пандемија со корона вирус од 2019г.(COVID-19) е инфективно заболување предизвикано од новооткриениот корона вирус 2 кој предизвикува тежок акутен респираторен синдром (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Глобалниата оптовареност со COVID-19 се карактеризира со голема варијабилност во стапката на смртност во државите. Предложени се неколку можни објаснувања, но не е јасно дали оваа варијабилност се должи на единствен доминантен фактор или на повеќе причини. Целта на овој труд беше да се презентира и анализира епидемиолошката состојба и оптовареноста со пандемијата COVID-19 во Косово и да се спореди со другите земји во Европа и светот.Материјал и методи: Јавноздравствен пристап и прегледот на документи се применети за да се презентира и анализира трендот на избраните епидемиолошки индикатори за COVID-19 врз основа на податоци од повеќе извори, како и епидата на СЗО и преглед на литература. Проценката на епидемиолошката состојба во земјите-членки на ЕУ/ЕЕА беше направена со користење на податоците за следење, рутински собрани од ECDC. Беа користени официјални медицински извештаи од Националниот институт за јавно здравје, други релевантни здравствени институции; Државниот завод за статистика и Министерството за здравство на Косово.Резултати: Според ECDC заклучно со 11 февруари 2021 година, во светот пријавени се 106.472.660 случаи на COVID-19 (во согласност со применетите дефиниции на случаи и стратегии за тестирање во погодените земји), вклучително и 2.323.103 смртни случаи. Пријавени се случаи со COVID-19 од: Африка: 3.673.181 случаи, Азија: 20.438.608 случаи, Европа: 34.681.426 случаи, Америка: 47.620.931 случаи; Океанија: 57 809 случаи, други: 705 случаи. Пријавени се смртни случаи од: Африка 95.128 смртни случаи, Азија 343.886, Америка 1.107.066, Европа 775.883, Океанија 1.210 и други 6 смртни случаи. Во Косово од 13 март 2020 година до 15 февруари 2021 година пријавени се 64.298 случаи на COVID-19 и 1.534 смртни случаи.Апсолутните вредности на индикаторите остануваат високи во сите земји во Европа, вклучително и оние со стабилни или трендови на опаѓање, што укажува дека трансмисијата е сè уште широко распространета. Текот на епидемијата во следните месеци ќе биде одреден од рамнотежата помеѓу четири фактори, со можни различни исходи: континуирано зголемување на вакцинацијата, сезонско намалување, ширење на новите варијанти на вирусот и зголемено однесување што придонесува за преносот на COVID-19.Заклучок: Наодите од овој труд можат да помогнат да се развијат политики и интервенции засновани на докази во Косово, за проценка на ризик за COVID-19 и заштита на општата популација и особено на ранливите групи со поголем ризик од COVID 19.

Introduction

The current pandemic of coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2)[1]. Genetic se-quencing of the virus suggests that it is a betacoronavirus closely linked to the SARS virus. By way of definition, a symptomatic COVID-19 case is a person who has developed signs and symptoms suggestive of COVID-19. Symptomatic transmission refers to transmission of SARS-CoV-2 from persons with symptoms. Epidemiology and virologic studies suggest that transmission mainly occurs from symptomatic people to others by close contact through respiratory droplets, by direct contact with infected persons, or by contact with contaminated objects and surfaces [2,3,4,5].

Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Around 30% of pregnant women with COVID-19 experienced preterm delivery, whereas the mean birth weight was 2855.9 g. Fetal death and detec-tion of SARS-CoV-2 were observed in about 2% [6]. Older people and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease and cancer are more likely to develop serious illness [7,8].

The cross-sectional study conducted on a sample of 69,054 university students in France showed self-reported prevalence of suicidal thoughts, severe distress, high level of perceived stress, severe depression, and high level of anxiety: 11.4%, 22.4%, 24.7%, 16.1%, and 27.5%, respectively. The following factors were associated with reporting at least 1 mental health outcome: female gender or nonbinary gender, precariousness, low-quality housing, history of psychiatric follow-up, symptoms compatible with COVID-19, social isolation and low quality of the information received [9].

This pandemic is characterized by a high variability in death rate (defined as the ratio between the number of deaths and the total number of infected people) across world countries. Several possible explanations have been proposed, but it is not clear whether this variability is due to a single pre-dominant factor or instead to multiple causes [10].

Since the outbreak of COVID-19 pandemic, several hypotheses have been proposed to explain the great variability in the death rate across countries. The Italian study provides evidence that one of the most crucial factors affecting the death rate is the availability of hospital beds [11].

To date there is only one treatment, systemic corticosteroids, known to reduce mortality in patients with severe COVID-19, limiting treatment options and putting more pressure on supportive care alternatives such as oxygen support [12].

There remains uncertainty around how effective a vaccine will be in reducing transmission and/or severity of illness or what duration of immunity it will confer, so it must be seen as a potential future tool to be used in conjunction with robust application of existing measures [13].

The aim of this paper was to present and analyze the epidemiological situation and burden of the COVID-19 pandemic in Kosovo compared to other countries in Europe and the world from its be-ginning up to February 2021.

Material and methods

Public health approach and desk review were applied to present and analyze the trends over time of selected epidemio-

logical indicators for COVID-19 based on multiple sources of data, as well as WHO epidata and literature review.

The assessment of the epidemiological situation in EU/EEA member states was done using the sur-veillance data routinely collected by ECDC and IHME. For all countries globally that have reported COVID-19 cases to date, the main indicator shown is the 14-day notification rate of reported COVID-19 cases per 100,000 population, which provides an estimate of the prevalence of active cases in the population. A 14-day notification rate of reported deaths per 1,000,000 population is also plotted on the time-series for each country to show trends in deaths compared to cases.

Data for Kosovo were used from official medical records from the National Institute of Public Health, other relevant health institutions, State Statistical Office and Ministry of Health of Kosovo.

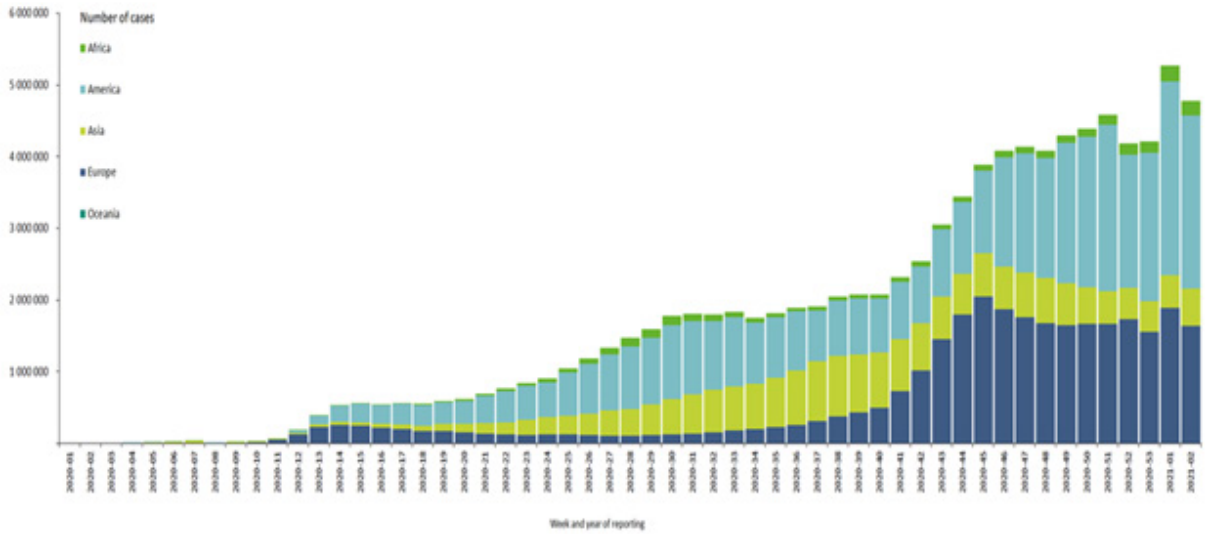
Results

Global situation

In January 2020, the World Health Organization (WHO) declared the outbreak of the new coronavirus disease in Hubei Province, China as a public health emergency of international importance [14]. The WHO stated that there was a high risk of the spread of the new coronavirus disease (COVID-19) to other parts of the world [15]. Since the start of the pandemics caused by SARS-CoV-2 and as of April 1, 2020, 206 countries have suffered from 885,344 cases and 44,214 deaths, with an average death rate of 4.99% 1. These numbers have been significantly increased and as of 01 November 2020, 46,382,791cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported, including 1,198,717deathsand recovered 30,927,352 [16]. Globally as of 24 January over 97 million COVID-19 cases and more than 2.1 million deaths have been reported by John Hopkins [17]. Distribution of cases of COVID-19 by continent (according to the applied case definition and testing strategies in the affected countries) is presented in Figure 1. [18]

Preliminary seroprevalence surveys in countries affected earlier in the outbreak have indicated that the pro-

Figure 1. Distribution of COVID-19 cases worldwide, as of week two 2021

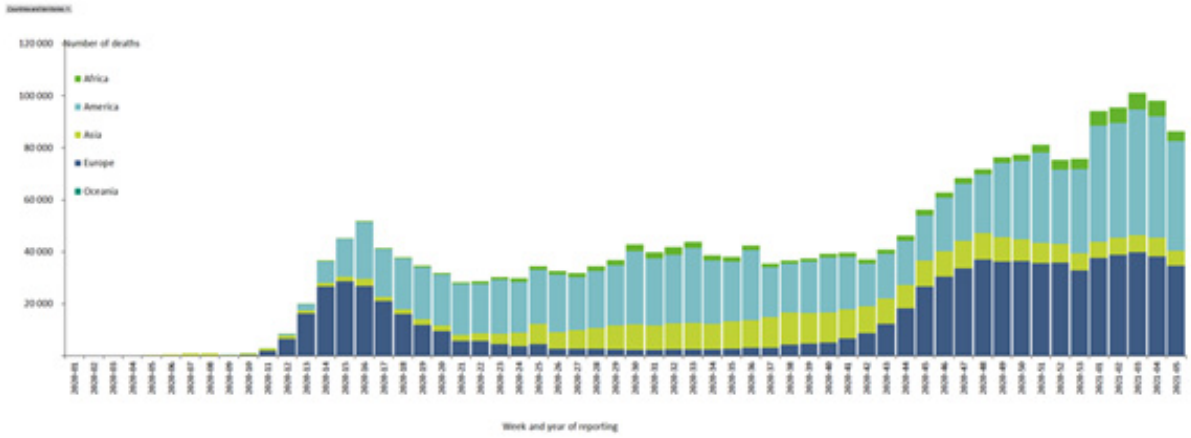


Source: European Centre for Disease Prevention and Control

portion of people having been infected is low, with most surveys showing prevalence below 10%, suggesting that most of the world's population remains susceptible to infection [19].

According to ECDC20as of 11 February 2021, 106,472,660 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported, in-cluding 2,323,103 deaths. COVID-19 cases have been reported from: Africa: 3,673,181 cases, Asia: 20,438,608 cases, Europe: 34,681,426 cases, America: 47,620,931 cases; Oceania: 57,809 cases, Others: 705 cases. Deaths have been reported from: Africa 95,128, Asia 343,886, America 1,107,066, Europe 775,883, Oceania 1,210 and Other 6 deaths (Figure 2).

Figure 2. Distribution of COVID-19 deaths worldwide as of week 5 2021



Source: European Centre for Disease Prevention and Control

Situation with COVID-19 in Europe

COVID-19 cases started increasing at the beginning of September driven by resurgence in the WHO European and Eastern Mediterranean regions that are surpassing levels reported during the first peak in March and April and there appears to be an acceleration of the pandemic globally. The cumulative cases increased for 18% to 10,552,074 cases (from 8,913,201 cases on 23 October 2020) and cumulative deaths increased by 6% to 279,958 deaths (from 264,468 deaths on 23 October 2020). The 5 countries and territories with the highest percentage change in a 14-day cumulative case incidence are: Liechtenstein (442%), San Marino (377%), Cyprus (357%), Serbia (354%), and Switzerland (321%). [18]

As of 18 December, 31 of the 55 IHR States Parties and 2 territories reporting cases in the WHO European Region have shown 14-days incidence >400 per 100,000 population: >701 {Lithuania (1,327), Georgia (1,284), Serbia (1,284), Luxembourg (1,214), Croatia (1,151), Slovenia (994), San Marino (989), Jersey (900), Sweden (837), Montenegro (837), Lichtenstein (807), Andorra (728), {601 – 700 –Switzerland (688), Czech Republic (677), Denmark (670), 501 – 600 – Hungary (598), Netherlands (597), Slovakia (593), Azerbaijan (575), Portugal (538), North Macedonia (529), Turkey (515), 401 - 500 {Estonia (498), Republic of Mol-

dova (485), Latvia (484), Bulgaria (473), Romania (440), Austria (436), Cyprus (428), Armenia (425), United Kingdom (407), Poland (407)}[18].

In Europe 10,866,134 cases have been reported; the five countries reporting most cases are: Russia (1,673,686), France (1,502,763), Spain (1,259,366), United Kingdom (1,073,882) and Italy (759,829). 277,125 deaths have been reported in Europeand the five countries reporting most deaths are: United Kingdom (47,250), Italy (39,412), France (38,289), Spain (36,495) and Russia (28,828)[18].

By the end of week 3 (ending Sunday 24 January 2021), the 14-day case notification rate for the EU/EEA, based on data collected by ECDC from official national sources from 30 countries, was 421 (country range: 26–1 429) per 100 000 population, decreasing for one week. Among 29 coun-tries with high case notification rates (at least 60 per 100,000), an increase was observed in four countries (Finland, France, Portugal and Spain). Pooled data from 20 countries for the same week show that there were 1.6 patients per 100,000 population in ICU due to COVID-19, which is 76% of the peak ICU occupancy observed during the pandemic. Pooled weekly ICU admissions based on data from 15 countries were 3.6 new admissions per 100 000, which is 42% of the peak rate to date. The 14-day COVID-19 death rate for the EU/EEA, based on data collected by ECDC from official national sources from 30 countries, was 103.2 (country range: 0.0–247.6) per million popula-tion. The rate has been stable for nine weeks. Among 29 countries with high 14-day COVID-19 death rates (at least 10 per million), an increase was observed in four countries (Ireland, Portugal, Slovakia and Spain).[20]

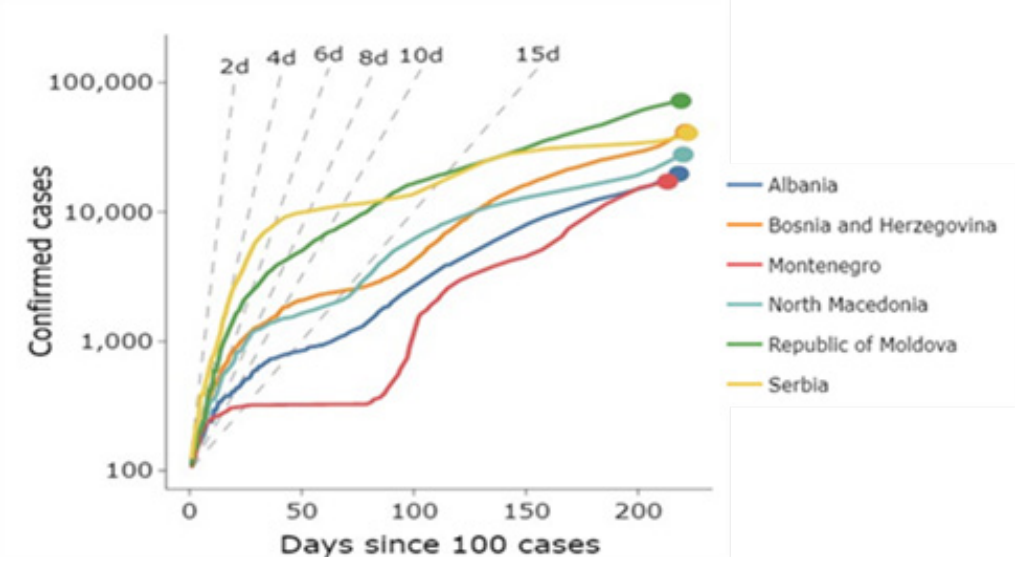
Despite the spread of new variants, daily reported cases have declined since earlyJanuary, to 169,300 per day on average in the last analyzed week compared to 198,400 the week before (Figure 3). Daily deaths in the last week decreased to 6,470 per day on average compared to 6,790 the week before (Figure 4). COVID-19 is number 1 cause of death in the European Region with 45,311 weekly deaths, followed by ischemicheart-disease with 44,253 deaths and stroke with 22,622 deaths. IHME estimation is that 12% of people in the European Region have been infected as of February 8, while in some countries or regions more than 20% have been infected: Portugal, parts of Spain, Czech Republic, Bosnia and Herzegovina, North Macedonia, Moldova, Armenia, and Azerbaijan. The infection detection rate in the region remains around45%. The daily death rate is greater than 4 per million in 32 countries[21].

Situation in the Balkans

Across the region of the Western Balkans, the situation with the COVID-19 pandemic is deteriorating, with a significant rise in infections and deaths (doubling rates) in almost every country (Monte-negro 377 per 100,000, North Macedonia 355, Bosnia and Herzegovina 332) (Figure 5).

Further spread of COVID-19 is very high and the epidemic in North Macedonia is in wide commu-nity spread. Extreme adherence to precautions and government preventive instructions is

Figure 5. Distribution of COVID-19 deaths worldwide as of week 5 2021



Source: Source: World Health Organization

required. North Macedonia was seeing sustained daily decrease in new cases: MOH reported 91,161coronavirus positive cases, 2,812 deathsand 79,621 recovered, as of 25thJanuary 2021[22].

Situation in Kosovo

In Kosovo,on 13th of March 20201, the first two cases were confirmed, a 77 year old man from Vitia and an Italian woman in her early 20s, who worked in Klina with Caritas Kosovo. The Gov-ernment of Kosovo decided to quarantine and block the entrances and exits of these two cities. On 14th of March, the third case was confirmed, a family member of the 77 year old from Vitia tested positive for coronavirus. On the same day, two other new cases were confirmed, a 42 year old man from Vitia and a 37 year-old woman from Malisheva. After the first case emerged in Malisheva, the Prime MinisterAlbin Kurti decided to quarantine the municipality. From 1 July until 31 July we had increased number of infected people with coronavirus, bringing the total number of 2,878 positive cases, 1,577 recoveries and 51 death

Figure 6. COVID-19 new cases per week in Kosovo

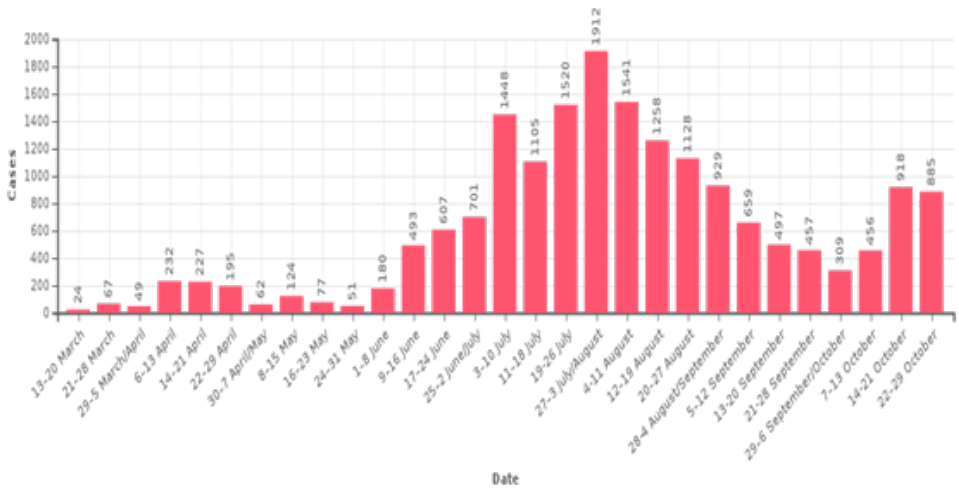


Figure 7. COVID-19 new deaths per week in Kosovo

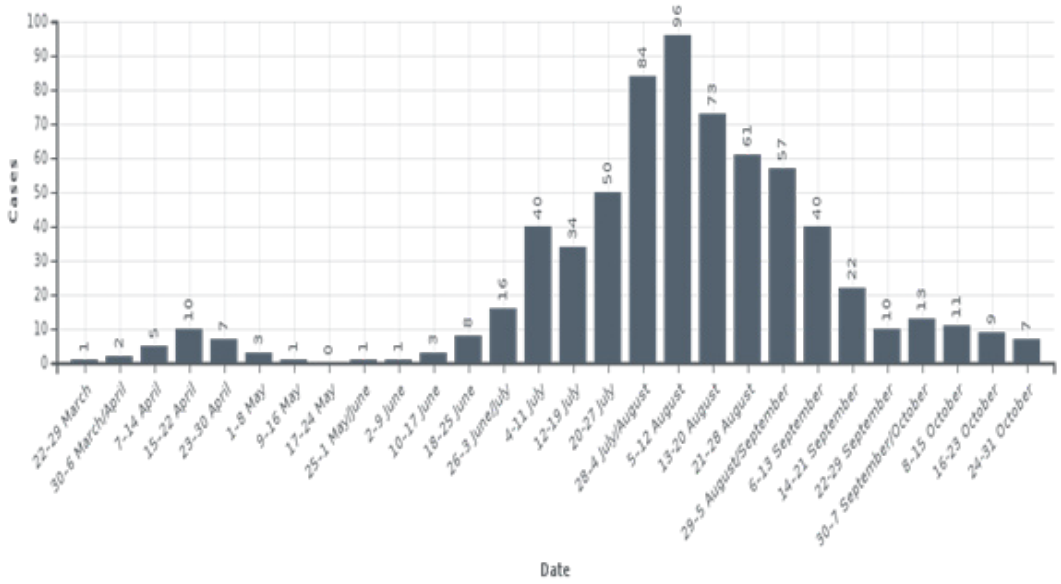


Figure 8. COVID-19 number of cases by district in Kosovo

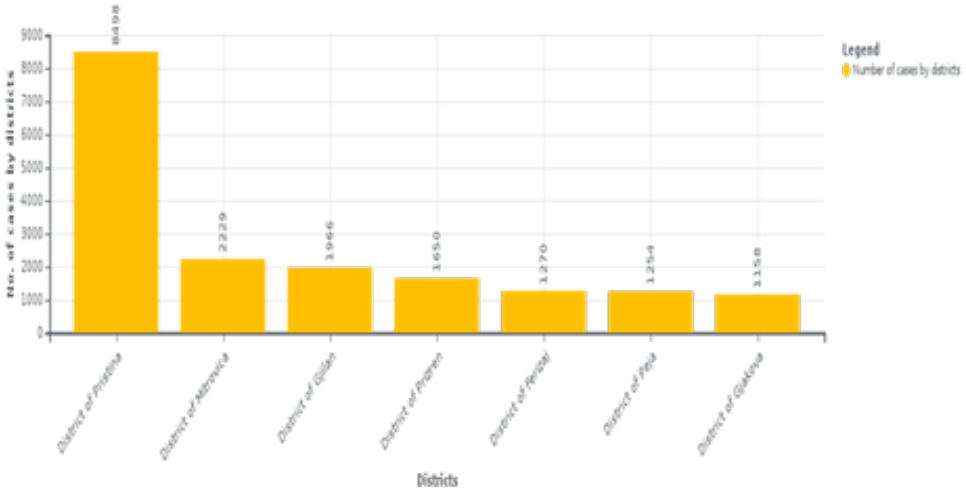
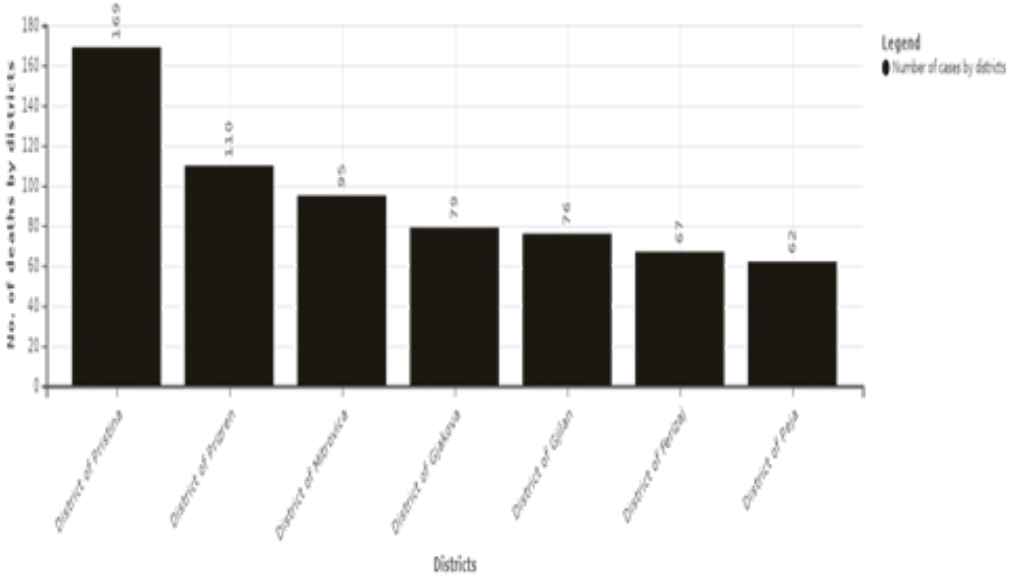


Figure 9. COVID-19 number of deaths by district in Kosovo



Source: National Institute of Public Health of Kosovo

cases. In August, there was a total of 13,454 positive cases, 9,585 recoveries and 525 death cases.On 1 September, eight new death cases with coronavirus were confirmed, in total 533 deaths and 147new positive cases i.e. 13,601 in total (Figure 6, 7, 8. 9).[23]

While the number of new COVID-19 cases in Kosovo rose sharply in November 2020, with a week-ly average of 715 new cases, the number started to significantly decline from mid-December. In January 2021, Kosovo recorded a weekly average of 300 new cases, bringing the total number of reported cases to more than 58,000 since the beginning of the epidemic[24].

On 2ndof February 2021 the MOH reported three deaths related to COVID-19 in the last 24 hours, bringing the death toll to 1,506. Meanwhile, 245 new cases were reported – 60,745 since the begin-ning of the pandemic. About 238 thousand people have been tested (2,615 in the last 24 hours). 189 people recovered in the last 24 hours– 52,810 in total. There are 6,429 active cases in the country. As of 15th February 2021 there have been 64,298 cases of COVID- 19 with 1534 deaths.[25, 26]

Discussion

While deaths in the European region were lower than observed in the earlier peak, given the time between cases and deaths, it is anticipated that deaths will continue to increase in the weeks ahead. Compared with the Northern Hemisphere spring, there has been a slower rise in deaths as cases have increased in the European region, as more cases are being reported among younger populations due to increased access to testing and increased social mixing. However, again more cases are starting to be reported amongst older age groups, which may lead to an increase in deaths in the coming weeks. Early in their outbreaks, many affected countries implemented strict control measures that were maintained for many months, some until a substantial decrease in transmission was observed. Public health interventions to the recent resurgence has lagged in many countries and have had a limited impact, so that many countries are now attempting short "circuit breaker" movement restrictions to interrupt transmission. Majority of countries in Europe are currently re-imposing restriction measures and limiting travel and social gatherings [20]. New mandates have been imposed in Austria, France, Greece, Kyrgyzstan, Luxembourg, the Netherlands, and Poland. Mandates have been lifted inAus-tria, Estonia, and Greece [21].

The Government of Kosovo has undertaken measures in place to help contain the spread of the COVID-19 virus; restrictions on freedom of movement remain in place across the country for people over the age of 65, who are only permitted to leave the house between 06:00-10:00 and 16:00-19:00. Weddings and religious ceremonies continue to be prohibited, while funerals may only be conducted with immediate family members. Since 23rd of December 2020, controls at the borders also remain in force for both Kosovo citizens and most foreign nationals who are still required to present a negative PCR test when entering Kosovo, or undergo a seven-day selfisolation period following arrival. On 15th of January 2021, regulations governing public gatherings have, however, been re-

laxed throughout Kosovo. The number of people permitted to gather in public spaces such as parks, squares and recreational centers has been extended from four to fifty. With Kosovo's parliamentary election scheduled for 14 February, a special mention was also made for public rallies, which must be limited to 50 persons. Municipalities have continued to be designated as low, medium or high risk depending on the number of infected inhabitants (150 infected individuals per 100,000 inhabitants respectively). Depending on their classification, municipalities face different measures. In low and medium-risk municipalities, operating hours for businesses, shopping centers and cultural institutions have now been extended by two hours to between 05:00 and 22:00. In high-risk municipalities, a curfew remains in force but has been pushed back, now applying from 21:30 until 05:00. Acting Prime Minister announced that vaccinations against COVID-19 will begin in February, with health professionals, people over the age of 65 and at-risk groups being the first to receive the vaccine. Estimations are that 20,000 citizens will be vaccinated per day. Agreements were reached with Pfizer/BioNTech, COVAX, and the Austrian state to provide vaccines[25].

Absolute values of the indicators remain high in all countries, including those with stable or decreas-ing trends in these indicators, suggesting that transmission is still wide spread. Although in most countries indicators show an improving epidemiological situation, in a number of countries reporting increasing case trends it is likely that hospitalisations and ICU admissions, and potentially deaths, will increase in the coming weeks.[20]

Daily cases have declined in the European Region, but daily deaths have declined only slightly. The epidemic trajectory over the next four months will be determined by the balance of four factors, with many different outcomes possible. Two factors are driving down transmission: the continued scale-up of vaccination, helped by the fraction of adults willing to accept the vaccine reaching 68% (from 31% in Kazakhstan to 91% in Denmark); and declining seasonality, which will contribute to declining transmission potential until August. Two factors, however, can slow or even reverse the declines that have begun: the spread of variants B.1.1.7 and B.1.351, and increased behaviors that favor COVID-19 transmission. Community transmission of B.1.1.7 and B.1.351 has been confirmed in many countries and will inevitably spread more widely. In places where both variants have been detected at the same time, such as Belgium, B.1.1.7 is spreading faster than B.1.351. Despite the spread of these more transmissible variants, lockdowns have been effective in reducing transmission where imposed. If daily case counts continue to decline and vaccination increases, behaviors are likely to change, but data on this change are currently very limited. In the reference scenario, putting all these factors together, IHME estimated that: daily infections will decline reaching below 200,000 by early April, 21 countries will have high or extreme stress on hospital beds, while 32 countries will have high or extreme stress on ICU capacity, cumulative deaths will reach 1.4 million by June 1 2021 (388,000 additional deaths from February 8 to June 1)[21].

While countries have adopted policy measures with unprecedented speed and scope, the Monitor highlights some key challenges ahead 27: Finding the right balance and sequencing of health, eco-nomic and social and policy interventions to produce optimal sustainable labor market outcomes; Implementing and sustaining policy interventions at the necessary scale when resources are likely to be increasingly constrained; Protecting and promoting the conditions of vulnerable, disadvantaged and hard-hit groups to make labor markets fairer and more equitable; Securing international solidari-ty and support, especially for emerging and developing countries; Strengthening social dialogue and respect for rights.

In managing occupational risks of Covid-19, employers must control exposure to the virus so far as is reasonably practicable, taking into account the possibility that some workers will be more vulnera-ble than others should they contract the disease. Strategies may include changes to the way in which work is carried out, use of barriers and personal protective equipment (PPE), and in some cases, ex-clusion or redeployment of individuals who are more vulnerable. The need for selective exclu-sion/ redeployment of vulnerable workers will depend on the likelihood of their contracting Covid-19 through their work (which will vary according to the job and the prevalence of infection in the local community), and on the extent of their personal vulnerability to severe illness should they get the disease.

Conclusion

Findings from this study can help to develop evidence-based policy interventions in Kosovo for risk assessment of COVID-19 and protection of general population and especially vulnerable groups with higher risk of COVID 19, in line with the WHO‘s 3 key messages at UN General Assembly: Equitable access to COVID-19 tools; Maintaining momentum on the Sustainable Development Goals and Preparing for the next pandemic now.

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Public health

ASSESSMENT OF HEALTH AND ECONOMIC BENEFITS OF WALKING IN THE REPUBLIC OF NORTH MACEDONIA USING HEALTH ECONOMIC ASSESSMENT TOOL (HEAT)

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Competing Interests: The author have declared that no competing interests

Abstract

Walking as a form of physical activity has immense health benefits, but it also has economic benefits. Walking is a very efficient activity that prevents certain diseases and enables better quality of life of people who already have some disease.A considerable contribution of walking is detected in cardiovascular diseases, type 2 diabetes, obesity and chronic pulmonary diseases. The aim of this study was to make a health and economic assessment of the benefits of walking in the Republic of North Macedonia by using the Health and Economic Assessment Tool (HEAT). Materials and methods:Health Economic Assessment Tool is a relatively new tool, developed by WHO experts whose expertise is in the field of Public health and is able to calculate the health effects of regular walking and/or cycling. This study was based on using this tool for walking mode for the first time in the Republic of North Macedonia in a population group of 191 participants between the age of 20 to 73 years, with the average age of 35 years.Results:Besides the aforementioned health benefits, HEAT calculates the economic benefits of walking. The tool applied to 191 participants resulted in a total economic value of 108 808.8€ for one yearas well as reduction in mortality rate. Conclusion: We found that less than one fifth of our assessed population spends time in walking according to the WHO, CDC and AHA recommendations. The rest of them, more than four fifths are not following these recommendations. Our assessed population was relatively young, the average age being 35 years old, and the population was healthy, but still the results from this survey were not satisfying.

Јавно здравје

ПРОЦЕНКА НА ЗДРАВСТВЕНИТЕ И ЕКОНОМСКИ ПРИДОБИВКИ ОД ПЕШАЧЕЊЕТО ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА СО УПОТРЕБА НА АЛАТКАТА ЗА ЕКОНОМСКА ПРОЦЕНКА И ЗДРАВЈЕ

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Извадок

Пешачењето како форма на физичка активност има огромни здравствени придобивки, но покрај нив и економски придобивки за човекот. Пешачењето е ефикасна активност која може да превенира одредени болести и да овозможи подобар квалитет на живот кај лица кои веќе имаат некоја болест.Значаен придонес од пешачењето е регистриран кај кардиоваскуларните болести, дијабет тип 2, обезност и хронични белодробни болести.Целта на ова истражување беше да се направи здравствена и економска проценка на пешачењето во Република Северна Македонија користејќи ја Health Economic Assessment Tool (HEAT) алатката.Материјали и методи: Health Economic Assessment Tool е релативно нова алатка, развиена од експерти на СЗО, чие поле на експертиза е јавното здравје и е оспособена да ги пресмета здравствените и економските ефекти од редовното пешачење и/или возење велосипед. Нашата студија беше базирана на употреба на оваа алатка за првпат во Република Северна Македонија за пешачење, на популациона група од 191 учесник, на возраст помеѓу 20 и 73 години, со просечна возраст од 35 години.Резултати: Покрај гореспоменатите здравствени придобивки, HEAT ги пресмета и економските бенефити од пешачењето. Алатката употребена за 191 учесник резултираше со целосна економска вредност од 108808,8 евра за една година и редукција настапката на морталитетот. Заклучок: Со ова истражување заклучивме дека помалку од една петтина од проценетата популација пешачи во склоп на препораките од СЗО, ЦКБ и АСА. Останатите, повеќе од четири петтини, не ги следат препораките за пешачење. Нашата популација беше релативно млада, просечната возраст беше 35 години, а дополнително и здрава, но и покрај тоа, резултатите од ова истражување не се задоволителни.

Introduction

Walking is the oldest and simplest form of engaging the muscle apparatus. Although nowadays walking is not appreciated as gym training (weight lifting, pilates, crossfit etc.), it is still the safest form of physical activity, since walking accidents happen rather rarely as opposed to accidents in gym training.

Overthe last century the working environment has become more and more digitalized with little physical loading and the working processes have been concentrated in offices and cubicles. Physical activity does not economically encumber people, and having in mind that preventive health programs are far more cost-effective than the curative ones, we can conclude that physical activity is primarily significant in prevention of health issues, sustaining and improving health of the entire population[1].

Walking, cycling, wheeling, sports, active recreation and play are popular ways to be active, and they can be practiced at any level of skill and for enjoyment by everybody.

The WHO Guidelines on physical activity and sedentary behavior provide evidence-based public health recommendations for children, adolescents, adults and older adults on the amount of physical activity (frequency, intensity and duration) required to offer significant health benefits and mitigate health risks[2].

Walking as a healthful form of physical activity began to receive attention in the 1990s due to new recommendations that emphasized moderate-intensity physical activity. In 1995, the American College of Sports Medicine and the Centers for Disease Control and Prevention published national guidelines on Physical Activity and Public Health[3].

The Committee on Exercise and Cardiac Rehabilitation of the American Heart Association endorsed and supported these recommendations.

WHO guidelines and recommendations provide details for different age groups and specific population groups on how much physical activity is needed for good health.

For adults from 18-64 years of age, individuals above 65 years and those with diabetes type 2, hypertension, cancer survivors and HIV infected, the recommended time for moderate physical activity is 150-300 minutes or at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate and vigorous-intensity activity throughout the week. Besides, all these groups of people should limit the amount of time spent being sedentary.

Physical inactivity is one of the leading risk factors for non-communicable disease mortality. People who are insufficiently active have a 20% to 30% increased risk of death compared to people who are sufficiently active[4].

Walking, as much as it seems trivial, futile and worthless is not that unimportant as it may seem. Every day there are scientific discoveries over the benefits of physical activity.

The objective of this study was to measure the health and economic benefits of walking. Even though the economic arguments should not be the only reason for decision making, expressing through a monetary unit is a facilitating way for the decision makers to understand results from the assessments and can also be a tool for creating intersectoral politics.

The aim of this study was to make a health and economic assessment of the benefits of walking in the Republic of North Macedonia by using the Health and Economic Assessment Tool.

Materials and methods

Health Economic Assessment Tool or HEAT is a quantitativetool initially developed in 2007 and upgraded to its 2017 version by WHO that is able to calculate the health and economic effects of regular walking and/or cycling. It quantifies the number of deaths occurring in a population over a given period of time by a basic calculation with multiplying a mortality rate by the population size and the assessment time[5]. The tool offers two types of calculations based on the comparative risk assessment approach. The risk of interest is compared between the reference and comparison case. Thus, according to the module the user chooses, there are single and two-case assessments. In the first one, the user only specifies walking level for the reference case and then this case is compared to an implicit case of no walking. In the two-case assessment, the user specifies levels for both the reference and comparison case. For this study we chose the single-case assessment, therefore we specified walking level for our reference case. The effects of walking or cycling are quantified as relative risks, comparing the risk of exposure in people or, in our case, population that regularly walks to the risk among people that are not exposed, or people that are not walking regularly. These relative risk estimates refer to long-term exposure; data provided by the user must represent estimates of long-term walking or cycling.

The assessment was done in the early months of the year 2020 (March and April), on the territory of the Republic of North Macedonia with multiple towns and cities. The data was obtained using a questionnaire that included 12 questions (five multiple choice questions and seven open-ended). In total, 191 pedestrians aged 20 to 73 years were included in the study. Twenty-three interviews were done in person and 168 through the Google Forms platform. The data was processed by a descriptive statistical method. The average age was 35 years with majority of participants between 20-35 years old. As previously mentioned, we used the single-case assessment and the option for calculating the impact for only one year, with reference case being set in the year of 2020. As our impact pathway we chose only physical activity to be taken into account. In regard to data unit or type, we worked with distance unit-kilometers and time unit-minutes and hours. As for spatial and temporal data adjustment, we used none since our survey was designed for habitual pedestrians and was long-term related.

To accomplish the set aim and realize the study, these data were indispensable:

- An estimate of the size of the study population
- An estimate of the average amount of walking which can be provided as average per person per day with the specifics of duration, distance, trips(count data), frequency and steps (pedometer data).Trip or count data needs to be combined with an estimate of average trip length to calculate the volume of walking. Pedometer data refers to numbers of steps for intentional brisk walking[5].

HEAT offers two types of generic values:

- Default values provided for HEAT assessment, but with available option for the user to overwrite if they prefer other values and
- Background values considered to represent the best scientific consensus, which the user cannot change.

Table 1. General default values used by HEAT[5]

Description	Value	Unit
Average number of trips per day using all likely modes	3	Trips per person per day
Average walking speed	5.3	Km/h
Average distance by walking trip	1.3	Km/trip
Time frame for calculating the mean annual benefit	10	Years
Average length of walking steps	72	Cm
Discount rate	5	%

Sometimes input data may not be adequate or sufficient for all calculations of impact. HEAT offers several options for adjustment or providing additional information in order to calculate the assessment. These data adjustment options for single-case assessment include:temporal and spatial adjustment, for long-term average input, and data from multiple locations and proportions of trips shifted from another mode[5].

Results

As presented in Table 2, majority of the respondents were female.

The smallest percentage of participants (7.8%)was in the age group of 66-73 years, and the highest percentage(59.1%) was in the age group of 20-35 years.

74.9% of participants had completed a high school. They live in 19 different towns and cities in the Republic of North Macedonia.

Regarding body mass index (BMI), majority of our assessed participants or 47.1% had BMI in range of 18.6-24.9, which is considered a normal healthy body weight.

The prevalence of participants that had hypertension in our assessed participants was 12%. Prevalence of diabetes type 2 and heart failure in both cases was 3.7% and the prevalence of chronic pulmonary disease was 4.2%

Table 2. Demographic and health characteristics of the respondents in the survey

Gender	
•Male	29%
•Female	71%
Age	
•20-35 y/o	59.1%
•36-50 y/o	21.4%
•51-65 y/o	11.5%
•66-73 y/o	7.8%
Education	
•Primary	7.9%
•Secondary	74.9%
•Higher	17.2%

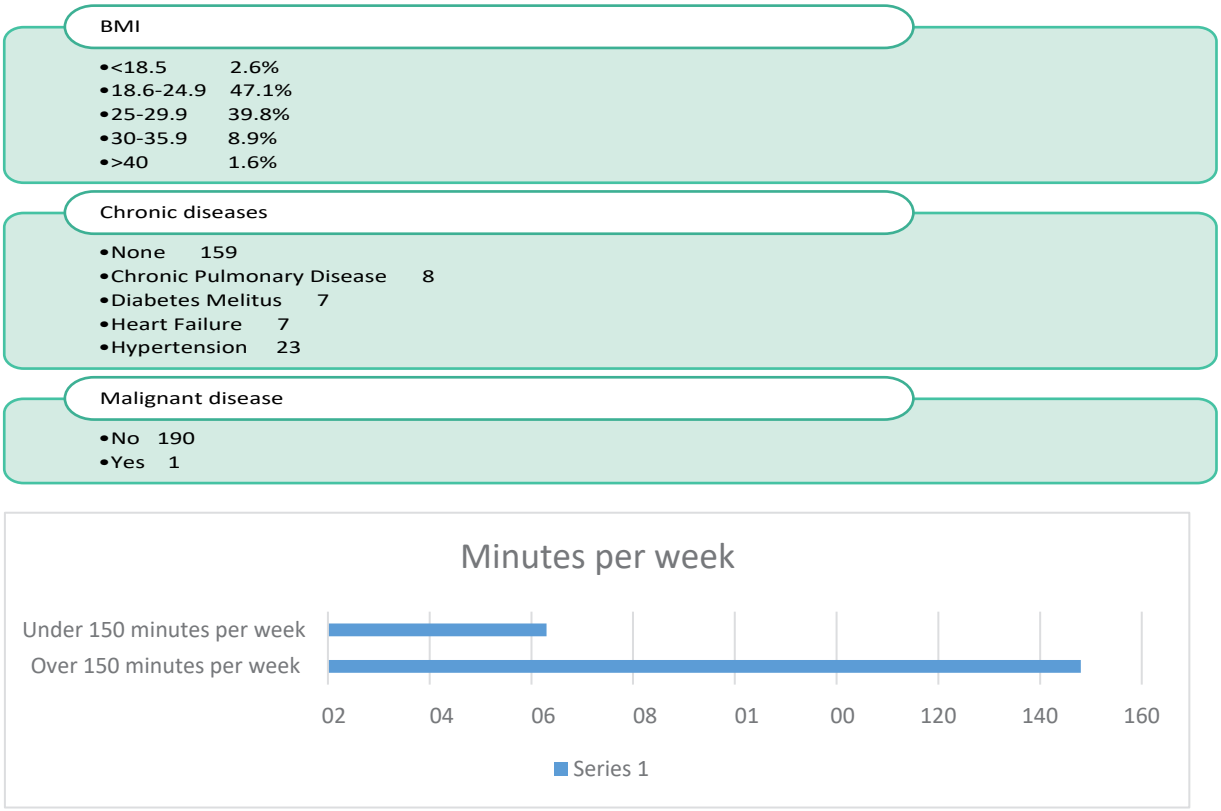


Figure 1. Time per week the respondents spent walking

Based on the given answers of the participants on the time they spent walking on a daily basis, we divided them in two groups. One group walked over 150 minutes and the remaining participants under 150 minutes per week as recommended by the WHO guidelines and recommendations4.

In regard to the time they spent walking per week, minority answered they were walking less than 150 minutes per week and the majority answered they were walking more than 150 minutes per week. On a daily basis, 22.2% walked under 30 minutes and 77.8% walked over 30 minutes.

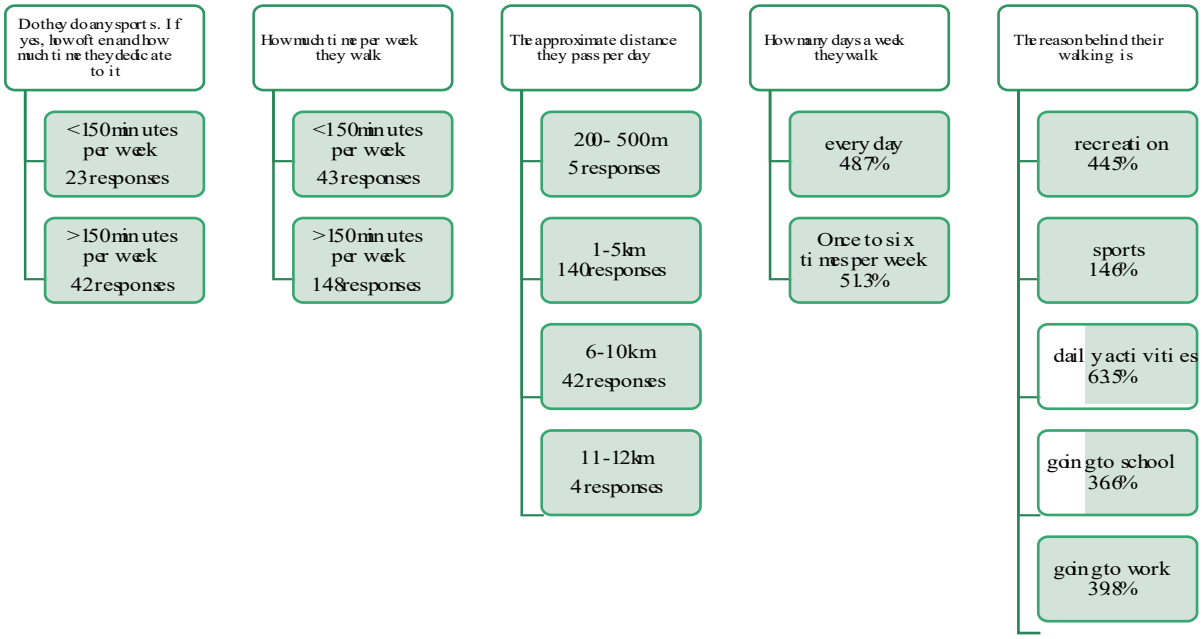


Figure 2. Detailed overview of respondents' walking habits

Majority of our participants or 63.5% were walking as a form of daily activity, meanwhile walking as a form of sport was the least answered. In our study, 63.5% or 121 person answered that they were walking as a form of daily activity, but for providing food, cleaning and housekeeping, etc. A total of 146 people answered they were walking when they were going to school or work. Eighty-five people answered they were walking as a form of recreational activity, and only 28 people or 14.6% answered they were walking as a form of sport.

The average time spent walking was 65 minutes and the average distance spent walking was 4.1km.

Table 3. Summary of the data analyzed by the HEAT tool

Population that walked a certain amount	Percentage	Assessed population	Increase of min per person per day	Impacts for mortality	Total economic impact Full assessment for 1 year	Annual discount rate	Total economic value for 1 year (EUR)
0.2km	0.5%	1	2 min/person/day	0.00007	35.4	5%	32.8€
0.5km	2.09%	4	6 min/person/day	0.0007	344	5%	328€
1km	14.1%	27	11 min/person/day	0.009	4640 €	5%	4420€
2km	21.4%	41	23 min/person/day	0.3	14100€	5%	13400€
3km	13.6%	26	34 min/person/day	0.03	13400€	5%	12800€
4km	6.2%	12	45 min/person/day	0.02	8260€	5%	7860€
5km	17.8%	34	57 min/person/day	0.006	29200€	5%	27900€
6km	5.8%	11	68 min/person/day	0.02	10600€	5%	10100€
7km	3.6%	7	79 min/person/day	0.01	6720€	5%	6400€
8km	3.6%	7	91 min/person/day	0.01	6720€	5%	6400€
9km	0.5%	1	102 min/person/day	0.002	960€	5%	914€
10km	8.4%	16	112 min/person/day	0.03	15400€	5%	14600€
11km	0.5%	1	125 min/person/day	0.002	960€	5%	914€
12km	1.6%	3	136 min/person/day	0.006	2880€	5%	2740€

Mortality is monetized using Value of statistical life (VSL) of 506039.23 euros/death. The Value of statistical life is derived from willingness to pay. VSL is not the value of an identified person's life, but an aggregation of individual values for small changes in risk of death. This value is different for every country and is obtained by a specific formula that derives the country specific values in local currency for the year 2015.

Mortality rate is a measure of the number of deaths in a particular population scaled to the size of death population, per unit of time. The mortality rate for a population is the weighted average of the mortality rate in the exposed population or the so called assessed population and the unexposed population or population that doesn't walk. Mortality rate depends on the contrast in mortality risk between the two groups as well as the size of the groups.

Based on the HEAT criteria, maximal distance that a pedestrian could walk is 12 km, so consequently to this, all of our respondents that gave answers that surpassed this requirement were excluded from the study. Only respondents that met the criteria were included in the study.

Regarding the distance passed on a daily basis, 158 people were walking less than recommended or more than 4/5 from the assessed population. Forty-one person or 21.4%, which is the highest number of respondents, answered they were walking 2 km per day. With the HEAT calculation, it was found that 0.3 premature deaths were prevented, and the economic benefit was calculated to be 13400 euros.

The majority of respondents, 41 of them, said they were walking 2 km per day. If these 41 people walked 7.62 km per day, 0.08 premature deaths would have been prevented, and the total economic impact for 1 year assessment would have been 39400 euros and the total economic value with annual discount of 5% would have been 37500 euros. The difference in economic value between walking 2 km and 7.62 km would be 24100 euros.

The total economic impact of full assessment for 1 year was higher from the total economic value for 1 year. This is due to annual discount rate of 5%, which is ensured by HEAT; the tool gives an opportunity to change this value if the country in which the research is being conducted has another value and these values are usually available by government agencies.

Discussion

Besides WHO4 and CDC (Center of disease control) recommendations6, American Heart Association (AHA)[7] also recommends at least 30 minutes of moderate physical activity daily, at least 5 days a week, minimum 150 minutes per week moderate physical activity or at least 25 minutes for 3 days a week or 75 minutes of intensive physical activity in a week.

In this study,22.5% participants answered they were walking less than 150 minutes per week and 77.5% were walking more than 150 minutes per week as recommended by CDC[6].

The World Health Organization recommends 10,000 steps per day[8].We used a converter (Kyle's converter) for steps to kilometers and 10,000 steps correspond to 7.62 km[9].

If the assessed 191 participants hypothetically walked 7.62 km, there would have been0.4 premature deaths prevented per year, the total economic impact for 1 year assessment would have been 183,000euros and total economic value with 5% annual discount would have been 175,000 euros. These numbers would make a tremendous impact on both, the health system and the economy.In economic terms, this impact would be 66191.2 euros.

The highest noted economic benefit was27,900 euros (Table 3). Logically, it imposes the question "why"? The rea-

son behind this is that respondents that said they were walking more than 5km, individually per answer werefewer than those that walked 5km.

On the other hand, as is to be expected, the least economic benefit would be from persons who walk 200 m or 0.2 km and that would be 32.8 euros, resulting in prevention of 0.00007 premature deaths.

A systematic review of the economy analysis for the active transport interventions in 2016 leads to a conclusion that evidences are insufficient[10].

A study in Palermo made an assessment of their city population of 470,000. The assessment consisted of the economic benefit from these people walking on average 10 minutes per day. They found that if these 470,000 people walked 10 minutes a day for ten years, there would be an economic benefit of 2.2 billion euros and 810 premature deaths would be prevented[11]. In our study, the average time spent walking was 65 minutes. If all of the participants in our study spent 65 minutes walking, there would be 1.83 million euros of economic benefit for ten years with 4 premature deaths prevented.

Another study realized in Aydin, Turkey, made an assessment project very similar to ours. They recruited 260 people for their research, and found that their average walking distance was 2.52 km and applied the HEAT tool. Their results showed that there would be 350,000 euros economic benefit per year and 2,848,000 euros benefit for 10 year assessment[12]. On the other hand, the average walking distance in our study was 4.1 km. Applying HEAT in 191 people with the average walking distance of 4.1 km would make an economic benefit of 128,000 euros per year, and 1,040,000 euros per ten years with 3 premature deaths prevented over 10 years. The difference between the economic benefit would probably be due to the difference in recruited population as well as the Value of statistical life which is different in both countries.

A similar type of study was conducted in Catalonia. The results obtained demonstrated that there would be 124,216,000 euros saved for men and 84,927,000 euros would be saved for women in one year if people who did not follow daily recommendations for physical activity walked for 20-30 minutes, the distance they normally drove for 5 minutes[13]. In our study, 16 participants walked below daily recommendations. If these 16 people walked for 30 minutes a day, there would be 7,290 euros of economic benefit per year and 72,900 euros per 10 years.

Nonetheless, walking as well as cycling are useful for decreasing levels of noise, air pollution and parking expenses[14], decreasing carbon emission, pollution of urban territory and traffic10. In addition to these benefits, the established and proven economic validity from investing in infrastructure for walking and cycling is to be emphasized, too. Furthermore, the goal of achieving safer pavements and convenient recreational grounds will be more approachable if active transport is actively promoted. According to a study in Norway, every car-driven kilometer incurs cost of 0.11 euros, while walking incurs gain of 0.37 euros[15].

By presenting the example in Barcelona, it is visible that increasing walking for 26.7% and cycling for 72.55% in the interval of 2009-2013, the pedestrian injury rate decreased for 26.7%.

As a result, the average economic benefit was estimated to be 47.3 million euros[16].

Data from the Republic Council on Road Traffic Safety, which is an advisory body of the National Assembly of the Republic of North Macedonia, state that pedestrians are the largest group of vulnerable traffic participants. The number of pedestrians dying from road accidents in 2012 compared to 2001 decreased for 50%, but yet the absolute number of pedestrian victims in road accidents is disproportionally high. In 2002, direct and indirect expenses of fatal injury as a result of a traffic accident were 8 million euros, and in 2009 this number went up to 10.6 million euros for accidents that included serious injuries[17]. In 2018, 27 pedestrians lost their lives in traffic accidents, of whom 14 were over 65 years old and 861 pedestrians were seriously injured[18]. 25-30% of deaths in traffic accidents are assigned to pedestrians[19]. This is why it is necessary to support safety measures, through proving separate walking tracks in both urban and rural environments. It has to be mentioned that car transport is increasing more and more when compared to active transport, which creates a pressure to expand the urban environment and road investing, but on the other hand it makes active transport less safe, less attractive and less practical.

In a study conducted in 2008, it was found that physical inactivity was responsible for 9% of premature deaths[20].

Another study examined risk reduction in differently active groups associated with BMI, physical activity and waist circumference. The study suggested that the greatest reduction in risk of premature deaths occurred when comparing inactive and moderately active groups, estimated by combining activity at work and recreational activity. The authors estimated that 20 minutes of walk burns 90-110kcal in people that have similar BMI, and they succeeded in calculating these numbers just by taking one person from the inactive group and transferring that same person to moderately active group and reducing their risk of premature death by 16-30%. They observed the highest impact amongst individuals with a normal BMI. In our study, respondents that walked below the recommended amount of 7.62km as said above, we hypothetically considered to be inactive. We divided them in groups by their BMI according to WHO examples[21]. Depending on BMI level there were75 participantswith BMI in the range of 18.5-24.9 or normal weight, 67 in the range of 25-29.9 that were overweight, 13 participantsin the range of 30-34.9 that were obese, 2 had BMI over 35 and 6 wereunderweight.According to these results, if applied that study to these 163 people, the highest impact of reducing the risk of premature death is expected to be in the 75 people with normal weight. By avoiding all inactivity, theoretically itreduces allcause mortality by 7.35%[22].

Of the 191 respondents, 23 had hypertension, 7 of them had diabetes mellitus type 2, 7 had heart failure, and 8 respondents had chronic pulmonary disease.

Walking at least 10,000 steps a day contributes to an increased glucose tolerance in population with diagnosed diabetes mellitus[23]. In our study, 6 out of 7 diagnosed participants, walked less than 10,000 steps a day Those 6 people, according to

their answers walked as a form of doing some daily activity or form of recreation and just one person answered he was walking as a form of sports activity. Seven participants had diabetes, and 4 of themhad BMI less or equal to 24.9; 2 had BMI of 32 and 33 and 1 person had BMI of 46. Six of the participants did not practice any form of sports, only 1 person answered he was practicing sports activity.

Increasing physical activity among adults at risk for, or with cardiovascular disease (CVD) can help prevent and manage the disease, and walking is an easy way for most adults to avoid inactivity and increase physical activity levels.The prevalence of walking among people at various degrees of CVD risk is unknown[24].

The variance in daily physical activity in heart failure (HF) patients is considerable. In a study that measured daily physical activity of patients with heart failure was found that 44% were active less than 30 minutes a day, whilst 56% were active more than 30 minutes a day25. Eightof our respondents had heart failure, 5 of them said they were walking less than 30 minutes and 3 of them over 30 minutes. In one study, 85% were walking less than 10,000 steps a day, and only 15% were walking more than 10000 a day[25]. In our study, all of theparticipants were walking less than 10000 steps a day. Approximately 65% of the patients with heart failure were overweight or obese[26]. Regarding their BMI, 3 patients were overweight, 2 were obese, 1 was underweight and 2 had normal BMI.

Hypertension is the leading cause of premature deaths and invalidities from cardiovascular diseases[27]. Ten thousand steps a day can significantly decrease blood pressure[28], irrespective ofthe intensity of the exercises[29]. Among our participants 23 answered that they had hypertension. Of these 23 people, 19 answered that they were walking less than 10,000 steps, 4 were walking more than 10,000 steps.Hypertension increases when BMI is increasing[30]. Of the 23 people, 9 had BMI less or equal to 24.9, 9 had BMI less or equal to 29.9, 4 had BMI less than 34.9.It is well known that exercising has hypotensive effect. It can prevent or decrease effects of metabolic and cardiovascular diseases, including arterial hypertension. But in our study, only 3 people gave positive answer for doing sports.

One study examined walking as a form of training and changes in quality of life and exercise in people with chronic obstructive pulmonary disease (COPD) and the results showed a small but significant decrease in dyspnea[31]. In our study, 7 of 8 participants were walking less than the recommended distance. Participants that were walking 1 and 2 km also had comorbidities and were older than 70 years. It imposes the question, if these people walked more frequently and longer distance, would their symptoms decrease? Another study also examined the correlation between physical activity and symptoms of COPD. They found that physical activity can lead to improvements in symptoms such as dyspnea and fatigue[32].

Our study has its flaws and downsides. Participants had a subjective perception of the distance passed on a daily basis and the time spent walking. There were different numbers of participants for the distance passed per day (number of participants per each kilometer) so we couldn`t chose comparative approach for certain matters such as mortality rate. There

were no previous studies that can be used to compare economic benefits of the walking in our country. In general, there are insufficient papers world wide discussing this issue. Another limitation is that majority of the recruited participants was in the age range of 20-35 years; when compared to the age group of 66-73 years, it was 7 times higher.

Conclusion

Walking is and should be an important element of life. There are numerous studies that show its benefit on health overall. This study demonstrated that our population does not follow the recommended amount of daily walking. It has to be emphasized that in this period of pandemic it is even more important to promote walking, since people are in their homes and do not conduct physical activities. Our assessed population was relatively young; the average age was 35 years; it was a healthy population and still the results obtained are not satisfying. The accrued financial benefit, specifically through the 108808.8 euros can be reassigned in other aspects of the health system or be redeployed in other social segments. Walking should be promoted from the earliest ages in order to create a behavioral model that should be practiced throughout lifespan. The benefits from walking should be promoted by teachers, health care providers, by public health experts and especially by media, social networks, different campaigns on local and national levels. Of course, the state is duty-bounded as well as the local authorities to create that safe, comfortable and pleasant environment for walking.

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Public health

CHANGES IN VOICE QUALITY OF THE CHILDREN WITH CLEFT/ LIP IN RELATION TO CHILDREN WITHOUT ANOMALY

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Abstract

Children with cleft palate/lip are exposed to risk for verbal communication disorders that include resonance, articulation, voice disorders, and expressive language. The aim of this paper was to evaluate the changes in the voice quality of the children with cleft palate in relation to children without anomaly. The study included 52 participants, 26 with previously corrected cleft palate / lip, and 26 respondents without anomaly who are between 3 and 6 years old. Subjective assessment of voice quality was performed by using the GRBAS scale. Perceptual scales are important in assessing the voice quality, determining the degree and severity of voice disturbance, and deciding on further clinical procedures. Although the instrumental approach to voice examination is relevant because it provides objectivity, the subjective impression in assessing voice quality is crucial. Statistical processing was performed by groups, group structure (gender and age), a certain highest value, as well as percentage participations. The results showed that 50% of the participants were diagnosed with certain changes in the voice. Children aged 3-5 years have a 2.25 times higher incidence of voice changes than children aged 6-8 years. The largest number of participants belong to group 0 - There is no change in voice quality which represents as much as 50% of the total number of patients in the first group. While *„3 - Pronounced changes in the voice"* were not identified in the respondents aged 3-5 years. In 50% of the total number of participants there is no change in voice quality and these are located in girls aged 3-5 years.

Јавно здравје

ПРОМЕНИ НА КВАЛИТЕТОТ НА ГЛАСОТ КАЈ ДЕЦА СО РАСЦЕП НА НЕПЦЕ/УСНА ВО ОДНОС НА ДЕЦАТА БЕЗ АНОМАЛИЈА

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Печатарски права: ©2021 Мира Јовановска, Мирјана Петровиќ –Лазиќ, Весна Лазаровска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Децата со расцеп на непце /усна се изложени на ризик од нарушувања во вербалната комуникација кои вклучуваат резонанца, артикулација, нарушувања на гласот и експресивниот јазик. Целта на овој труд беше да се согледаат промените на квалитетот на гласот кај децата со расцеп на непце во однос на децата без аномалија. Во истражувањето беа вклучени 52 испитаници од кои 26 сопретходно корегиран расцеп на непце/усна, а 26 испитаници без аномалија на возраст од 3 до 6 години. Субјективна проценка на квалитетот на гласот е извршена со примена на скалата Грбас. Перцептивните скали се значајни во проценка на квалитетот на гласот, одредување на степенот и тежината на пореметувањето на гласот, како и во одлучување за понатамошните клинички постапки. И покрај тоа што инструменталниот пристап во испитувањето на гласот е релевантен бидејќи обезбедува објективност, субјективниот впечаток во проценка на квалитетот на гласот е клучен. Извршена е статистичка обработка по групи, структура на групите (пол и возраст), одредена е највисока вредност, како и процентуални учества. Резултатите покажаа дека кај 50% од испитаниците се дијагностицирани одредени промени во гласот. Децата на возраст од 3-5 години имаат 2,25 пати поголема инциденца на промени на гласот во однос на деца на возраст од 6-8 години. Најголемиот број на испитаници спаѓаат во групата 0 - *Не постои промена во квалитетот на гласот* кој што претставува дури 50% од вкупниот број на пациенти во првата група. Додека „3 - *Изразени промени во гласот*",не се идентификувани кај испитаниците на возраст од 3-5 години. Кај 50% од вкупниот број на испитаниците не постои промена во квалитетот на гласот и овие се лоцирани кај девојчиња на возраст од 3-5 години.

Introduction

Correct, clear and aesthetically pleasing voice is a means of communication between people and through speech, as a perfect form,represents the most comprehensive human activity.[1]

Voice disturbance can be named as anything that reduces the effect of communication and makes the voice less pleasant whereby the speaker for an exemplary strong and pleasant voice consumes too much energy. Voice disorder exists when one or more aspects of the voice e.g., strength, height, quality or resonance deviates from the norms of age or gender of the interlocutor.[2,3]

When we talk about voice disorders in preschool children, we usually think of childhood hoarseness. Hoarseness or dysphonia is the medical and speech therapy name for any deviation from the normal features of pitch and volume of the voice.

Dysphonia can occur at any age, even at the earliest one, and often requires intervention by various professionals, not only phonologists and otolaryngologists, but also the speech therapist himself. Increased strain of the laryngeal musculature is possible to be replaced by intensity of the neck muscles during speech especially in boys. Prevention and early detection of voice disorders are very important so that they do not linger in later years. Changes in the voice of children are most often observed in the period from the third to the sixth year, which is associated with the specifics and limited possibilities of the child's voice in this period.[4]

Some research show that changes in voice quality, especially in the form of hoarseness, are present in more than 50% of preschool children. The most common cause is hyperkinetic dysphonia which most often occurs due to incorrect or inappropriate use of the voice.[5] The voice in hyperkinetic dysphonia is most often hoarse, with a lot of noise and hoarseness.

Children with cleft lip / palate are at risk for verbal communication disorders that include resonance, articulation, voice disorders, and expressive language.[6]

Many researchers note an increase in the symptom of hoarseness in patients with cleft palate compared to the normal population; however, the exact prevalence is currently unknown. Previous reports of dysphonia indicators for the cleft palate population are 12% to 43%.7, These are similar to, until present, rates of hoarseness in the normal paediatric population, estimated to be 6 to 34%.[8, 9,10,11]

Researchers have set up many different hypotheses to explain this possible increase in hoarseness, the most common being laryngeal compensation for abnormal velopharyngeal valve.[12,13]

Many patients with cleft palate also have velopharyngeal insufficiency (VPI), secondary to palatal muscle orientation. Velopharyngeal insufficiency, which may persist after surgical cleft correction, may cause speech hypernasality and difficulty articulating specific consonants due to the inability to build up sufficient air pressure in the oral cavity. Studies report an incidence of hypernasality in patients with cleft palate of 25% to 40%.[14]

Patients with cleft palate with VPI often use compensatory mechanisms to increase articulation. Some of these mechanisms include palatal stops, posterior nasal fricative, velar

fricative, pharyngeal stops, pharyngeal fricative, and glottal stops.14

Glottal stops, in particular, have been implicated in vocal cord abnormalities and voice disorders such as hoarseness.[15,16]

In fact, the Cleft Palate Foundation literature states: "Children with velopharyngeal disorder may also have voice disorders. In this case, your child's voice may sound "breathing" and he or she can get tired easily. This problem is usually caused by the strain he or she puts on the vocal cords while trying to build up the pressure necessary for normal speech.[11]

There are studies in which no link has been found between hoarseness in patients with cleft palate and VPI, which calls into question the long-standing theory of laryngeal compensation as a source of hoarseness.[17]

The aim of this paper is to evaluate the voice changes in children with cleft palate / lips in relation to children without such anomaly.

Material and methods

In the Institute for Rehabilitation of Hearing, Speech and Voice - Skopje 28 patients were diagnosed with cleft lip / palateduring the two years 2019 and 2020. 26 of them are covered by speech therapy. A total of 52 participants are included in the study. Inclusion criteria:

- Respondents with previously repaired cleft palate
- Age of 3-8 years

The participants are divided into 2 groups. The first group consists of 26 (n = 26) children with previously repaired cleft lip / lip, of which 18 are girls and 8 are boys at the age of 3-8 years. The second group - control consists of 26 (n = 26) children without anomaly. The groups matched by age and gender.

The participants were examined individually in a speech therapy office in which the impact of possible noise from the environment was minimized. Before the beginning of the examination, instructions for the course of the examination about the expected activities that are expected from the participantsare given. The examination was performed by three vocal therapists. The therapists were in direct contact with the patient at a distance of one metre and independently assessed the voice. The degree of agreement between the three vocal therapists using the Kappa coefficient was examined. The degree of agreement between the first and second therapist is good (kappa = 0.490, $p < 0.001$), as well as between the second and third (kappa = 0.610, $p < 0.001$) also between the first and third (kappa = 0.481, $p < 0.001$) which has been shown to have a high degree of agreement among vocal therapists.

Perceptual voice assessment was used as a method, which is a subjective method for assessing dysphonia. It is a non-invasive method that does not require additional equipment. The questionnaire for perceptual assessment of the voice GRBAS was used. The auditory-perceptual scale GRBAS is a focused phonetic component in assessing the quality of the voice and is most often used in practice. This scale, developed in Japan by the Japanese Society of Speech Therapists and Phoniatrics (Webb et al., 2004), is considered as the gold standard for perceptual voice assessment and is commonly used by experts around the world.[18]

It is used to analyse voice quality according to five parameters: G - overall grade of dysphonia or abnormality of the voice, R - roughness or psychoacoustic impression of improper vibrations of the extinguishers; B - breathiness - refers to the psychoacoustic sensation of air flow through the glottis; A - asthenia which is a weakness in the voice; S - strain (hyperfunction) in the voice during phonation.

Each parameter of the GRBAS scale is rated on a scale from 0 (normal voice) to 3 (severe pathology). That is, it is used in the evaluation where the quality of the voice is described as follows: when there is no change in the quality of the voice a score of 0 is determined, slight changes in the quality of the voice are marked with a score of 1, moderately changed voice with a score of 2, while changes in the voice with a grade 3. The score is calculated so that for each parameter is used the average value obtained by the therapist, i.e., the average grade that is determined for all three vocal therapists.[18]

In this research, statistical processing was performed by groups, group structure (gender and age), a certain highest value, as well as percentage participations.

Results

Out of a total of 52 children examined in 2019 and 2020, 15.4% are children - patients with cleft palate / lip at the age of 3-5 years, while 34.6% are children - respondents who have been diagnosed deformities at the age of 6 - 8 years.

The distribution of examined patients by years of research is 46 respondents in 2019 and only 6 in 2020, i.e., 88.5% and 11.5% by years, respectively. Hence, the results of the analysis of the obtained results as much as 88.5% refer to the diagnoses determined by the examinations in 2019, which is a dominant level of responsiveness. Due to the negligibly small number of respondents (patients) in 2020 (only 6), which refers to only one group of children aged 3-5 years, in this study the processing and analysis of test results, obtained by the examinations, refer to both years together.

Table 1: Distribution of covered patients by age and sex, shows the distribution of respondents who have been diagnosed with changes and who have not been diagnosed with any changes, by age and sex. It is evident from the numbers in the table that in the research, 50% of the respondents were diagnosed with some changes in the voice, while the other 50% of the respondents were not diagnosed with any deviations.

From the 26 diagnosed respondents who have a certain type of voice change, which are divided into 4 groups, listed above in the text below the table, the conclusion is that children aged 3-5 years have a 2.25 times higher incidence of voice changes related to children aged 6-8 years, of which girls in this group aged 3-5 years have 2 times higher incidence of voice changes than boys (ratio 6: 3 girls to boys).

In the group of participantsaged 6-8 years a decrease in diagnosed patients is evident, by 67% in boys aged 6-8 years compared to those aged 3-5 years, and by 50% in girls aged 6-8 years. 8 years compared to those of 3-5 years and, by 50% in girls.

The other participantsfrom the control group are of the same age and sex but certainly without cleft palate as an anomaly and without voice disorders.

Table 1. Distribution of covered patients by age and sex

Age	First group (n=26)		Control group (n=26)	
years	boys	girls	girls	girls
3-5	6	12	6	12
6-8	2	6	2	6
total	8	18	8	18
	26		26	

The following, Table 2, shows the distribution of diagnosed patients with voice changes, who are disaggregated into 4 groups, as follows: 0- There is no change in voice quality; 1- Slight changes in voice quality; 2- Moderately altered voice and 3- Pronounced voice changes.

Table 1. Distribution of diagnosed patients by categories of voice changes

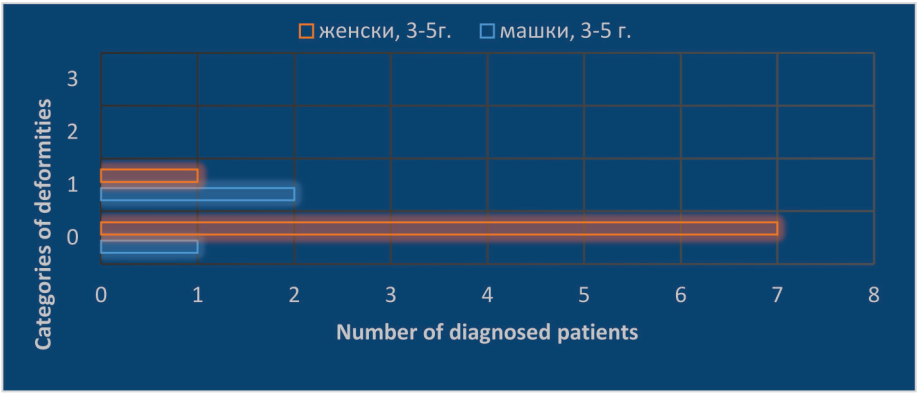
	First group				Control group			
	boys		girls		boys		girls	
	3-5 years	6-8 years	3-5 years	6-8 years	3-5 years	6-8 years	3-5 years	6-8 years
There is no change in voice quality 0	2		14		6	2	12	6
Slight changes in voice quality 1	4		2					
Moderately altered voice 2		2		2				
Pronounced voice changes 3								

The structural analysis of the obtained results in the first group - 26 patients with cleft palate / lip, shows that, analysed by categories of deformities, in the respondents aged 3-5 years, in the category "O - There is no change in voice quality" , 87.5% are girls, while only 12.5% are boys, out of the total of 16 diagnosed patients (participants). What is significant about this group is that it includes the largest number of respondents with diagnosed deviations in general, which represents as much as 54% of the total number of patients in this First group. These 54% are located in girls aged 3-5 years.

In the category "1 - Slight changes in voice quality", out of a total of 6 patients diagnosed aged 3-5 years, the ratio between boys and girls is

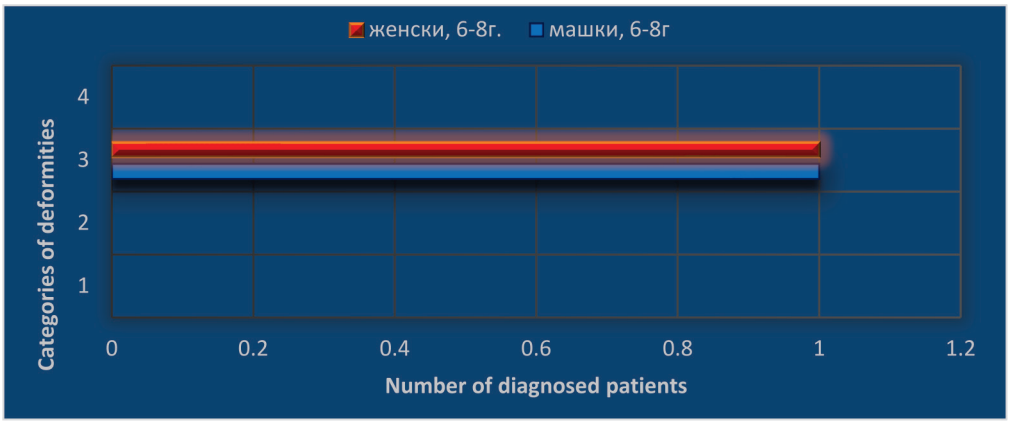
inversely proportional to the previous diagnosis (category), i.e., 1/3 are girls, while as much as 2/3 are boys, out of the total of 6 diagnosed patients (participants). In the categories "2 - Moderately altered voice" and "3 - Pronounced changes in the voice", during the study, no deviations were identified in the participants aged 3-5 years.

Picture 1. Changes in cleft palate patients voice according to categories of deformities 2019-2020



Among the participants aged 6-8 years, the analysis of the data shows that in children with cleft palate in the category "2 - Moderately altered voice", there is an even distribution in boys and girls (50-50%), out of a total of 2 diagnosed children aged 6-8 years in this category.

Picture 2. Changes in cleft palate patients voice according to categories of deformities 2019-2020



Discussion

The results obtained in this research show that 50% of the respondents were diagnosed with some changes in the voice, while the other 50% of the respondents were not diagnosed with any deviations. In the category "O - There is no change in voice quality", 87.5% are girls, while only 12.5% are boys, out of a total of 16 respondents. What is significant in this group is that even in 50% of the total number of respondents there is no change in voice quality and these are located in girls aged 3-5 years.

According to the results of the research, it can be seen that there are no registered respondents with cleft palate / lip in whom there are pronounced changes in the voice in relation to the control group.

From the 26 participants (patients) diagnosed with some kind of devia-

tion in voice change, which are divided into 4 groups, listed above in the text below the table, the conclusion is that children aged 3-5 years have a 2.25 times higher incidence of voice changes in relation to children aged 6-8 years, of which girls in this group aged 3-5 years have 2 times higher incidence of voice changes than boys (ratio 6: 3 girls to boys). Out of a total of 2 diagnosed children aged 6-8 years in this category are with equal distribution among boys and girls (50-50%), in the category "2 - Moderately altered voice".

The values of the parameters obtained from this research show that even in 50% of the total number of respondents there is no change in voice quality as shown by the research of other authors regarding voice disorders in children with cleft palate that may occur due to compensatory mechanisms of speech.[17]

The results showed that there is a change in the voice of children with cleft palate / lips who have ORL infections often resulting in occasional hearing loss recorded by audiometry.

Studies show that in addition to the characteristics of speech disorders in the form of articulatory features and increased nasal air emissions, voice disorders may occur in these patients, especially in boys.[13]

Although future research on voice disorders in patients with cleft lip / palateis needed, now it seems reasonable to include voice therapy strategies in the speech and language intervention plan for these patients with this type of anomaly.[19]

Subjective assessment of the voice quality is the analysis of the voice with its own hearing. Despite modern technology, the trained human ear is indispensable in the assessment of the voice and the most important "apparatus" in examining the subjective or psychoacoustic characteristics of the voice. Considering that subjective impression is crucial in communication, the role of perceptual voice assessment in clinical terms is extremely important. This instrument is characterized by simplicity in application and economy. Perceptual assessment is inevitable in the domain of interpretation of the objective ways of evaluating the quality of the voice, it is a mean of diagnosis and assessment of the success of the therapy of voice disorder. Perceptual assessment results may be influenced by different criteria of the examiner as well as differences in the experiences of the examiners.[20,21]

The reliability of the Grbas scale has been examined by De Bodt et al. (De Bodt, Wuyts, Van de Heyning, &Croux, 1997). The results of the research of these researchers show that the reliability of this scale is satisfactory. Aguero et al. (Agüero, Tulli, Moscardi, Gonzalez, &Uriz, 2011) examined the reliability of the Grbas scale and compared the results obtained with other methods of subjective assessment of voice quality. (The Consensus Auditory-Perceptual Evaluation of Voice - CAPE-V; Buffalo Voice Profile - BVP; Vocal Profile Analysis Scheme - VPA). The results of these studies show that the Grbas scale is the most reliable compared to other methods with good reliability for all parameters of the voice, except for the scale S whose certainty was moderate. When compared to GRBAS, CAPE-V showed slightly better assessor reliability. [22,.23]

The shortcomings of subjective voice assessment can be overcome by researching the correlation between acoustic and perceptual parameters of voice quality as well as reaching an agreement on terminology and using numerical rating scales. [24]

Ongoing work on more effective assessment focuses on a physio psychoacoustic model linking voice production, acoustics, and perception.[20,25]

Conclusion

In addition to the proper stimulation of speech and language development in children, it is extremely important to monitor possible changes in the state of the voice in childhood, especially in children with certain congenital anomalies.

When it comes to perceptual assessment of voice, previous research indicates some shortcomings, such as the competence and experience of examiners, as well as mutual disagreement in assessing the degree of expression of certain characteristics of voice quality.

The main disadvantage of perceptual voice evaluation is the problem of description. There are no reliable verbal terms describing vocal features, although there is a constant need to define descriptive terminology.

To get more accurate results, more research on voice changes in children with palate cleft palate and velopharyngeal dysfunctionshould be done in future, and also, at the same time, checking the state of hearing.

The obtained more accurate results give an accurate insight into the condition of the voice in children with this type of congenital anomaly. If there are changes in the voice, then the condition is more complex and accordingly the speech therapy will be the same. This is very important for its proper course and success.

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Public health

THE PRIORITIZATION OF ZOONOSES IN THE REPUBLIC OF NORTH MACEDONIA – DO WE NEED ONE HEALTH APPROACH

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Abstract

Zoonoses have a different impact on public health, determined by geographical and socio-economic factors, which requires their prioritization for prevention and control purposes to be performed at the national level. Prioritization of zoonoses is a mechanism used in policy-making, primarily in allocating available resources.The aim of the paper was to compare two different methods used for prioritization of zoonoses by the Institute of Public Health (IPH) and Food and Veterinary Agency (FVA). Material and methods: IPH used a method prepared by the U.S. Centers for Disease Control and Prevention (CDC), - One Health Zoonotic Disease Prioritization (OHZDP) tool, adapted to national conditions (2019). FVA used a standardized semi-quantitative method based on the OIE Methodological Manual (List and Categorization of priority diseases in animals including those transmitted to humans). A total of 21 zoonoses were selected, based on their importance for the human and veterinary sector. These diseases were ranked according to the stated criteria of the two previously conducted prioritizations and their comparison was performed. Results: With the prioritization conducted by IPH and FVA the first 5 ranked zoonoses were: hemorrhagic fevers with renal syndrome, leishmaniasis, tularemia, brucellosis and listeriosis. With the prioritization carried out by the FVA the first 5 ranked zoonoses were: bovine brucellosis, bovine tuberculosis, salmonellosis, avian influenza and West Nile fever. A Cumulative Annual Incidence was taken as a control parameter. Regarding this, the 5 first ranked zoonoses were: echinococcosis, brucellosis, Lyme fever, leishmaniasis and tularemia. Conclusions: A comparative analysis of the separate lists of priorities for human and veterinary medicine shows that only a certain percentage overlap. Also, the presence of a number of zoonoses with endemic character, but also a more pronounced risk of new emergent diseases, determines the need to provide consensus on the methodology of prioritization of zoonoses, and its formalization and institutionalization, as a crucial step towards identification and prioritization of zoonoses that would be the subject of joint programs and interventions.

Јавно здравје

ПРИОРИТИЗАЦИЈА НА ЗООНОЗИТЕ ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА – ДАЛИ Е ПОТРЕБЕН ПРИСТАП НА ЕДНО ЗДРАВЈЕ

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Цитирање: Јаневски Б, Тозија Ф, Ристовска Г, Попоска-Тренеска В. Приоритизација на зоонозите во Република Северна Македонија – дали е потребен пристап на Едно Здравје. Арх. Ј Здравје 2021;13(2). 39-48

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Клучни зборови: зоонози, приоритизација, јавно здравје, Едно Здравје

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Печатарски права: ©2021 Блажо Јаневски, Фимка Тозија, Гордана Ристовска, Владимир Микиќ, Василка Попоска- Тренеска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Зоонозите имаат различен импакт врз јавното здравство, детерминирано од географските и социоекономските фактори, што условува нивната приоритизација за цели на превентива и контрола да биде изведена на национално ниво. Целта на трудот беше да се споредат два различни метода што се користат за приоритизирање на зоонозите од Институтот за јавно здравје (ИЈЗ) и Агенцијата за храна и ветеринарство (АХВ). Материјал и методи: ИЈЗ користеше метод подготвен од U.S. Centers for Disease Control and Prevention (CDC), - One Health Zoonotic Disease Prioritization (OHZDP) алатка, прилагодена на националните услови (2019). АХВ користеше стандардизиран полуквантитативен метод заснован на методолошкиот прирачник на OIE (List and Categorization of priority diseases in animals including those transmitted to humans). Беа селектирани вкупно 21 зоонози, врз основа на нивната важност за хуманиот и ветеринарниот сектор. Овие зоонози беа рангирани според наведените критериуми на двете претходно спроведени приоритизации и беше извршена нивна споредба. Резултати: Со приоритизација спроведена од ИЈЗ и АХВ (семиквантитативен метод Rist CDC), први 5 рангирани зоонози беа: хеморагични трески со бубрежен синдром, лајшманијаза, туларемија, бруцелоза и листериоза. Со приоритизација спроведена од АХВ (модификација на квантитативниот метод на OIE), први 5 рангирани зоонози беа: бруцелоза кај говеда, туберкулоза кај говеда, салмонелоза, авијарна инфлуенца и западнонилска треска. Како контролен параметар беше земена кумулативната годишна инциденција (КГИ). Првите 5 рангирани зоонози согласно КГИ беа: ехинококоза, бруцелоза, лајмска треска, лајшманијаза и туларемија. Заклучоци: Споредбената анализа на одделните листи на приоритетни зоонози за хумана и ветеринарна медицина покажува дека само одредени зоонози се преклопуваат. Исто така, присуството на голем број зоонози со ендемичен карактер, но и поизразен ризик од појава на нови заболувања, ја одредува потребата да се обезбеди консензус за методологијата на приоритизација на зоонози, како и нејзино формализирање и институционализација, како клучен чекор кон идентификување и приоритизирање на зоонози кои би биле предмет на заеднички програми и интервенции.

Introduction

Zoonoses are infectious diseases that can be transmitted between animals and humans, directly or indirectly, and especially through direct contact and / or through food. Zoonoses pose a persistent public challenge due to the dynamic and complex nature of the problem[1]. Apart from the basic characteristics of infectious diseases that make them a subject of special interest for human and veterinary medicine, zoonoses have a special feature that makes them a common problem for both disciplines. The importance of zoonoses for human medicine and public health stems from their pathogenicity to humans, but also the economic losses they can directly and indirectly inflict on farmers and business operators, as well as their overall socio-economic impact[2-4].

Prioritization is defined as a process of evaluation of a group of entities and their ranking in order of their importance or urgency, i.e. systematization in relation to certain predefined criteria - a process of defining priorities in most areas of public health3. Defining the priorities in the field of infectious diseases and classification of the most important pathogens in terms of their importance for a certain country - prioritization is applied by several institutions and countries. Prioritization as an instrument is especially important when creating certain policy and allocating public health resources in a given country.

In the past, recognized prioritization methods were used by a range of health professionals to identify infectious diseases in the domain of public health and animal health, for national surveillance and risk assessment programs, including zoonoses. Prioritization methodologies have been developed and discussed for different goals and priorities. Methods, depending on the selection criteria and the ranking of pathogens, are defined as qualitative, semi-quantitative and quantitative[5]. Different methods have been used by researchers. The published materials on the process of prioritization of diseases differ in the number of pathogens that are ranked, the number of criteria by which they are ranked and the methods used. Quantitative methods are applied when there is empirical data, such as disease burden, and socio-economic impact as well as when there are effective surveillance systems. Semiquantitative and qualitative methods are used when data are insufficient or not available at all[2].

The aim of the paper was to compare two different methods used for prioritization of zoonoses by the Institute of Public Health (IPH) and Food and Veterinary Agency (FVA).

Materials and methods

IPH used the method developed by the U.S. Centers for Disease Control and Prevention (CDC), - One Health Zoonotic Disease Prioritization (OHZDP) tool, adapted to national conditions (2019)[5].

FVA used the standardized semi-quantitative method based on the OIE Methodological Manual (List and Categorization of priority diseases in animals including those transmitted to humans). The methodology is based on the document of the World Organization for Animal Health - Office International des Epizooties (OIE)[6]. The methodology is officially adopted by the Food and Veterinary Agency[7].

The categorization itself is conducted in three phases:

- Preparation of a List of infectious diseases in animals that are categorized and prioritized (with special reference to zoonoses) and a list of infectious diseases - zoonoses in humans, according to the national legislation for zoonoses that are legally regulated in human and veterinary medicine [8, 9].

- Provision and processing of data on zoonoses in the human population and animal population.

- Implementation of categorization and prioritization of zoonoses from the previously defined list in accordance with certain criteria and values and comparison with the list of IPH and the cumulative annual incidence (CAI) [10].

Phase 1 List of zoonoses that are categorized and prioritized

The lists of zoonoses that are categorized and prioritized are prepared on the so-called legal basis, i.e. only the diseases that are legally regulated are included. The list of infectious diseases in animals that are categorized and prioritized is prepared as a joint combined list of diseases that are legally regulated in accordance with the national legislation of North Macedonia and a list of diseases that are legally regulated in accordance with EU legislation. This list also includes zoonoses that are important from the aspect of veterinary public health (foodborne infections and intoxications and vector borne diseases).

Phase 2

The first prioritization was made by the Institute of Public Health (IPH), in cooperation with representatives of the FVA, with the methodology of the U.S. Centers for Disease Control and Prevention (CDC), - One Health Zoonotic Disease Prioritization (OHZDP) tool, adapted to national conditions (2019). Prioritization is based on the One Health Approach methodology developed by CDC Atlanta in several steps[5]:

First step - preparation of a working group with representatives from the human and veterinary sector and preparation of a list of zoonoses that should be ranked. The list of diseases that are subject to ranking (prioritization) is composed of selected zoonoses and vector communicable diseases that are subject to mandatory reporting in the public health sector and in the veterinary sector. Second step - defining criteria for selection of public health significance of zoonoses, selected in the first step. Third step - developing questions by defining a categorical question for each of the criteria selected in the second step. Fourth step - ranking of the criteria with individual ranking of the criteria specified in step 2 by each representative, and then the individual grades are combined and a common list of ranked criteria is obtained. Fifth step - ranking the zoonoses where each zoonosis is scored based on the answers for each criterion, the scores for each disease are summed and normalized according to the maximum score, thus obtaining the final list of priority diseases.

Results

List of ranked zoonoses according to the methodology of IPH is presented in Table 1.

Table 1. List of ranked zoonoses according to the methodology of IPH

Zoonosis	Total points	Normalized result	Rank
Hemorrhagic fevers with renal syndrome	24.00	1.00	1
Leishmaniasis	23.17	0.97	2
Tularemia	23.17	0.97	3
Brucellosis	22.58	0.94	4
Listeriosis	21.92	0.91	5
West Nile Virus Infections	21.67	0.90	6
Salmonellosis	20.67	0.86	7
Leptospirosis	19.75	0.82	8
Tetanus	19.75	0.82	8
Echinococcosis	19.08	0.80	10
Verotoxigenic E. coli infection	18.42	0.77	11
Trichinellosis	17.83	0.74	12
Avian Influenza (HPAI, LPAI)	17.67	0.74	13
Anthrax	16.50	0.69	14
Lyme fever	16.33	0.68	15
Rabies	13.75	0.57	16
Q Fever	13.00	0.54	17
Prion diseases	11.25	0.47	18
Pestis	10.25	0.43	19
Encephalitis (arthoborne)	9.75	0.41	20
Campylobacteriosis	9.00	0.38	21
Rift Valey Fever	0.00	0.00	22
Japanese encephalitis	0.00	0.00	22
Glanders	0.00	0.00	22
Giradiasis	0.00	0.00	22
Shigelosis	0.00	0.00	22

The second categorization and prioritization were conducted by the FVA (2019 and 2020). For each disease in the List of the 4 criteria the value

from 0 to 3 is determined. After assigning the values for each disease the total numerical value is determined, which can range from 0 to 3. After obtaining the total numerical value, diseases are sorted in order of the total numerical value from the highest to the lowest value. The zoonoses are extracted from the list and their order is given in Table 2.

Table 2. List of ranked zoonoses in veterinary health according to FVA

Zoonosis	A1	B2	C3	G4	Total score
Bovine Brucellosis	3	3	3	3	**12**
Bovine Tuberculosis	3	3	3	3	**12**
Brucellosis in goats and sheep (with the exception of Brucella ovis)	3	3	3	3	**12**
Salmonellosis (zoonotic salmonella) of importance in public veterinary health	3	3	3	3	**12**
Avian Influenza (HPAI and LPAI)	2	3	3	3	**11**
West Nile Virus Fever	0	3	2	2	**7**
Verotoxigenic E. coli	0	3	2	2	**7**
Rabies virus infection	0	3	0	3	**6**
Echinococcosis	3	3	0	0	**6**
Campylobacteriosis	3	3	0	0	**6**
Listeriosis	3	3	0	0	**6**
Trichinellosis	3	3	0	0	**6**
Anthrax	2	3	0	0	**5**
Equine Encephalomyelitis	2	0	2	0	**4**
Glanders	0	3	0	0	**3**

Table 3. List of zoonoses and vector borne diseases that are subject to mandatory reporting as diseases or microbiologically proven causes of disease in humans, and annual incidence of occurrence in North Macedonia in the period 2013-2019

	CAI	IPH	FVA
Hemorrhagic fevers with renal syndrome	0	0.69	0.250
Leishmaniasis	0.7	0.94	1.000
Tularemia	0	0.57	0.250
Brucellosis	1	0.8	0.500
Listeriosis	0.1	0.97	0.000
West Nile Virus Infections	0	0.54	0.000
Salmonellosis	0.2	0.68	0.000
Leptospirosis	0	0.47	0.000
Tetanus	0	0.82	0.000
Echinococcosis	0	0.74	0.500

Verotoxigenic E. coli infection	0	0.82	0.000
Trichinellosis	0.1	0.97	0.000
Avian Influenza (HPAI, LPAI)	0	0.43	0.000
Anthrax	n.d	0.86	1.000
Lyme fever	n.d	0.77	0.000
Rabies	n.d	0	0.000
Q Fever	n.d	0.91	0.500
Prion diseases	n.d	0.38	0.500
Pestis	n.d	0	0.000
Encephalitis (arthoborne)	n.d	0.9	0.583
Campylobacteriosis	n.d	0	0.000
Rift Valey Fever	n.d	0	1.000
Japanese encephalitis	n.d	0.74	0.917
Glanders	n.d	0	0.250
Encephalitis Arboborne	n.d	0.41	0.000

Phase 3

A total of 21 zoonoses that are important for the human and veterinary sector were selected. These diseases were ranked according to the stated criteria of the two previously prioritized and their comparison was performed.

With the prioritization conducted by IPH and FVA (semi-quantitative method Rist CDC) the first ranked 5 zoonoses were: hemorrhagic fevers with renal syndrome, leishmaniasis, tularemia, brucellosis and listeriosis.

With the prioritization carried out by the FVA (quantitative method modification of OIE), the first 5 ranked zoonoses were: bovine brucellosis, bovine tuberculosis, salmonellosis, avian influenza and West Nile fever.

A Cumulative Annual Incidence was taken as a control parameter. In the cumulative annual incidence, the first 5 ranked zoonoses were: echinococcosis, brucellosis, Lyme fever, leishmaniasis and tularemia.

A comparative overview of the ranked zoonoses from the two prioritizations compared to CAI is given in Table 4.

Table 4. Comparative analysis of the top five ranked zoonoses with CAI.

Ranking	IPH	FVA	Cumulative Annual Incidence
1	Hemorrhagic fevers with renal syndrome	Bovine Brucellosis Brucellosis in goats and sheep	Echinococcosis
2	Leishmaniasis	Bovine Tuberculosis	Brucellosis
3	Tularemia	Salmonellosis (zoonotic salmonella) of importance in public veterinary health	Lyme fever
4	Brucellosis	Avian Influenza (HPAI and LPAI)	Leishmaniasis
5	Listeriosis	West Nile Virus Infections	Tularemia

Discussion

A certain number of countries are prioritizing infectious diseases: the Netherlands[11], Germany[12]; Canada [13,14]. Prioritization is also carried out by international organizations (WHO, OIE) or government agencies (ECDC) (EFSA) [15-19].

In Macedonia until 2019 there was no formalized and official prioritization of zoonoses. Establishing a system of scientifically based prioritization of zoonoses enables policy makers as well as risk managers to make evidence-based decisions (Cardoen 2009) and to develop targeted programs and interventions. To date, a number of different models have been developed, using different approaches and techniques.

Selecting or developing an appropriate method is a crucial step in implementing prioritization. Rist (2014) emphasizes the fact that the initial step in joint activities is the identification of diseases and / or pathogens that are of the greatest importance, so that limited financial and human resources can be effectively directed. Cardoen (2009) emphasizes the semiquantitative method as a method that overcomes the problems that arise with quantitative methods - lack of data and the problems that arise in qualitative methods as subjectivity. The choice of a national method is conditioned by the available data, their uniformity and the level of legislative and regulatory regulation of zoonoses at a given moment. An important factor in determining the methodology is the ultimate goal of prioritization.

Second, the selection of criteria on the basis of which the prioritization would be carried out is the most sensitive point, although it is the basic determinant for the performance of the method. It should be borne in mind that the choice of criteria is largely conditioned by both the context and the ultimate goal of prioritization. Quantitative methods are less arbitrary; real values are used, and the disadvantage is that they are extensive and require detailed processing of large amounts of data, and there can always be a problem that certain data may be missing.

Allocation of limited resources is a continuous problem of state institutions in charge of prevention and control of zoonotic agents and alimentary infections and intoxications[1]. The results from qualitative and semi-quantitative approaches are highly dependent on the perception of individual experts, which requires further validation of the methodology and comparative analysis with other types of methodologies. Having in mind that the selection of categorization and prioritization criteria is a crucial element in the validity of the process itself, public health decisions should take into account all factors, including social values, public perception and opinion, as well as opinion of professional circles, actual policy and economic factors.

Regarding the comparative prioritizations, it can be seen that there are differences in the results. The results of the prioritization conducted only from the aspect of veterinary medicine do not correspond to the occurrence and incidence of zoonotic diseases in the human population and the prioritization conducted to the IPH.

According to CAI, the diseases with the highest incidence are echinococcosis, brucellosis, Lyme fever, leishmaniasis and tularemia per 100,000

inhabitants. The mentioned CAI also differ from the list of prioritization of IPH and FVA.

Only one disease (brucellosis) has been identified in all three lists. Tularemia and leishmaniasis have been identified in two lists, the other zoonoses are present only on individual lists.

If the most realistic data is taken, the actual occurrence of zoonoses in the human population, i.e. the cumulative annual incidence, it follows that the results of the prioritization of the two institutions do not overlap, and furthermore, they also differ from the actual situation on the ground.

The different ranking of individual zoonoses and the inability to provide a correlation with the values of the cumulative incidence indicate the need for a uniform integrated method of prioritization of zoonoses and the need to focus on zoonoses that have the most significant load.

In the context of the prioritization of zoonoses in the Republic of North Macedonia, two main factors are imposed in the development of the method.

The first factor and the main obstacle in this approach is the lack of an appropriate officially recognized methodology for the two segments of zoonoses (human medicine and veterinary medicine) as well as their insufficient integration and in some cases compatibility. This in turn results in an uncoordinated and therefore not always effective response to public health challenges and threats. It is necessary to provide a unique and flexible methodology that would be recognized and accepted by both sectors and which would simultaneously meet the needs of both sectors, taking into account their different priorities, opportunities and resources.

The second factor is that at the moment there is no uniformity of presentation of data between sectors at the national level and also at the international level. Therefore, the data from the EU institutions are used (in cases when there is data for North Macedonia), or international institutions when such data are not available at EU level. In all aspects, the prioritization method should be efficient in ranking, standardization, reproducibility and transparency.

The selection of criteria was made in accordance with the recommendations or methodologies of other authors. Efforts have been made to ensure a balanced share of the criteria in terms of human health and veterinary health. The findings are not analyzed in terms of their epidemiological and epizootic criteria, given that the main goal is to determine the different outcomes of prioritization when applying certain different methodologies, and display the results of the ranking.

The presented methodology has to be reproducible, standardized and transparently based on publicly available data, which allows its application to continue.

The first important point is that the medical and socio-economic impact, as well as the burden on public health is largely conditioned by the geographical and time period of occurrence2, which requires the prioritization to take place at the national level and in certain time periods. The second important point is enabling and using a unique and integrated methodology for the human and veterinary sector. The different ranking of individual zoonoses and the inability to provide

a justified correlation with the values of the cumulative incidence indicate the need for a uniform integrated method of prioritization of zoonoses and the need to focus on the zoonoses that have the highest burden, and not the zoonoses for which there is greater awareness.

Continuous implementation over a period of time, with subsequent new inputs as a result of changes in prevalence and values of other criteria would allow obtaining a real picture. The development and implementation of an appropriate effective and applicable method for prioritizing diseases is imposed as a priority. A strong contribution to the common prioritization methodologies is the provision of a common position for effective and efficient supervision, coordinated and integrated laboratory capacity, multi-sectoral projections and forecasting, the construction of joint control and prevention strategies.

Conclusion

The result of the prioritization process is a ranked list of zoonoses of equal importance to the human and veterinary sectors. Prioritization is an effective tool in creating and implementing health policies, especially in the parts where there is an overlap of sectors with different priorities (zoonoses, human and veterinary medicine).

A comparative analysis of the separate lists of priorities for human and veterinary medicine shows that only a certain percentage overlap. Zoonoses, and especially emergent and re-emerging diseases, pose a serious threat to both humans and animals. This presupposes an equal integrated response in both the human and veterinary sectors. Also, the presence of a number of zoonoses with endemic character, but also a more pronounced risk of new emergent diseases, determines the need to provide consensus on the methodology of prioritization of zoonotic diseases, and its formalization and institutionalization, as a crucial step towards identification and prioritization of zoonoses that would be the subject of joint programs and interventions.

Determination of uniform model can be an initial step in the formal identification and prioritization of zoonoses and pathogens that are of utmost importance to the state and with effective directing of financial resources. The method, based on the internationally recognized methodology, provides a process in which a priority list of zoonoses is prepared on a quantitative method, which allows to reduce the subjective approach to the lowest possible level, given that decisions are based on data, and not on estimation and opinions.

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Public health

THE ROLE OF AGE ON SPEECH DEVELOPMENT IN SUBJECTS WITH COCHLEAR IMPLANTS

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Abstract

The cochlear implant has been approved as a method of treating bilateral deep deafness since the 1980s, and since then candidate selection methods have changed several times. Initially, the candidates were only adult patients, and in 1990 the cochlear implant was approved for the first time in children under 2 years of age by the US Food and Drug Administration. In 2000, the same US Administration reduced the limit to one year. The aim of this study was to determine the effect of age at cochlear implantation on speech recognition abilities. Concerning the age groups in which the subjects were assigned to, the best results on the tests were achieved by the group who underwent cochlear implantation at the youngest age. In conclusion, the benefit from cochlear implant in subjects with pre-lingual hearing impairment of the most severe degree has to be stressed and it is much bigger in comparison to individual amplifying hearing aids. If cochlear implant is placed at the youngest age, the results might lead to even 100% of active involvement in the social life of individuals with this kind of impairment.

Јавно здравје

УЛОГАТА НА ВОЗРАСТА ВРЗ РАЗВОЈОТ НА ГОВОРОТ КАЈ СУБЈЕКТИ СО КОХЛЕАРНИ ИМПЛАНТИ

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Клучни зборови: оштетен слух, кохлеарен имплант, рехабилитациски третман, развој на говор

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Кохлеарниот имплант е одобрен како метод за лекување на билатералната длабока глувост уште од осумдесеттите години, а оттогаш методите на селекција на кандидатите се менувале повеќе пати. Најпрво кандидати биле само возрасни пациенти, а во 1990 година за прв пат се одобрил кохлеарниот имплант и кај деца со најмалку наполнети 2 години живот, од страна на Американската администрација за храна и лекови. Во 2000 година истата Американска администрација го намалила лимитот на една година. Целта на ова истражување беше да се утврди влијанието на возраста при вградувањето на кохлеарниот имплант врз успешноста на говорниот развој. Во однос на возрасната група според која испитаниците беа поделени, најдобри резултати покажа групата кај која имплантацијата беше направена на најмала возраст. Во заклучокот сакаме да потенцираме дека бенефитот од кохлеарниот имплант кај лицата со прелингвално слушно оштетување со најтежок степен е многу поголем во однос на индивидуалните слушни амплификатори. Кога кохлеарниот имплант ќе се вгради во најрана возраст резултатите можат да доведат дури и до 100% активно вклучување на лицето во социјалната средина.

Introduction

Early detection of hearing impairment as a prerequisite for timely speech and language treatment in the so-called critical period of speech and language development enables optimal integration of a child in the society. Subjects with severe sensorineural hearing loss greater than 90 dB cannot benefit from the most contemporary conventional hearing aids. In such cases, the unique help is offered by the most modern achievement of microelectronics in the medicine – the cochlear implant, which replaces the function of the inner ear.

The revolutionary changes in the technology of cochlear implant happened in 1990 and consequently it resulted in clinical approach to cochlear implantation. The improvement of implants, especially in the strategy of speech encoding has offered a larger spectrum in the selection of candidates for cochlear implantation[1,6]. Hearing and speech perception in different subjects has shown different results. No matter what the performances and specifics of the implants are, some subjects show more rapid improvement in the skills and some do not.

Research results about speech perception in early implanted children[7,8] showed that speech perception abilities developed significantly rapidly owing to the structure of the central nervous system. The fact that children learn the language spontaneously in the early development, without any didactic instructions, has to be taken into consideration. Moreover, the advanced technical performances of speech processors enable easier and faster rehabilitation[9].

The aim of this study was to determine the influence of age at which subjects received a cochlear implant on the successfulness of speech development.

Material and methods

The study comprised 31 subjects based on the following inclusion criteria:

- Children with auditory status that met the criteria forcochlear implantation by a specialist in otorhinolaryngology – audiology;
- Children with a limited benefit from binaural adequate hearing aids who were undergoing a rehabilitation process for development of hearing and speech perception;
- Children in general health condition and intellectual status determined by a pediatrician – neurologist;
- Opinion of a speech and language therapist regarding the hearing amplifier and the degree of development of hearing and speech perception;
- Parent's readiness and their real expectations;
- Motivation and collaboration of the family.

Each subject or his/her parents gave a consent for participation in the testing.

Test for recognition of monosyllabic words (open-set) was used as a method of the investigation. This method helps in the estimation of the ability of an individual to identify monosyllabic words. There are no adequate pictures for each word. Each word is said only once and the individual is required to repeat the word. The test is performed with no help of lip reading.Subjects are scored taking into account the number of phonemes or words repeated correctly.The evaluation of the results in our study was made at 6, 12 and 24 months.

For the statistical analysis of data, the following statistical methodologies were used: To determine the significance of differences among subjects

prior to and after placement of cochlear amplifier and after cochlear implantation, as well as among subjects with cochlear implant at 6, 12, 24 months following implantation non-parametric tests for two or several dependent variables (McNemar's test and Cochran's Q test) were used.

Non-parametric Spearman Rank Order Correlations was used for determination of the correlation, i.e., association between age of the implanted subjects with cochlear implant and the scores obtained at the test. Differences for p value <0.05 were considered statistically significant.

Results

This study included 31 subjects with the age ranging from 6 to 32 years; the mean age being 13±6.2 years.

The mean age at cochlear implantation was 100.4±75.1 months. The youngest age at implantation was 10 months and the oldest 324 months.

Table 1. Age of subjects (months)/ Age (in months) at cochlear implantation

Parameter	N	mean	SD	Std.Error	Min.	Max.
Age	31	13.0	6.2	1.1	6	32
Age at implantation	31	100.4	75.1	13.1	10	327

The study was conducted by using the Test for recognition of monosyllabic words (open set – understood).

Table 2 illustrates the results obtained from the Test for recognition of monosyllabic words depending on the age of the subjects at cochlear implantation and 6 months after intervention.

The results showed that only 1 child from the youngest age group could not understand any word; there were 2 such subjects in the second age group and 4 in the third age group. The maximum number of understood words (4) in this study period was registered in 1 subject from the first and 1 subject from the second age group, and in none from the third age group.

Table 2. Test for recognition of monosyllabic words (open-set) 6 months after intervention

6 months		Up to 5 years	5.3 - 10 years	> 10 years	Total
No.	0	1	2	4	7
%		11.11%	16.67%	40.00%	
No.	1	1	1	0	2
%		11.11%	8.33%	0.00%	
No.	2	1	5	4	10
%		11.11%	41.67%	40.00%	
No.	3	5	3	2	10
%		55.56%	25.00%	20.00%	
No.	4	1	1	0	2
%		11.11%	8.33%	0.00%	
Total		9	12	10	31

Twelve months after the realized intervention there were no subjects from the youngest age group who could not understand any word; there was 1 subject in the second, and 3 in the third age group.

The maximum number of understood words was 6 and was registered in 1 subject from the first and 1 from the third age group, and in 2 subjects from the second age group (Table 3).

Table 3. Test for recognition of monosyllabic words (open-set) 12 months after intervention

Table 3. Test for recognition of monosyllabic words (open-set) 12 months after intervention

12 months		Up to 5 years	5.3 - 10 years	> 10 years	Total
No.	0	0	1	3	4
%		0.00%	8.33%	30.00%	
No.	2	3	0	0	3
%		33.33%	0.00%	0.00%	
No.	3	0	5	1	6
%		0.00%	41.67%	10.00%	
No.	4	4	1	3	8
%		44.44%	8.33%	30.00%	
No.	5	1	3	2	6
%		11.11%	25.00%	20.00%	
No.	6	1	2	1	4
%		11.11%	16.67%	10.00%	
Total		9	12	10	31

The number of words from the Test for recognition of monosyllabic words that the subjects from all three age groups could understand 24 months after intervention was from 2 to 8. In the group of children with the intervention accomplishedat 5 years of age, 1 (11.1%) child could understand the meaning of 8 monosyllabic words, 3 (25%) children who underwent implantation at the age between 5.3 and 10 years, whereas there were no subjects in the third age group who could understand 8 of the offered 10 monosyllabic words (Table 3).

Table 4. Test for recognition of monosyllabic words (open-set) 24 months after intervention

24 months		Up to 5 years	5.3 - 10 years	> 10 years	Total
No.	0	0	1	2	3
%		0.00%	8.33%	22.22%	
No.	2	0	1	0	1
%		0.00%	8.33%	0.00%	
No.	3	2	0	0	2
%		22.22%	0.00%	0.00%	

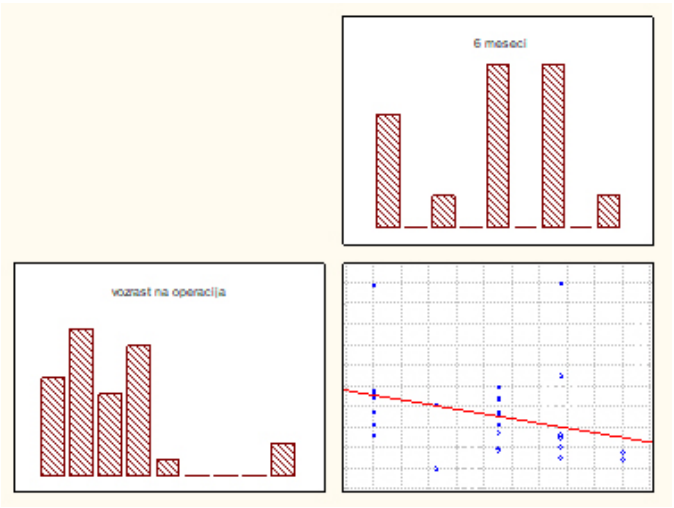
No.	4	0	2	2	4
%		0.00%	16.67%	22.22%	
No.	5	2	1	0	3
%		22.22%	8.33%	0.00%	
No.	6	2	2	1	5
%		22.22%	16.67%	11.11%	
No.	7	2	2	4	8
%		22.22%	16.67%	44.44%	
No.	8	1	3	0	4
%		11.11%	25.00%	0.00%	
Total		9	12	9	30

There was a negative correlation between the age at cochlear implantation and the number of understood monosyllabic words. It meant that a larger number of monosyllabic words could be understood by children in whom the cochlear implantation was finished at the youngest age, and vice versa. The values of the calculated Spearman's coefficient of -0.46 after 6 months, -0.24 after 12 months, and -0.4 after 24 months were statistically significant (Table 4).

Table 4. Correlation – age at surgery/number of understood monosyllabic words

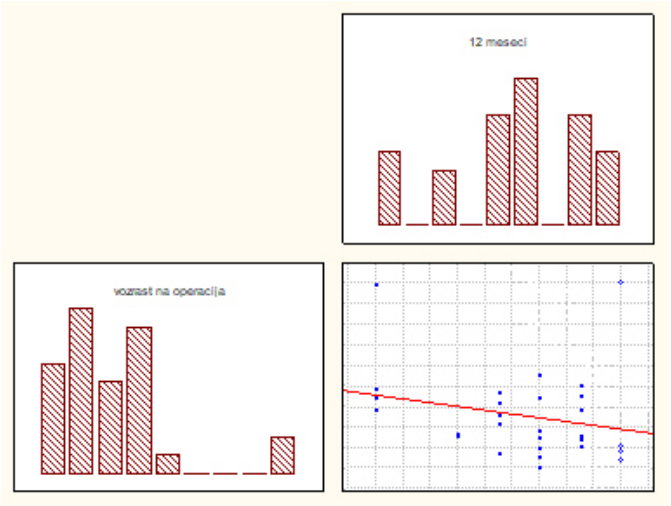
Age at surgery/ Number of understood monosyllabic words	Spearman Rank Order Correlations		
	R	p-level	Sig.N.Sig.
After 6 months	-0.46	p<0.05	Sig.
After 12 months	-0.34	p<0.05	Sig.
After 24 months	-0.4	p<0.05	Sig.

Figure 1. Correlation - age at surgery/number of understood monosyllabic words



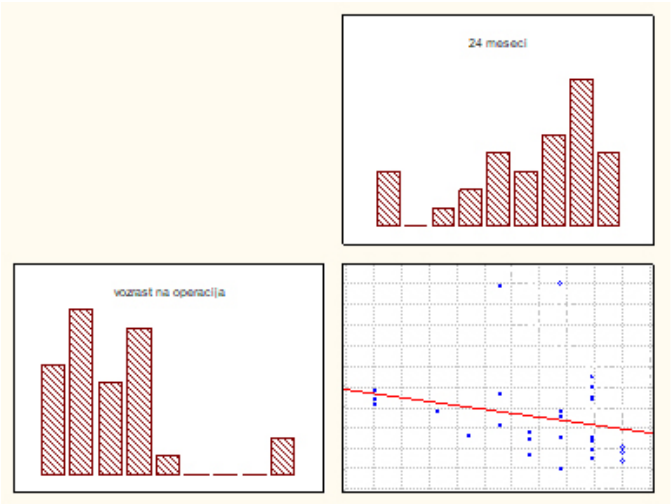
Spearman Rank Order Correlations=-0.46;p<0.05

Figure 2. Correlation - age at surgery/number of understood monosyllabic words



Spearman Rank Order Correlations=-0.3; p<0.05

Figure 3. Correlation - age at surgery/number of understood monosyllabic words



Spearman Rank Order Correlations=-0.4p; <0.05

Discussion

Numerous studies have been conducted worldwide in order to determine the importance of age at cochlear implantation on speech development. May-Mederake B.[10,11] completed two studies including 28 children implanted prior to 2 years of age, who were examined regarding the development of speech, vocabulary and grammar skills. Her findings are consistent with ours and have pointed out to the fact that implantation at a younger age yields better results. Early auditory stimulation enables faster speech and language development.

In the study conducted by Anderson *et al.*[12] and Baumgartner WD.*et al.*[13] similar results were also obtained, confirming that a higher level of speech perception performance can be achieved at earlier ages of implantation.

Allum JH[14]in his study divided the subjects into three age groups: up to 7 years of age, 7-year-olds and older than 7 years. He made the measurement immediately after the implant

activationat 1, 3 and 6 months, and then every 6 months until 24 months following implantation. All children presented with faster rates of progress and higher scores after 6-12 months. Children aged 7 and over showed better results at preoperative tests because of the experience with the hearing amplifiers. After implantation, they had poorer results than the children under 7 years of age. There are many other studies that have examined the importance of age when implantation was made[15].

In the period between 1994 and 2004 different results have been published regarding the discrimination of speech in children with cochlear implant.

Myamotoet *al.* examined 29 children, of whom one half showed good results with the open-set test after implantation.

Ozbergeret *al.* demonstrated that post-implantation performances were much better in children who were implanted before the age of two compared to children who were implanted at the age between two and three years. Geers *et al.* showed that speech perception performance was much better if implantation was realized by the age of three years, which is crucial for obtaining information from the environment as well as for developing the cognitive and linguistic skills including speech development[16,17].

The variability in speech perception performance among different individuals depends on many factors including age at implantation, way of communication, support from the family, and deafness duration. Myamotoet *al.* consider that 35% of these factors are the reason for the difference in the degree of speech perception.

Conclusion

The results presented in the literature as well as the results obtained in our study have shown that age is one the most important factors for normal and proper speech development. The younger the age, the better results are achieved. Our findings have revealed that cochlear implant is efficient even in older children, but then the development of speech perception is slower; there is unclear articulation, poor vocabulary and irregular grammar usage. Although these children listen, they supplement their verbal communication with lip reading and occasional use of gestures.

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Public health

DIABETES MELLITUS AND HYPERTENSIVE CEREBRAL HEMORRHAGE

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Abstract

Diabetes mellitus is an increasingly common public health problem and affects the population health. In many studies, DM is very often in a close correlation with many cardiovascular diseases and brain hemorrhage in general. The aim of the paper was to determine whether the presence of diabetes mellitus has influence on the occurrence of cerebral hemorrhage. Material and methods: The study included 61 patients diagnosed with hypertensive intracerebral hematoma in the hemispheres of the brain. Results: The prevalence of diabetes in the group of survivors of intracerebral hemorrhage was 26.67%, while in the group of subjects in whom the disease ended lethally diabetes had an insignificantly higher prevalence of 43.75% (Chi-square: 1.61df = 1, p = 0.21). Analysis of the prevalence of diabetes regarding the mobility of the respondents showed that there were no respondents with diabetes in the group of patients who could function independently, while there were 7 (24.14%) respondents with diabetes in the group who required help or aid for accomplishing their daily activities, and 5 (50%) in the group of respondents who were completely dependent on someone else in performing the everyday functioning. Statistical analysis showed these differences as insufficient to be statistically confirmed as significant (Fisher exact test, p = 0.105). Conclusion: In patients who have had cerebral hemorrhage with lethal outcome diabetes mellitus is a very common phenomenon, as well as in patients who have survived but subsequently have decreased mobility. But these differences are not statistically significant. Measures for reduction of the incidence of diabetes mellitus are needed. These measures include early detection of the disease, treatment and prevention of disability.

Јавно здравје

ДИЈАБЕТЕС МЕЛИТУС И ХИПЕРТЕНЗИВНИ МОЗОЧНИ КРВАРЕЊА

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Клучни зборови: дијабетес мелитус, јавно здравје, мозочни крварења

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Печатарски права: ©2021 Иван Панговски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Дијабетес мелитус (ДМ) претставува јавноздравствен проблем кој е се повеќе присутен и влијае на здравствената состојба на населението. Во повеќе студии ДМ се доведува до корелација со кардиоваскуларни заболувања, а и мозочните крварења воопшто. Цел на трудот е да се утврди дали присуството на дијабетес мелитус влијае на исходот на мозочно крварење. Материјал и методи: За целите на ова истражување беше формиран примерок од 61 пациент со дијагноза хипертензивен интрацеребрален хематом во хемисферите на мозокот. Резултати: Застапеноста на дијабетесот во групата испитаници кои го преживеале интрацеребралното крварење е 26,67%, додека во групата испитаници кај кои болеста завршила летално дијабетесот има несигнификантно поголема застапеност од 43,75% (Chi-square:1,61df=1,p=0,21). Анализата за застапеноста на дијабетес во однос на мобилноста на испитаниците покажува дека нема испитаници со шеќерна болест во групата пациенти кои можат самостојно да функционираат, додека шеќерна болест имаат 7 (24,14%) испитаници во групата со можност за дневни активности со помош на помагало, и 5 (50%) во групата испитаници кои во обавувањето на секојдневните функции се комплетно зависни од туѓа помош. Статистичката анализа на овие разлики покажа дека не се сигнификантни (Fisherexact p=0,105). Заклучок: Кај пациентите кои имаат мозочно крварење со летален исход почесто е присутен ДМ, како и кај пациенти кои преживале но после тоа имаат намалена мобилност. Но овие разлики не се статистички значајни. Потребни се мерки за намалување на инциденцата на дијабетес мелитус. Овие мерки вклучуваат рано откривање на болеста, лекување и спречување на попреченост.

Introduction

WHO point to an increasing number of population with all types of diabetes each year. It is of great concern the fact that more and more children are facing with diabetes at an early age. According to many authors, this, among other things, is due to the fact that there is a daily increase in the number of people in the world population who have weight problems or rapid weight gain and it's considered to be one of the most influential factors in a person's ability to develop lifelong diabetes[1,2].

In addition, other factors such as hereditary, irregular physical activity, unhealthy and fast diet, increased stress levels in the population, which indicate that diabetes is becoming a public health problem in RN Macedonia. The occurrence of diabetes mellitus may in itself be a risk factor for onset of some cardiovascular diseases such as cerebral hemorrhages.

DM is a major public health problem worldwide. Current global estimates show that this condition affects 415 million people and is expected to escalate to 642 million by 2040. Other 193 millions of people with diabetes remain undiagnosed due to the mild or asymptomatic nature of the condition, especially in type 2 DM (T2DM). The Middle East region and North Africa (MENA), which include all Arab states, are currently burdened with recurrence of the highest incidence of diabetes (10.7%, age-adjusted) and in North America and the Caribbean it is 11.5%. This scenario is likely to continue for the next two decades, and possibly wider.

According to the definition of the American Diabetes Association, DM is a metabolic disease characterized by hyperglycemia caused by a disorder in insulin secretion, a disturbance in its action or the presence of both of these disorders[1].

DM has been known since the time of ancient Greece, and today, because of the dramatic increasing in prevalence, it takes the form of a pandemic and may in the future become one of the leading causes of morbidity and mortality. Today, DM is considered a chronic progressive disease, affecting more than 170 million people worldwide, and the forecast is that this number will double in 10 years. The median incidence of diabetes is 2-5%, the lowest in rural China < 1%) and highest among Pima Indians in North America (about 50%). There are no reliable data on the frequency in Serbia, but it is estimated that about 600,000 people suffer from this disease and that every year 16,000 new patients are discovered[3].

In the Republic of North Macedonia, diabetes mellitus is one of the most common diseases and according to the data from the National System for Electronic Records in the field of health, about 85,000 patients have been diagnosed with diabetes mellitus.

- Diabetes mellitus - type 1 - This type of diabetes commonly occurs in younger age and is present in about 3,000 people.

Diabetes mellitus type 2 covers 96% of all diagnosed cases of which 47% are on insulin therapy, and the rest use oral antidiabetic therapy [4,5].

The number of registered people with diabetes who are currently on insulin therapy in North Macedonia is 40,000, of which 3,000 are people with type 1 diabetes and 37,000 with type 2. This number is growing every year. According to the data from the International Diabetes Federation, total prevalence (diagnosed and undiagnosed diabetes) of diabetes is 9.8% of the population aged 25-70 years[5].

Intracranial hemorrhage (ICH) is a significant medical event that covers up 15% of strokes. The incidence of ICH is approximately 25 per 100,000 persons per year and has a mortality rate of 40% within one month of its manifestation. ICH may appear in multiple intracranial compartments and may be caused by a variety of pathologies. Neuroimaging is essential for the treating physician to understand the location and the extent of bleeding, the risk of impending brain injury and direct treatment of most often emergency patients. Stroke is a focal (or global) circulation disorder in the cerebral parenchyma caused by occlusion or rupture of a blood vessel and insufficient oxygen supply to the brain parenchyma with consequent death of brain cells. From a clinical point of view, stroke is a sudden development of signs focally (or globally) lasting more than 24 hours or leading to death without apparent cause of death other than vascular[6].

The aim of this study was to determine whether the presence of diabetes mellitus affects the occurrence of cerebral hemorrhage.

Material and methods

For the purposes of this study, a sample of 61 patients with a hypertensive intracerebral hematoma in the hemispheres of the brain was analyzed. The sample was randomly selected including patients with localized hypertensive intracerebral hemorrhage supratentorially, treated at the University Clinic for Neurosurgery at the Clinical complex Mother Theresa in Skopje. The statistical analysis was made by the statistical programs Statistica 7.1 and SPSS 13.0.

Table 1. Gender structure of study group

Variable	N (%) mean ± SD
men	34 (55.74%)
women	27 (44.26%)
age	59.56 ± 8.3 rank 45-78

The gender structure of the respondents consisted of 34 (55.74%) men and 27 (44.26%) women. 73% of respondents who participated in the study had a live and 26% dead outcome due to cerebral hemorrhage.

Table 2. Presence of diabetes in relation to the functional outcome of respondents

variable	group	
	Alive n=45	Dead n=16
DIABETES MELLITUS		
no	33 (73.33%)	9 (56.25%)
yes	12 (26.67%)	7 (43.75%)

Of those respondents who survived the bleeding, 26% had and 73% did not have some type of DM. Of those who did not survive the bleeding, 43% had and 56% did not have any type of diabetes.

Table 2. Prevalence of diabetes in terms of mobility of respondents

variable	group		
	Independently	**with aid**	**Nailed**
	n = 6	n = 29	N = 10
DIABETES MELLITUS			
no	6 (100%)	22 (75.86%)	5 (50%)
yes	0	7 (24.14%)	5 (50%)

Table 3 shows the distribution of respondents in relation to their mobility and the emergence of DM. The prevalence of diabetes in the group of respondents who survived intracerebral hemorrhage was 26.67%, while in the group of subjects in whom the disease ended lethally diabetes had an insignificantly higher prevalence of 43.75% (Chi-square: 1.61df = 1, p = 0.21). The analysis of the prevalence of diabetes regarding the mobility of the respondents showed that there were no respondents with diabetes in the group of patients who could function independently, while there were 7 (24.14%) respondents with diabetes in the group who required help or aid for performing daily activities, and 5 (50%) in the group of respondents were completely dependent on someone else in performing everyday functioning. The statistical analysis showed these differences to be insufficient in order to be statistically confirmed as significant (Fisher exact p = 0.105).

Discussion

Diabetes mellitus had insignificantly higher representation of 43.75% which may be a non-significant representation but still relatively high in patients with lethal outcome. In the literature there are several studies that discuss the same or similar topic with different sample and methodology as in our study. One of the studies included 135 patients with the mean age of patients with cerebral hemorrhage 67.5 ± 12.7 years and of the control group 70.5 years. Diabetes mellitus was found in 39 patients with cerebral hemorrhages (33.1%) and in 30 (22.2%) control subjects (p = 0.054). The prevalence of diabetes mellitus in patients younger than 60 years was 7.4% in the control group and

27.8% in the group with cerebral hemorrhage (p = 0.042). The study did not find a significant relationship between diabetes mellitus and cerebral hemorrhage (except in patients under 60 years of age) and diabetes mellitus did not cause bleeding in certain areas of the brain. However, more studies are needed to correlate diabetes mellitus and intracerebral hemorrhage in the same population to reach a definitive conclusion2. Also, it has to be pointed out that in the examined sample some of the respondents were smokers and regular consumers of alcohol as well as persons exposed to stress and other risk factors that can be directly related to cerebral hemorrhage. Thus, it cannot be determined with certainty, at least in this sample of patients that diabetes was a direct cause of cerebral hemorrhages.

Conclusion

Diabetes is more common in patients with lethal cerebral hemorrhage, as well as in patients who have survived but subsequently have reduced mobility. Measures are needed to reduce the incidence of diabetes mellitus. These measures include early detection of the disease, treatment, and prevention of disability. It is especially important to take prevention measures at the population level, epidemiological and public health methods such as: monitoring the trend at the population level (register, epidemiological studies), political-health-educational measures, tax reduction of healthy food, continuing education for taking steps to a healthy lifestyle.

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Clinical science

EVALUATION OF PEDIATRIC PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH BIOLOGICAL THERAPY TOCILIZUMAB (ACTEMRA)

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common chronic disease in childhood. It manifests a heterogenic group of symptoms of arthritis, lasting at least 6 weeks and it appears before the age of 16. Patients who had no good therapeutic response to conventional therapy with Methotrexate were treated with biological therapy. The aim of this paper was to evaluate 9 patients who were receiving Tocilizumab at the Department of Rheumocardiology, University Clinic of Pediatric Diseases in Skopje. Materials and methods: Our study included 9 patients treated at our Department with biological therapy with Tocilizumab. Prior to initiation of the biological therapy, all patients underwent laboratory investigations, purified protein derivative (PPD) skin test for tuberculosis, X ray of the lungs and heart, and analysis of hepatitis markers. All patients were treated with amp. Actemra (tocilizumab) 8 mg/kg/tt i.v. Two of the patients had a severe form of the disease (one with severe systemic form and one with severe oligoarticular form of JIA). All presented patients had clinical remission of the disease. Conclusion: Therapy with tocilizumab in patients with juvenile idiopathic arthritis is a good therapeutic choice. The results obtained in our study have shown a significant therapeutic effect of tocilizumab even in severe forms of the disease.

Клинички испитувања

ЕВАЛУАЦИЈА НА ПЕДИЈАТРИСКИ ПАЦИЕНТИ СО ЈУВЕНИЛЕН ИДИОПАТСКИ АРТРИТ ТРЕТИРАНИ СО БИОЛОШКА ТЕРАПИЈА ТОЦИЛИЗУМАБ (ACTEMRA)

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Цитирање:Нешковска-Шуменковска М, Софијанова А, Кацарска Р, Кузевска-Манева К, Ѓуркова-Ангеловска Б, Јовановска. Евалуација на педијатриски пациенти со јувенилен идиопатски артрит третирани со биолошка терапија Тоцилизумаб (Actemra). Арх. Ј Здравје 2021;13(2). 62 -68.

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Клучни зборови: јувенилен идиопатски артрит, Тоцилизумаб, деца

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Печатарски права: ©2021 Марија Нешковска-Шуменковска, Аспазија Софијанова, Розана Кацарска, Константина Кузевска-Манева, Бети Ѓуркова-Ангеловска, Валентина Јовановска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Јувенилниот идиопатски артрит е најчеста форма на хронично заболување во детската возраст, кое се манифестира со хетерогена група на симптоми на артрит коишто траат најмалку 6 недели, а се појавиле пред 16-годишна возраст. Пациентите кои не дадоа добар тераписки одговор на конвенционалната терапија со Метотрексат, беа префрлени на биолошка терапија. Целта на оваа студија беше да изврши евалуација на 9 пациенти кои примаа тоцилизумаб на Одделот за реумокардиологија на Универзитетската клиника за детски болести во Скопје. Материјали и методи: Во нашата студија беа вклучени 9 пациенти третирани на нашиот Оддел со Тоцилизумаб во период од 2010-2020 година. Кај сите пациенти пред започнување на терапијата беа направени лабораториски иследувања, прочистен протеински дериватевен кожен тест за туберкулоза (ППД), РДГ на градите, и маркери за хепатит. Сите пациенти беа третирани со амп. Актемра 8мг/кг/тт и.в. Два пациента имаа тешка клиничка презентација на јувенилен идиопатски артрит (првиот со тешка системска форма на болеста, а вториот со тешка олигоартикуларна форма). Кај сите третирани пациенти настана ремисија на клиничката слика по спроведување на терапијата. Заклучок: Биолошката терапија со тоцилизумаб кај пациентите со јувенилен идиопатски артрит е добар тераписки избор. Резултатите покажаа сигнификантен тераписки ефект дури и кај потешките облици на болеста.

Introduction

Juvenile idiopathic arthritis is the most common chronic disease in childhood. It is manifested with a heterogenic group of symptoms of arthritis, lasting at least 6 weeks, which appear before the age of 16[1,2]. Juvenile idiopathic arthritis is divided in 7 subgroups according to ILAR classification:

1. Oligoarticular arthritis - arthritis of one to four joints in the first 6 months from the beginning of the disease (there are persistent and extended forms of this type),
2. Rheumatoid factor (RF) positive polyarticular arthritis – arthritis of five or more joints in the first 6 months from the beginning of the disease; RF is positive in the last three months.
3. RF negative polyarticular arthritis - arthritis of five or more joints in the first 6 months from the beginning of the disease; RF is negative.
4. Systemic juvenile idiopathic arthritis (sJIA) - fever, rash on the body, hepatosplenomegaly in duration of 2 weeks at least.
5. Arthritis with enthesitis - sacroiliitis, lumbosacral pain, HLA B27 genotyping, ankylosing spondylitis,
6. Psoriatic juvenile arthritis - psoriasis and arthritis,

7. Undefined JIA – extra-articular manifestations of the disease are: chronic uveitis, hepato/splenomegaly, pleuritis, pericarditis. These manifestations are often part of a systemic form of juvenile idiopathic arthritis[3]. Therapeutic procedures include basal therapy with NSAID, and tabl. Methotrexate as DMARD (disease-modified antirheumatic drug)[4,5]. Patients who have had no good response to therapy with Methotrexate are candidates for biological therapy (Biological DMARDS). Components of biological therapy have endogen proteins who specifically induced the immune response in the body, especially through the cytokine pathway[6,7,8].

The aim of this paper was to evaluate pediatric patients who received biological therapy with Tocilizumab.

Material and methods

In the period of 10 years (2010 - 2020), a total of 115 patients with diagnosis of juvenile idiopathic arthritis were followed-up and treated at the Department for Rheumocardiology. Of all these patients 97 received Methotrexate therapy, 9 patients received biological therapy with Adalimumab (Humira) and with Tocilizumab (Actemra). All 9 patients received 8 mg/kg i.v. every four weeks. All patients were treated according to the International League of Associations for Rheumatology (ILAR) classification criteria. Of the 9 evaluated patients, 5 were males and 4 females. Patients were aged from 7 - 19 years (mean age 14 years). Prior to initiation of the biological therapy with Tocilizumab in all 9 patients, they underwent laboratory analysis (blood count, CRP, hepatic transaminases, lipids), PPD, X-ray of the lungs and the heart, rheumatoid antibody (RF, ANA, ADNA, anti-ccp, anti-ssa, anti-ssb, lupus cells). Patients were classified according to the ILAR classifications of patients with systemic form of juvenile idiopathic arthritis, monoarticular, oligoarticular, polyarticular (RF positive), polyarticular (RF negative), arthritis with

enthesitis (sacroiliitis), psoriatic form and undefined form. HLA genotyping was also made. According to their place of birth, our patients were divided in two groups (patients from town and patients from village). Osteodensitometry was performed in two of our patients because of suspicion for osteoporosis.

Results

According to gender, of 9 patients 5 were male (55%) and 4 female (44%). We evaluated our patients according to duration of therapy with Tocilizumab.

Table 1. Patients treated with biological therapy Tocilizumab (Actemra) according to duration of therapy.

Duration of therapy with Tocilizumab	5 years	4 years	3 years	1 year
Number of patients	4	1	2	2
Percentage (%)	44%	11%	22%	22%

Table 1. shows that according to duration of therapy 4 patients of our 9 patients were treated with Tocilizumab for 5 years; therapy lasted 4 years in 1 patient, 3-year-therapy received 2 patients and 1-year-therapy received 2 patients. Thus, most of the patients received therapy with Tocilizumab in a period of 5 years.

Table 2. Patients treated with Tocilizumab (Actemra) therapy according to ILAR classification

Systemic	Monoarticular	Oligoarticular	RF positive Polyarticular	RF negative Polyarticular	Sacroiliitis	Undefined arthritis
1	0	3	1	3	1	0

Table 2. shows that according to the ILAR classification, 1 patient was with a systemic form of the disease,1 with sacroiliitis, 3 patients were with oligoarticular form, 4 patients were with polyarticular form of the disease. Table 2 shows that most of the patients were with oligoarticular juvenile idiopathic arthritis and RF negative polyarticular form of juvenile idiopathic arthritis (33%).

Two patients were with severe clinical presentation of juvenile idiopathic arthritis (one with systemic form presented with tachycardia, chest pain and signs for pericarditis, treated with Verapamil, and the other patient was with severe oligoarthritis presented with pericarditis, contractures of the joints, and was treated with diuretics and anti-inflammatory drugs). Both patients continued with biological therapy with Tocilizumab (amp. Actemra) and presented with a good therapeutic effect.

In the other 7 patients, therapy with Tocilizumab showed a good therapeutic effect resulting in a reduced number of inflamed joints and better quality of life.

We evaluated our patients according to allergic manifestations while they were receiving therapy with Tocilizumab.

Table 3 Allergic manifestation in patients treated with Tocilizumab

Allergic manifestations	Number of patients
Urticaria (rash)	2
Severe abdominal cramps	1
No allergy manifestation	6

Allergic manifestations appeared in 3 of our patients, two of them manifested urticaria, and one had severe abdominal cramps (Table 3). Thus, therapy was discontinued for a short period, and after that they all completed the biological therapy.

Regarding rheumatoid antibody, 3 of our 9 patients had negative rheumatoid antibodies, two had positive ANA (antinuclear antibodies) 1:160, the other antibodies were negative. Osteoporosis was registered in 2 of our patients, which was detected with osteodensitometry. HLA genotyping was realized in 3 of our patients. One patient with sacroiliitis had HLA B27, and the same genotyping had two of the patients (monozygotic twins) with oligoarticular form of the disease. From 9 patients treated at our Clinic after 14 years, 6 patients were transferred to the University Clinic for Adult Rheumatology; of these, 4 were males and 2 were females, the other patients continued to be followed at our Clinic.

Disscusion

Immunological system has a central role in maintaining identity and integrity of the body. Basal immunological reactions based on the ability of the immunological system to recognize strange molecules and antigens, and to have a good response, and, on the other side, to recognize its own molecules. Reaction of the body to pathogens can be nonspecific and specific. In rheumatology, this reaction is nonspecific presented by cytokines like IL-1, IL-6 and TNFα.

In 2014, our Department published a study presenting 4 patients who received biological therapy. Patients had different forms of the disease. In a patient with arthritis with enthesitis, HLA B27 was found by using HLA typing test. In a patient with systemic form and oligoarticular form with chronic eye inflammation of anterior eye segment, positive ANA antibodies were found. All patients were treated according to the ILAR criteria, and had good therapeutic response (ACR Pedi 70-90%)10. After completion of this study, we have continued to evaluate patients who received biological therapy and we published the results obtained in other studies. In our series of patients, all showed a good response to therapy with Actemra in combina-

tion with Methotrexate. One patient received a combination of Tocilizumab and Leflunomide (ARAVA), but he also showed a good response to therapy. Therapeutic effect was good in a patient with severe systemic form and severe oligoarticuar form of the disease [4,5,11].

Osteoporosis is a typical systemic manifestation of rheumatic arthritis. There were 2 patients in our study who had osteoporosis detected with osteodensitometry. One of these patients received bisphosphonates (Pamindronate) in addition to the biological therapy, other patient was given Ca and vit. D and he is a candidate for bisphosphonate therapy[13]. Tociliziumab is a recombinant human anti-IL-6 antibody. In clinical trials realized in three phases in patients with RA in Japan, Tocilizumab monotherapy at a dose of 8 mg/kg showed clinical efficacy equaling that of tumor necrosis factor (TNF) inhibitor in combination with Methotrexate. This combination is also used in pediatric population with a success. The safety profile of Tocilizumab appears to be satisfactory. However, several serious infections have been reported in different studies and therefore, careful monitoring is important during the use of this therapy. In 3 of our patients allergic reactions appeared after one application, and hence, after this, the patients were given Tocilizumab therapy [7,8,9].

The University Clinic for Rheumatology published 2 studies about safety of treatment with Actemra in a patient with early, and severe rheumatoid arthritis in 2017 and 2020. The studies were multicenter open-label. Both studies proved the safety of using biological therapy with Tocilizumab and with a very good therapeutic response. The effect of the clinical response to Tocilizumab was fast and seen after just two weeks of application. Moreover, the magnitude of the effect increased in the studies with the increase of the duration of treatment [14,15].

Many studies have confirmed benefits from the biological therapy with Tocilizumab: CHARISMA study, CHERIS study (studies show best results in patients with oligoarticular form of disease), TENDER study (evaluated efficacy of Tocilizumab in patients with systemic form of disease), which showed reducing of fever episodes after 12 weeks of therapy[6].

HLA B27 genotyping is often associated with JIA with enthesitis (sacroiliitis) and in children with oligoarthritis or polyarthritis. With regard to this, our results are similar to those published by some other authors. HLA typing is also a good predictive factor in patients with juvenile idiopathic arthritis[16,17,18].

In pediatric population, the combination of Tocilizumab (Actemra) and Methotrexate has shown better results. In patients who are unable to tolerate Methotrexate, a combination of Tocilizumab and Leflunomid (Arava) can be used 7.

The goal of the therapy with Tocilizumab is to prevent joint erosions, maintenance of their function and control of the pain[9]. Therapeutic approach is multidisciplinary. The team included in the treatment of these patients consists of pediatric rheumatologist, adult rheumatologist, ophthalmology specialist, physical therapy and psychological support of the family.

Conclusion

In summary, the use of the biological therapy with Tocilizumab in combination with Methotrexate in pediatric population is safe and patients have good therapeutic responses. Tocilizumab prevents join erosions, and maintains their function. Tocilizumab is a good therapeutic choice in treatment of juvenile idiopathic arthritis. In this study we have presented our experience in treatment of patients with biological therapy (Tocilizumab).

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Clinical science

MONITORING THE REDUCTION AND MAINTENANCE OF PERIPROSTHETIC BONE TISSUE IN CEMENTLESS PRIMARY HIP ENDOPROSTHESIS WITH ALENDRONATE THERAPY

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Key words: TPH, Alendronate therapy, bone tissue density, DXA

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Abstract

Loss of periprosthetic bone tissue in primary hip endoprostheses is common in clinical practice. This loss can be progressive and in extreme conditions can jeopardize the longevity of the prosthesis. In order to monitor the function of Alendronate therapy for bone maintenance, the study included 50 patients with implanted total cement-free hip endoprosthesis (TPH). The first group of 25 patients received Alendronate, calcium and vitamin D3 orally postoperatively. The second group of 25 patients were examined postoperatively without therapy. Patients were followed by radiographic and dual-energy X-ray absorptiometry (DXA) at 6 and 12 months. The study showed that in patients with TPH there was a difference in the X-ray findings as well as occurrence of osteolysis in certain Gruen zones, which was confirmed by changes in the state of bone mineral density (BMD) and bone mineral content (BMC) in the interval between 6 and 12 months using the DXA method. Alendronate therapy after TPH implantation allows reduction of periprosthetic bone mass loss, maintenance of bone mineralization and implant hardening.

Клинички истражувања

СЛЕДЕЊЕ НА РЕДУКЦИЈА И ОДРЖУВАЊЕ НА ПЕРИПРОСТЕТИЧНО КОСКЕНО ТКИВО КАЈ БЕЗЦЕМЕНТНА ПРИМАРНА ЕНДОПРОТЕЗА НА КОЛК СО АЛЕНДРОНАТНА ТЕРАПИЈА

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Клучни зборови: ТПК, алендронатна терапија, густина на коскено ткиво, DXA

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Печатарски права: ©2021 Илир Шабани, Милан Самарџиски, Виктор Камнар, Нерон Поповски, Антонио Гавриловски, Шабан Мемети. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Губењето на перипростетичното коскено ткиво кај примарните ендопротези на колкот е честа појава во клиничката пракса. Ваквиот губиток може да биде прогресивен и во екстремни услови да ја загрозува долготрајноста на протезата. Заради наблудување на функцијата на алендронатната терапија за одржување на коскеното ткиво во студијата беа вклучени 50 пациенти со вградена тотална безцементна ендопротеза на колк (ТПК). Првата група од 25 пациенти постоперативно примаа орално алендронат, калциум и витамин Д3. Втората група од 25 пациентипостоперативно беа иследувани без примена на терапија. Пациентите беа следени со радиографски и двојно-енергетска рендгензрачна апсорптометрија (DXA) на 6 и 12 месеци. Студијата покажа дека кај пациентите со ТПК постои разлика во РТГ наодите како и појава на остеолиза во одредени Gruenovi зони, што се потврди со промени и во состојбата на вредностите на коскената минерална густина(BMD) и коскената минерална содржина (BMC) во интервалот помеѓу 6 и 12 месеци со помош на DXA методот. Алендронатната терапија по вградување на ТПК овозможува намалување на перипростетичната загуба на коскената маса, одржување на минерализацијата на коскеното ткиво и зацврстување на имплантот.

Introduction

Poor bone quality is a significant risk factor when implanting a total hip arthroplasty (TPH). The loss of bone mass affects the longevity and stability of the implant. With the reduction of bone mass, complications such as periprosthetic fractures of the femur or loosening of the prosthesis occur immediately [1,2].

Periprosthetic bone loss is present in both cement and non-cement hip prostheses. When an endoprosthesis is implanted, the proximal part of the femur is surrounded by a spongy bone. The distal end of the endoprosthesis is in contact with a predominantly cortical bone. This provides a variety of biological and biomechanical conditions for TPH implantation. During exercise, body weight changes from proximal to distal. This imbalance of load forces causes bone resorption mechanisms under Wolf's law. This bone loss is seen in the proximal femur [3-5].

Bobin *et al.* found that periprosthetic bone resorption was more pronounced in large femurs with a broad but porous sheath. To avoid resorption, the bending coefficient of the implant should be less than that of the surrounding bone. Postoperative weight gain and aseptic relaxation also play a role in the periprosthetic bone loss [6-8].

With dual energy X-ray absorption (DXA), even small changes in bone mass near the metal implant can be accurately tracked. Recently, DXA has been accepted as an accurate method for monitoring periprosthetic bone mineral density (BMD). Periprosthetic BMD decreases more rapidly during the first 6 months after TPH. After the initial period of rapid loss, the plateau phase is reached during the first year after surgery, and changes in BMD in the periprosthetic bone are minimal over the next few years [9-18].

DXA studies have also shown that patients with low BMD preoperatively have the highest BMD loss after TPH implantation [19].

The positive effect of bisphosphonates on bones has been scientifically proven. These osteoactive drugs reduce the loss of bone density and increase bone mass in postmenopausal women with or without osteoporosis [20-25]. Devogelaer *et al.* gave 5,10 and 20 mg of Alendronate daily to 516 postmenopausal women with osteoporosis in their multicenter study. A daily dose of 10mg significantly and gradually increased the bone mass of the lumbar spine, hip and overall skeleton during a 3-year-follow-up. The increase in BMD was 5.5% in the femoral neck and 7.2% in the trochanter. This continuous daily dose was well tolerated, and no improvement was found in the results with increasing dose [26].

Black *et al.*, in their randomized study showed that postmenopausal women with low bone mass, receiving 5 and 10 mg of Alendronate daily, had a lower incidence of several types of fractures, including hip fractures [27].

To our knowledge, there are not enough studies published on the effects of bisphosphonates on periprosthetic bone loss after primary TPH implantation.

The aim of this scientific study was to evaluate the value of Alendronate application in reducing periprosthetic bone loss after implantation of a total cement-free hip endoprosthesis.

Material and methods

The clinical material consisted of 50 patients treated at the University Clinic for Orthopedic Diseases with implantation of a total hip endoprosthesis in the period from 2018 to 2020 due to degenerative hip diseases.

The age distribution of patients was between 35-65 years, of whom 35 female and 15 male patients. All patients in the study were clinically and osteodensitometrically without visible signs of osteoporosis. All patients underwent spinal anesthesia with anterolateral hip approach, with standard verticalization 3 days after operative treatment and standard postoperative rehabilitation. The first group of patients (25) were permanently treated with Alendronate bisphosphonate therapy as well as with standard vitamin therapy and calcium substitution. The second group of patients (25) were without therapy and were only examined.

Methodology: This study was based on a clinical trial using two diagnostic methods: native hip radiography and dual energy with X-ray absorption (DXA). Densitometric analysis refers to 7 Gruen zones of thefemur, through which periprosthetic osteolysis formed in the femur after implantation of a total hip endoprosthesis (TPH) is implanted.

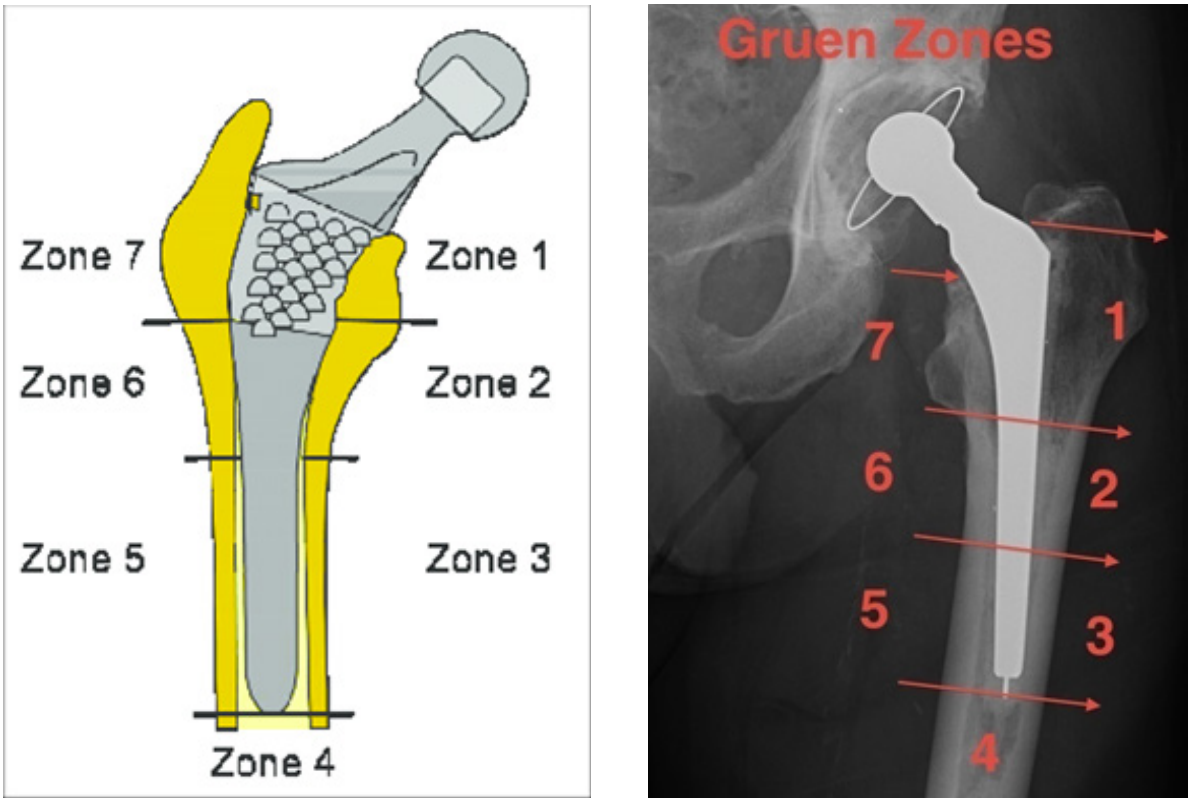


Figure 1. Schematic and X ray representation of the Gruen Zones

The results of both examinations were obtained and analyzed at time points, 6 and 12 months from the day of surgery.

The analysis consisted of comparing the results for BMD (bone mineral density) and BMC (bone mineral content) obtained at different time points in both groups.

Results

Patients in the study group, treated with medication, and patients in the control group, without medication treatment protocol were homogeneous in terms of gender structure (p=0.76). Female patients were the majority of examinees in both groups -68% (17) and 72% (18), respectively.

Table 1. Gender distribution

Gender	Group			p-level
	N	SG n (%)	CG n (%)	
Female	35	17 (68)	18 (72)	χ^2=0.095
Male	15	8(32)	7 (28)	p=0.76 ns

χ^2 (Pearson Chi-square)

No statistically significant difference was found in the age of patients in both groups (p=0.09). SG subjects were insignificantly younger than CG subjects (52.3 ± 9.7 vs 56.8 ± 8.6).

Tables 2,3,4 show the average and mean values of the BMC parameter in subjects from both groups, measured in the 7 Gruen zones of the femoral stem, at two time points (6 and 12 months after implantation of a total hip endoprosthesis).

According to the results shown in Table 2, six months after implantation of the total hip endoprosthesis, patients receiving bisphosphonate therapy with Alendronate and patients without drug therapy had significantly different bone mineral composition in the 4th Gruen zone (p=0.034). The BMC parameter had a significantly lower mean value in this zone in the group of patients with drug therapy (median 1.87 vs 3.58).

In the other zones, with the exception of Zone 2, lower values for the BMC parameter were measured in SG patients compared to CG patients in this time control points, but the differences were not sufficient to be confirmed as statistically significant.

At one year of surgery, Table 3, bone mineral composition was significantly different between the two groups in zone 2 (p=0.008), and this significance is due to a significantly higher BMC value in Alendronate therapy patients (median 2.92 vs 1.53).

BMC presented slightly higher values in patients on Alendronate therapy compared to patients without this type of therapy in the other 6 Gruen's zones of the femoral stem.

Six months after surgery (Table 4), no significant difference in bone mineral density (BMD parameter) was found between patients treated with Alendronate and those without medication. The differences between the two groups in all 7 Gruen zones of the femoral stem were insignificant.

Table 2. Evaluation of BMC at 6 months

BMC 6 months				
zone	GROUP	mean ± SD	median (IQR)	p-level
Z1	SG CG	4.19 ± 3.7 4.51 ± 3.6	2.85(1.23 – 7.11) 3.25 (2.02 – 7.13)	Z=0.43 p=0.67 ns
Z2	SG CG	3.51 ± 2.8 3.09 ± 2.7	2.35 (1.12 – 5.31) 1.85 (1.02 – 5.14)	Z=-0.66 p=0.51ns
Z3	SG CG	3.05 ± 1.9 3.94 ± 2.3	2.75 (1.63 – 3.42) 3.65 (1.73 – 5.56)	Z=1.19 p=0.23ns
Z4	SG CG	2.45 ± 1.5 3.36 ± 1.7	1.87 (1.23 – 3.54) 3.58 (1.98 – 4.72)	Z=2.11 p=0.034sig
Z5	SG CG	2.67 ± 1.4 3.67 ± 1.9	2.63 (1.45 – 3.36) 3.06 (2.31 – 4.6)	Z=1.9 p=0.057ns
Z6	SG CG	3.72 ± 3.2 4.41 ± 3.3	2.36 (1.35 – 3.97) 3.12 (1.98 – 6.32)	Z=0.85 p=0.39ns
Z7	SG CG	3.41 ± 3.1 3.83 ± 2.9	1.95 (1.23 – 6.02) 2.76 (1.03 – 6.37)	Z=0.56 p=0.57 ns

p (Mann-Whitney U Test)

At the control examination one year after the surgical intervention (Table 6), significantly higher values for the BMD parameter were measured in patients with Alendronate therapy in all 7 Gruen Zones (p=0.0001,p=0.0002,p=0.000004,p=0.000003,p=0.000002, p=0.000007, and p<0.0001, respectively).

The mean value of bone mineral density in the examined and control group in the 1st Gruen zone was 1.43

Table 3. Evaluation of BMC at 12 months

BMC 6 months				
zone	GROUP	mean ± SD	median (IQR)	p-level
Z1	SG CG	4.75 ± 3.7 3.54 ± 2.4	3.64 (1.98 – 7.47) 2.63 (2.0 – 5.45)	Z=0.95 p=0.34ns
Z2	SG CG	4.08 ± 2.7 2.33 ± 2.2	2.92 (1.83 – 5.83) 1.53 (0.95 – 3.12)	Z=2.67 p=0.008sig
Z3	SG CG	3.58 ± 1.8 3.21 ± 2.3	3.21 (2.35 – 3.98) 2.45 (1.25 – 4.11)	Z=1.03 p=0.3ns
Z4	SG CG	3.07 ± 1.5 2.57 ± 1.6	2.65 (1.98 – 4.11) 2.25 (1.32 – 3.03)	Z=1.31 p=0.19ns
Z5	SG CG	3.29 ± 1.4 2.73 ± 1.4	3.11 (1.98 – 3.93) 2.34 (1.63 – 3.85)	Z=1.31 p=0.19ns
Z6	SG CG	4.32 ± 3.1 4.32 ± 3.1	3.12 (2.12 – 5.12) 2.75 (1.9 – 5.11)	Z=1.37 p=0.17ns
Z7	SG CG	4.14 ± 2.9 3.04 ± 2.3	2.94 (1.87 – 6.3) 2.11 (0.92 – 5.37)	Z=1.44 p=0.15ns

p (Mann-Whitney U Test)

and 0.68, respectively; in the 2nd Gruen zone 1.63 and 1.01, respectively; in the 3rd Gruen zone 1.88 and 1.12, respectively; in the 4th Gruen zone 1.98 and 1.13, respectively; in the 5th Gruen zone 2.12 and 1,12, respectively; in the 6th Gruen zone 2.32 and 1.12, respectively; and, in the 7th Gruen zone, the mean BMD values of 2.1 in SG and 1.12 in CG were measured.

Table 4. Evaluation of BMD at 6 months

BMD 6 months				
zone	GROUP	mean ± SD	median (IQR)	p-level
Z1	SG CG	0.97 ± 0.3 1.11 ± 0.7	0.97 (0.76 – 0.99) 0.89 (0.64 – 1.45)	Z=0.02 p=0.98ns
Z2	SG CG	1.27 ± 0.6 1.39 ± 0.7	1.12 (0.91 – 1.35) 1.23 (0.87 – 1.87)	Z=0.04 p=0.97ns
Z3	SG CG	1.49 ± 0.6 1.56 ± 0.7	1.24 (1.12 – 1.63) 1.45 (1.02 – 1.98)	Z=0.05 p=0.96ns
Z4	SG CG	1.41 ± 0.8 1.54 ± 0.7	1.21 (0.98 – 1.32) 1.28 (1.09 – 2.12)	Z=1.29 p=0.19ns
Z5	SG CG	1.65 ± 0.8 1.55 ± 0.7	1.42 (1.11 – 1.82) 1.23 (1.06 – 1.87)	Z=0.44 p=0.65ns
Z6	SG CG	1.93 ± 0.97 1.83 ± 1.1	1.67 (1.24 – 2.09) 1.43 (0.98 – 2.31)	Z=0.93 p=0.35ns
Z7	SG CG	2.01 ± 1.7 1.61 ± 0.8	1.67 (1.25 – 1.83) 1.4 (1.03 – 1.9)	Z=0.93 p=0.35ns

p (Mann-Whitney U Test)

Discussion

Studies investigating periprosthetic BMD have shown that the most significant bone loss occurs in the first 3 to 6 months after endoprosthesis implantation, followed by a period of stabilization during the first postoperative year [9,27].

Few studies have investigated the effect of Alendronate on this periprosthetic bone loss. A prospective randomized trial examined 13 patients treated for coxarthrosis with a cement-free hip endoprosthesis. Patients were randomized to receive only calcium or calcium Alendronate. This study showed that in patients treated with Alendronate, bone loss was significantly lower than in the control group

Table 5. Evaluation of BMD at 12 months

BMD 6 months				
zone	GROUP	mean ± SD	median (IQR)	p-level
Z1	SG CG	1.71 ± 0.7 0.93 ± 0.6	1.43 (1.13 – 1.98) 0.68 (0.51 – 1.23)	Z=3.87 p=0.0001sig
Z2	SG CG	2.02 ± 0.9 1.15 ± 0.5	1.63 (1.35 – 2.34) 1.01 (0.73 – 1.53)	Z=3.74 p=0.0002sig

Z3	SG CG	2.38 ± 1.5 1.24 ± 0.4	1.88 (1.56 – 2.32) 1.12 (0.97 – 1.37)	Z=4.59 p=0.000004sig
Z4	SG CG	2.26 ± 1.1 1.18 ± 0.4	1.98 (1.63 – 2.43) 1.13 (0.94 – 1.23)	Z=4.65 p=0.000003sig
Z5	SG CG	2.48 ± 1.2 1.22 ± 0.5	2.12 (1.71 – 2.72) 1.12 (0.89 – 1.28)	Z=4.76 p=0.000002sig
Z6	SG CG	2.63 ± 1.2 1.32 ± 0.6	2.32 (1.87 – 3.13) 1.12 (0.83 – 1.87)	Z=4.5 p=0.000007sig
Z7	SG CG	2.43 ± 1.02 1.18 ± 0.5	2.10 (1.64 – 2.84) 1.12 (0.89 – 1.32)	Z=5.05 p=0.000000sig

p (Mann-Whitney U Test)

(0.9% vs. 17.1% for proximal Gruen zones and 2.6% vs. 9.9% for all Gruen- zones)[20,22].

In our group of patients, the results showed an increase in BMD in all Gruen zones for all patients individually over a period of 6 months (measured 6 and 12 months after surgery), indicating the benefit of Alendronate in reducing periprosthetic osteolysis.

Our results from examining the values of BMD, but also of BMC, support the potential benefit of Alendronate in improving denture implantation, as studies show that the mechanism of action of Alendronate is expressed through an increase in bone mass and of the cortical and trabecular bones, with the greatest growth being in the trabecular bone, which is necessary for the implantation of the cement-free stem.

Conclusion

Alendronate is a proven inhibitor of periprosthetic bone loss that occurs after primary implantation of a total cement-free hip endoprosthesis. Our preliminary study reaffirms the effect of bisphosphonate therapy as an inhibitor of periprosthetic bone loss and aseptic implant loosening.

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Clinical science

APPLICATION OF HIGH-INTENSITY LASER IN PAIN TREATMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS

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Abstract

Osteoarthritis is a rheumatic disease characterized by degeneration and decay of cartilage in the joints. As the disease worsens, the joint space narrows causing numbness and pain, which often impairs movement. In addition to pharmacological therapy, low-intensity laser (LILT), high-intensity laser (HILT) and exercise are used to treat osteoarthritis (OA) of the knee. HILT is a new modality in our country and the experience from its application is small, especially in the treatment of OA of the knee. Aim of the paper was to compare the effect of HILT with LILT in the treatment of OA of the knee. Material and methods: This was a randomized comparative unilateral blind study involving 72 patients divided into two groups. The first group was treated with HILT, the second group treated with LILT. Outcome measure was the visual analogue scale (VAS) for pain, which was made on the first and tenth day of treatment. Statistical significance was defined as $p < 0.05$. Results: We found a significant difference between the two groups in terms of VAS score after 10 therapies in favor to a significantly lower score, that is, less pain in the HILT group ($p = 0.0035$). The comparison of the VAS score between the two times in the two groups separately showed that in both, the HILT and the LILT groups, the VAS score after 10 days of therapy was significantly lower compared to thatat 0 time, for consequently $p = 0.00001$vsp = 0.00001. Conclusion: Treatment with HILT and LILT significantly reduces pain and stiffness in patients with OA. Patients treated with HILT had better results, i.e., had a significant reduction in pain than patients treated with LILT. HILT was more effective than LILT.

Клинички истражувања

ПРИМЕНА НА ВИСОИНТЕНЗИВНИОТ ЛАСЕР ВО ЛЕКУВАЊЕ НА БОЛКА КАЈ ПАЦИЕНТИ СО ОСТЕОАРТРИТ НА КОЛЕНО

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Клучни зборови: високоинтензивен ласер, нискоинтензивен ласер, остеартитис на колено, ВАС скала

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Печатарски права: ©2021 Валентина Коевска, Ериета Николиќ-Димитрова, Билјана Митревска, Цветанка Геракароска-Савевска, Марија Гоцевска, Билјана Калчовска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Остеоартритисот е ревматолошко заболување кое се карактеризирасо дегенерација и распаѓање на ,рскавицата во зглобовите. Со влошување на болеста, зглобниот простор се стеснува предизвикувајќи вкочанетост и болка, што често го нарушува движењето. Освен фармаколошка терапија, во лекувањето на остеоартитисот (ОА) на коленото се применува нискоинтензивен ласер (НИЛТ), високоинтензивен ласер (ВИЛТ) и вежби. ВИЛТ е нов модалитет во нашата земја и искуството од неговата примена е мало, особено во лекувањето на ОА на коленото. Цел на трудот е да се спореди ефектот на ВИЛТ во однос на НИЛТ во лекувањето на болката кај остеоратитис на коленото. Материјал и методи: Рандомизирано, компаративно, едностранo слепо истражување во кое учествуваа 72 пациенти поделени во две групи. Првата група беше лекувана со ВИЛТ, а втората група со НИЛТ. Како мерка за исход беше користена визуелно аналогна скала (ВАС) за болка, која беше направена на првиот и десеттиот ден од лекувањето. За статистичка значајност беше земено $p<0,05$. Резултати: Согледавме сигнификантна разлика помеѓу двете групи во однос на ВАС скорот по 10 терапии, во прилог на сигнификантно понизок скор, односно помала болка во ВИЛТ групата ($p=0,0035$). Споредбата на ВАС скорот помеѓу двете времиња во двете групи поединечно покажа дека и во ВИЛТ и во НИЛТ групата висината на VAS скорот по 10-дневна терапија беше сигнификантно понизок споредено со оној во 0 време за консеквентно $p=0,00001$наспроти $p=0,00001$. Заклучок: Третманот со ВИЛТ и НИЛТ значајно ја намалува болката, вкочанетоста и значајно ја подобрува функционалоста кај пациентите со ОА. Пациентите третирани со ВИЛТ имаат подобри резултати, односно имаат значајно намалување на болката, во однос на пациентите кои се третирани со НИЛТ. ВИЛТ беше поефикасен отколку НИЛТ.

Introduction

Osteoarthritis (OA) is a very common cause of chronic musculoskeletal pain and disability in the adult population. In fact, all people over 60 years have some degenerative changes in their joints; 70-85% of them have signs and symptoms such as pain and short-term morning stiffness. One of the most common forms of osteoarthritis found in clinical practice is osteoarthritis of the knee (OAK). Radiographic evidence of OAK is present in about 30% of men and women over the age of 65[1].

Pain and functional limitations lead to a reduction in quality of life and reduced participation in social and societal activities[2]. Osteoarthritis of the knee is characterized by degeneration and disintegration of the cartilage of the joint which over time leads to narrowing of the joint space. The ligaments and surrounding tendons may be affected, and bone growths may develop, or the-so-called osteophytes. Pain, morning stiffness, and limited knee mobility are characteristic symptoms of OAK. Over time, typical deformities, such as varus or valgus may develop. Pain occurs due to changes in the synovial membrane, bone microfractures in the subchondral bone, mechanical irritation from osteophytes, and involvement of extraarticular structures of the knee such as bursitis, tendinitis, entesopathy, and enthesitis and eye spasm.Last but not least, pain is influenced by psychological andsocial factors[3].

Analgesics, nonsteroidal anti-rheumatic drugs, glucosamine sulfate, and chondroitin sulfate are recommended to reduce pain and improve functional ability. So far, several physical modalities such as tension, low-intensity laser and therapeutic ultrasound have been shown to be effective in treating OAK pain[4,5,6].

Several recent studies have shown results where low-intensity laser therapy (LILT) reduces pain in patients with OAK[7,8,9,10]. High-intensity laser is a relatively new non-invasive physical modality in the treatment of OAK. In 2020, several reviews of research on the effectiveness of high-intensity laser therapy (HILT) in the treatment of pain were published. In the conclusion, the authors commented that in the future more research is needed with a larger sample of patients[11,12]. The results of several randomized trials of patients showed a significant reduction in pain and improvement in physical function in OAK [13,14.] LILT has a biostimulatory effect. It occurs primarily locally in tissues that have absorbed the laser beam. Its main action is to accelerate the regeneration of damaged and diseased tissues, reduces swelling and pain and has an anti-inflammatory effect. The advantage of these lasers is their minimal thermal effect[15].

In Ray M.'s review, several studies from 1980-2017 were analyzed examining the impact of laser therapy on both HILT and LILT in animal models. The laser has been shown to have a bistimulatory effect on cartilage and surrounding muscle and ligament tissue in joints as well as a positive effect on pathoanatomical changes in OA. It has also improved symptoms in this disease along with functioning, particularly emphasizing the HILT effects[16].

High-intensity lasers also have a thermal and mechanical effect and

induce an electromagnetic field, as well as photoelectric, electrochemical, and other changes in exposed tissues. The advantage of HILT is that byincreasing power the depth of penetration is increased, and thus the effects in deep structures, despite the presence of regression of the quantity and quality (coherence, polarization) of light electromagnetic energy[17,18]. HILT in the tissue causes a photochemical effect, such as increased oxygenation in the mitochondria and formation of ATP, which leads to an increased absorption of edema by increasing metabolism and microcirculation[19].

A systematic search of PubMed, SAGE, HINARI databases showed that a small number of studies have compared the impact of HILT and LILT on pain and physical functioning in patients with OAK. So far, in our country no comparative study of the impact of HILT and LILT in patients with osteoarthritis of the knee has been conducted. This is a motive to conduct research in our country, which results would contribute to a better and higher quality treatment of patients with knee OA and enable better quality of life. The results of the research would help to establish protocols for treatment of OA with physical therapy.

The aim of this study was to compare the effect of HILT and LILT in reducing pain in OAK.

Material and methods

This was one-sided blind randomized comparative study, conducted at the University Clinic for Physical Therapy and Rehabilitation in Skopje. The study included 72 patients who had previously been diagnosed with osteoarthritis of the knee based on the clinical picture and X-ray.

Inclusion criteria: patients with pain due to osteoarthritis of the knee no longer than 3 months.

Exclusion criteria: application of corticosteroids and hyaluronic acid in the last 3 months, malignant diseases, fractures, tendon injury, meniscus, ligament, diseases of the hip and ankle, operated knee, rheumatoid arthritis, diseases with contraindications to laser therapy, personal reasons.

Patients were assigned into two groups.

1. The first group consisted of patients receiving a high-intensity laser therapy
2. The second group consisted of patients receiving a low-intensity lasertherapy.

Patients in both groups received 10 sessions of laser therapy. They were monitored for one month, during which period two controls were performed. The first control was after 10 sessions of treatment, and the second control was at the end of the 30 days follow-up.

A visual analog scale (VAS) was used to assess pain. It is a one-dimensional measure of pain intensity (0-100 mm), used in different adult populations, including those with rheumatic diseases (20). A higher result indicates a greater intensity of pain. We noted the intensity of pain as 0 if there was no pain (0-4 mm), 1 for mild pain (5-44 mm), 2 for moderate pain (45-74 mm) and 3 severe pain (75-100 mm).[21]). The pain assessment was made at the beginning and 10 days after the treatment of the patient. Assessment of physical function, stiffness, and

knee pain was determined by the WOMAX index (or Western Ontario and McMaster Universities Osteoarthritic Index). The index contains 24 questions, 5 related to pain, 2 to stiffness and 17 to physical function. It can be used to monitor the course of the disease or to determine the effectiveness of various interventions (pharmacological, surgical, physiotherapy, etc.)[22].

High-Intensity Laser Treatment Protocol

For high-intensity laser therapy, a VIKARE electro-medical device of Italian production was used with a power of 4-8 W. The application uses a standardized protocol presented in the device, every day, for a total of 10 days. The patient receives 8.00 J / cm2 per one session, for a period of 10 minutes. The patient lies in a supine position with a knee flexion of 30^0. The application of laser radiation is by scanning transversally and longitudinally on the anterior, medial and lateral side of the knee joint with special emphasis on the femoral and tibial epicondyle [23].

Low-Intensity Laser Treatment Protocol

For low-frequency laser treatment, Eco Medico Laser device of Electronic Design, Ser.N^{0}1116 made in Serbia was used. A standardized protocol for application presented in the device was used. The application dose is 5J / cm^2, with a power of 200Hz. The patient lies in a supine position, with a knee flexion of 30^0. Knee skin is cleansed with alcohol. The application is performed with a probe atacupuncture-trigger painful points on the medial, anterior and lateral side of the knee, a total of 14 points. Each point takes a third of 25 seconds, the total duration of one application is 6 minutes. The patient is treated daily, with a weekend break, receiving 10 sessions in a 2-week-period. The patient and the doctor wear goggles during the application of LILT and HILT. The data obtained during the study were statistically analyzed using the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). A significance level of $p < 0.05$ was used to determine the statistical significance.

Results

The distribution of patients by gender in the HILT and LILT groups showed representation of 23 (63.89%) vs 31 (86.11%) women, and 13 (36.11%) vs 5 (13.89%) men, respectively. We observed a significantly higher proportion of male patients in the group treated with HILT ($p = 0.0294$) (Table 1).

The mean age of patients in the HILT and LILT groups was 61.36 ± 8.14 vs 60.36 ± 7.45 without a significant difference between the two groups ($p = 0.7105$). The proportion of patients in the age groups of 50-59 and 60-69 years was equal in both the HILT and the LILT groups, that is, 13 (36.11%) vs 14 (38.89%), consequently. In both groups, the proportion of patients aged 40-49 was lowest, followed by 70-79. The analysis of BMI indicated an average value of 30.68 ± 4.49 kg / m^2 in the HILT and 30.29 ± 4.49 kg / m^2 in the LILT group without a significant association between the BMI level and the group to which the patients belonged ($p = 0.6162$).

Table 1. General characteristics by groups

Parameters	groups		p
	HILT N=36	LILT N=36	
Gender- N (%)			
Female	23 (63.89%)	31 (86.11%)	Pearson Chi-square test=4,7407; df=1; p=0,0294*
Male	13 (36.11%)	5 (13.89%)	
Age (years)			
± SD	61.36±8.14	60.36±7.45	Mann-Whitney U Test: Z=0.3716;p=0.7105
Min/Max	45/76	45/72	
Median (IQR)	62 (55-68)	61 (55-66.5)	
Agegroups - - N (%)			
40-49	2 (5.56%)	3 (8.33%)	Fisher-Freeman-Halton exact test: p=0.8094
50-59	13 (36.11%)	14 (38.89%)	
60-69	13 (36.11%)	14 (38.89%)	
70-79	8 (22.22%)	5 (13.89%)	
BMI (kg/m²)			
± SD	30.68±4.49	30.29±4.49	Mann-Whitney U Test: Z=0.5012;p=0.6162
Min/Max	22.25/40.40	22.55/40.40	
Median (IQR)	30.24 (27.51-33.47)	29.38 (27.35-32.43)	

*significant for p<0.05

Anamnestic data

The anamnestic data on knee pain by groups is given in Table 2. Most of the patients from both groups (HILT/LILT) had no experience of previous knee pain - 26 (72.11%) vs 29 (80.56%) respectively, without a significant association of the existence of this type of experience with the group to which patients belonged (p = 0.4051). The time from the last episode of pain was without a significant difference between the groups and it was 7.64 ± 8.96 months for the HILT and 8.11 ± 8.66 months for the LILT group. In 50% of patients from both groups, the time to the last episode of pain was longer than 5.5 months, and the longest time in both groups was 36 months. Previous treatment of knee pain was reported by 20 (55.56%) patients in the HILT and 17 (47.22%) of those in the LILT group. We found no significant association between the positive history of previous treatment and the group to which patients were assigned (p = 0.4793).

Most of the patients in the HILT group,12 or 60%, was previously treated with antirheumatic drugs followed by physical + antirheumatic drugs, 5 (25%), and physical therapy, 3 (15%) patients. In the LILT group, most of the knee pain was treated with physical + antirheumatic drugs, 7 (41.18%), followed by an equal proportion of 5 (29.41%) who were treated with physical therapy, i.e., only with antirheumatic drugs. The

analysis did not establish a significant association between the group to which patients belonged and the type of previous treatment of knee pain (p = 0.1742).

Table 2. Analysis of anamnestic data on knee pain by groups.

Parameters	groups		p
	HILT N=36	LILT N=36	
Pain for the first time - N (%)			
No	26 (72.11%)	29 (80.56%)	Pearson Chi-square test=0.6930; df=1; p=0.4051
Yes	10 (27.78%)	7 (19.44%)	
Last episode (month)			
± SD	7.64±8.96	8.11±8.66	Mann-Whitney U Test: Z=-0.2083;p=0.8349
Min/Max	0/36	0/36	
Median (IQR	5.5 (0-12)	5.5 (3-12)	
Previous treatment- N (%)			
No	16 (44.44%)	19 (52.78%)	Pearson Chi-square test=0.5004; df=1; p=0.4793
Yes	20 (55.56%)	17 (47.22%)	
BMI (kg/m²)			
Physical therapy	3 (15%)	5 (29.41%)	Fisher-Freeman-Halton exact test: p=0.1742
Physical therapy+ NSAIL	5 (25%)	7 (41.18%)	
NSAIL	12 (60%)	5 (29.41%)	

*significant for p<0.05

Table 3. Comparison at VAS scale for knee pain between groups and intergroups at two times.

VAS		N	± SD	Min/ Max	Median (IQR)	p
0-time	HILT	36	7.14±1.62	3/10	7 (6-8)	Mann-Whitney U test: Z=0.7433; p=0.4573
	LILT	36	6.81±1.62	3/10	7 (6-8)	
10-therapies	HILT	36	2.22±1.74	0/5	2 (1-4)	Mann-Whitney U test: Z=-2.9169; p=0.0035*
	LILT	36	3.56±1.78	0/7	4 (2-5)	
Wilcoxon signed-rank test 0/10: VILT- Z=5.2316; p=0.00001* NILT- Z=5.0119; p=0.00001* *significant <0.05						

Knee pain in patients of both groups was assessed according to VAS at two times, at 0 time and after 10 therapies (Table 3). At0time the average VAS score in the HILT andLILT group was 7.14 ± 1.62 vs 6.81 ± 1.62, with a min / max value in both groups of 3/10 or 50% of patients in whom the pain had a VAS score higher than 7. We found no significant difference between the two groups regarding VAS score level(p = 0.4573). After 10 therapies, the average VAS score in the HILT and LILT groups was 2.22 ± 1.74 vs 3.56 ± 1.78 with a min / max score of consequently0/5 vs 0/7 and 50% of patients with VAS score lower than consequently 2 vs 4. There was a significant difference between the two groups in terms of the VAS score level after 10 therapies in favor of a significantly lower score or less pain in the HILT group (p = 0.0035) (Figure 1).

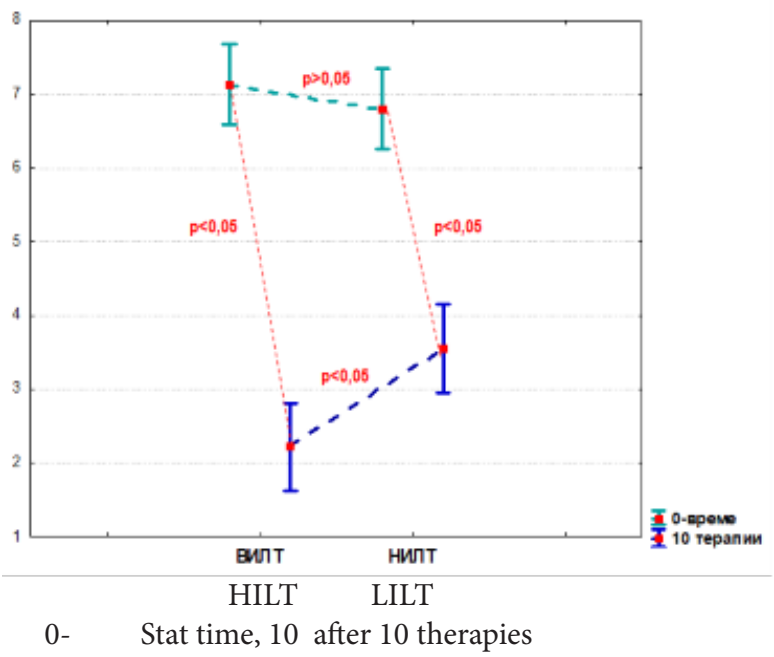


Figure 1. Comparison of VAS for group and intergroup knee pain at two times

Additionally, we compared the VAS score between the two times in the two groups separately.We found that in both groups, HILT and LILT, the VAS score after 10 days of therapy was significantly lower compared to that at 0 time for consequently p = 0.00001vs p = 0.00001(Figure1).

Discussion

Our study included two equal groups of 36 (100%) subjects; the first was treated with high-intensity laser therapy (HILT), and the second with low-intensity laser therapy (LILT). The general characteristics by groups are given in Table 1. We observed a significantly higher proportion of male patients in the group treated with HILT (p = 0.0294). The mean age in the HILT andLILT groups was without a significant difference between the two groups (p = 0.7105). Also, there was no significance between the BMI level and the group to which patients belonged (p = 0.6162).

In 50% of patients from both groups, the time to the last episode of pain was longer than 5.5 months, and

the longest time was 36 months. We found no significant association between the positive history of previous treatment and the group to which patients belonged (p = 0.4793). The analysis showed no significant association between the group to which patients belonged and the type of previous treatment of knee pain (p = 0.1742).

VAS scale

At 0 time we did not find a significant difference between the two groups in terms of the VAS score (p = 0.4573). We found a significant difference between the two groups in terms of the VAS score after 10 therapies in favor to a significantly lower score, i.e., less pain in the HILT group (p = 0.0035).

Additionally, we compared the VAS score between the two times in the two groups separately. We found that in both groups, HILT and LILT, the VAS score after 10 days of therapy was significantly lower compared to that at 0 time for consequently p = 0.00001vs p = 0.00001.

Our study demonstrated statistically significantly better results in the group of patients treated with HILT than in the group treated with LILT. In the available literature, LILT is considered an effective modality in the treatment of knee OA[24]. In previous studies, it was used alone or in combination with acupuncture or exercise[25,26]. In several studies, the authors did not find an allergic effect of LILT in patients with OA of the knee [27, 28]. In contrast, other authors demonstrated efficacy in the treatment of pain with LILT[26,29,30]. In addition, LILT was shown to be superior to ultrasound therapy in treatment of patients with OAK[29].

In our study, we examined the effectiveness of LILT in treating pain by using VAS at least 1 week after treatment. The results obtained in our study about the LILT impact are similar to several previous studies that applied the same outcome measure[29,30]. LILT reduces pain directly by reducing the conduction velocity of sensitive nerves and raising the pain threshold, or indirectly by increasing tissue oxygenation and subsequently reducing swelling[30]. Meanwhile, it has been reported in the literature that LILT reduces the intensity of the inflammatory process[31] and improves microcirculation[32]. Recently, HILT has been used in the treatment of pain in neurological and musculoskeletal disorders. For e.g., the study of Paul et al comprising former athletes with osteoarthritis showed HILT to be effective in reducing chronic pain [33]. In addition, HILT has been shown to be effective in reducing low back pain [34,35,36], chronic ankle pain [37,] neck pain [38], and carpal tunnel syndrome [39]. HILT also showed a positive short-term effect in frozen shoulder[40], a long-term positive effect in reducing lateral epicondylitis inflammation[41], and in Bell's palsy[42].

Several recent surveys from 2015 and 2017 that reviewed the results of several studies about the LILT treatment of OA reported that LILT had limited effects on the treatment [43], 4[4]. In contrast, a number of randomized trials on the efficacy of HITL in the treatment of chronic pain has increased in recent years. One of them is our studywhere HILT has proven to be a simple, non-invasive, and effective choice for physiotherapy or physical modalities. HILT is simple to apply ("point-and-shoot") and has almost-no side effects. The only known side

effect is a temporary change in skin color (redness) and a burning sensation if the head of the laser probe is located near the surface of the skin. The study conducted by Villiani et al. demonstrated that analgesic effect and better functionality in OA of the knee can be achieved, after application of only 5 procedures, continuously every day[45].

There are several studies in the literature that have examined only the analgesic efficacy of VAS with HILT in OA of the knee [46,11,13]. One of them is the study of Kim et al. [46], which included 28 patients, who showed a significant reduction in pain (P <0.05) after half a month of knee treatment. Similarly, in the study of Stiglitz-Rogoznica et al. 11 where 96 patients were randomized, pain was also evaluated at theVAS scale before and after 10 days of treatment. The results showed a statistically significant reduction in pain (p <0.001). In the randomized pilot study of Ilieva and Angelova comprising 72 patients, the results showed that there was a significant reduction in pain after seven days of treatment in the group of patients treated with HILT (p <0.001)[47].

There are several studies in the literature that comparedthe effectiveness of HILT with conservative physical therapy (ultrasound, interference currents, and exercise). One of them is the study of Goal-Joo[48], where patients were assigned into two groups and received 12 treatments. The results of VAS and K-VOMAK showed that HILT wa sa more effective in pain treatment of patients with OAK than conventional therapy.

A recent one-sided blind comparative study by Nazari et al. published in 2020 compared the efficacy of HILT with conventional physical therapy in OA of the knee. In this study, the results of HILT were superior to conventional physical therapy in relieving pain and improving function. The study was conducted in 93 respondents, who were randomly assigned into three groups; the first one treated with HILT and exercise, the second with conventional physical therapy and the third group with exercise only. The HILTgroup was treated for 12 sessions. The results of VAS, timed up and go test, 6-min walk test, Western Ontario and McMaster Universities Osteoarthritis (WOMAC) questionnaire showed a significant improvement in the first group treated with HILT and exercise[49].

This study conducted in our institution supports the fact that the effect of the laser depends on the characteristics of the laser it self such as wavelength and coherence. The effectiveness of HILT is based on the specific and high-peak power of the laser pulse with a certain frequency and width of the pulse. Thanks to this high-energy peak, a large amount of energy is supplied in a short time (vertical effect), unlike the traditional delivery of the same amount of energy for a longer time and the risk of heating and tissue damage (horizontal effect). The advantage of HILT compared to LILT is that by increasing power the depth of penetration increases, and thus the effect in deep structures. The reduction of pain occurs through the so-called “Gate control system”. This system is the result of the stimulating effect of radiation on the regeneration of nerve fibers. The anti-inflammatory effect is realized by modulating the components of the inflammatory reaction, exudation, change and pro-

liferation, blocking cyclooxygenases and lipoxygenases and synthesis of prostaglandins and prostacyclin.

Conclusion

The results of our study showed that treatment with HILT and LILT significantly reduces pain in patients with OA. Patients treated with HILT showed better results, i.e., had a significant reduction in pain compared to patients treated with LILT. The use of HILT has been shown to be clinically relevant in providing a rapid and potent pain-reducing effect.

In the future, these findings might be compared to changes in muscle contraction and strength. The effect of laser therapy, especially HILT, on the cartilage of the knee, can also be the subject of further research if we start from the assumption that it can improve cartilage regeneration. New comparative studies are needed in the future where the sample and follow-up time should be longer to see the long-term effect of HILT. All this would contribute to the development of an appropriate protocol for the treatment of OA of the knee.

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Clinical Science

COMPARATIVE ANALYSIS OF HIDDEN BLOOD LOSS IN TOTAL KNEE ARTHROPLASTY

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Abstract

The aim of the study was to investigate the influential factors for hidden blood loss after a total knee arthroplasty and their relationship with the total blood loss. Total knee arthroplasty (TKA) is a crucial treatment of late-stage knee osteoarthritis. Measured blood loss is significantly inconsistent with the hemoglobin (HB) drop postoperatively. Fifty-four patients, 20 males and 34 females, were retrospectively analyzed. The preoperative blood loss and therefore the hidden blood loss following TKA were calculated by the Gross formula. The typical perioperative blood loss was found to be 780±220 ml and therefore the average hidden blood loss was 280±180 ml. No significant differences were found in hidden blood loss for males compared to females. Hidden blood loss may not be reduced by hemostasis during operation with a deflated tourniquet.

Клинички испитувања

КОМПАРАТИВНА АНАЛИЗА НА СКРИЕНАТА ЗАГУБА НА КРВ ПРИ ИЗВЕДУВАЊЕ ТОТАЛНА АРТРОПЛАСТИКА НА КОЛЕНОТО

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Компаративна анализа на скриената загуба на крв при изведување тотална артропластика на коленото. Арх Ј Здравје 2021;13(2) 91-95

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Клучни зборови: тотална артропластика на колено, скриена крвозагуба, турнике

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Печатарски права: ©2021 Антонио Гавриловски, Илир Шабани, Вилијам Велковски, Теодора Тодорова, Шабан Мемети. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Целта на овој труд беше да се пронајдат факторите кои влијаат врз скриениот губиток на крв како и нивниот сооднос со целосната крвозагуба при тотална алоартропластика. Тоталната алоартропластика на коленото (ТКА) е важна процедура во третманот на остеоартритисот на коленото во напредната фаза. Измерената загуба на крв често пати е несразмерна со падот на хемоглобинот (HB) постоперативно.

Ретроспективно беа анализирани 54 пациенти, 20 мажи и 34 жени. Периоперативната загубана крв и скриената загуба на крв по ТКА беа пресметани со формулата на Грос (Gross).

Просечната периоперативна загуба на крв беше 780±220 ml, а просечната скриена загуба на крв беше 280±180 ml.

Не беа најдени значителни разлики кај скриената загуба на крв кај мажите во споредба со жените. Скриената загуба на крв не може да се намали со внимателна хемостаза за време на операцијата.

Introduction

Total knee arthroplasty (TKA) may be a gold standard treatment for end-stage knee osteoarthritis. This surgery is considered the foremost effective treatment for severe knee osteoarthritis with good or excellent long-term outcomes[1,2,3]. It represents a serious orthopaedic surgery which involves a significant blood loss due to bone cuts and soft tissue releases. Approximately 15 million transfusions are performed annually worldwide caused by TKA[4].

In this surgery the blood loss consists of the visible blood loss from the wound drainage, into the tissues which is hidden and the surgical field. The measured blood loss usually consists of measurement of the drained blood and therefore the real blood loss could also be underestimated. Despite the usage of a tourniquet during TKA and the significant improvement in surgical techniques, this surgery is related to a large amount of post-operative blood loss and remains a topic for discussion among surgeons. Lotke et al. came to a conclusion that the mean blood loss in TKA when calculated from pre-operative drop by hemoglobin was 1518 ml, which needed a minimum of one transfusion[5]. Transfusion increases the danger of transmission of infectious diseases, anaphylactic, hemolytic and immunologic reactions. Also, it could lead to a longer hospital stay and increased mortality[6].

The existing results of influential factors in these patients remain controversial. Identifying the factors of surgical blood loss may be a crucial step towards establishing an efficient blood management strategy and reducing the necessity of peri-operative transfusion. Cushner and Friedman et al. discovered that the gender of patients may influence the blood loss; transfusion rates were higher in females probably owing to lower pre-operative hemoglobin levels, but they excluded the correlation with the age and duration of the surgery[7].

The aim of our study was to detect and recognize the potential influencing factors of hidden blood loss in patients with knee osteoarthritis, treated with total knee arthroplasty.

Materials and methods

The study was performed at the University Clinic for Orthopaedic Surgery from December 2018 to December 2019. A total of 54 patients, of whom 20 males and 34 females with knee osteoarthritis were retrospectively analyzed. We calculated the perioperative blood loss and consequently the hidden blood loss by using the Gross formula[7].

The formula is as follows: for male, PBV = k1 xh3 + k2 xw + k3 (h– height (m); w – weight (kg); k1=0.3669, k2 = 0.03219 and k3 = 0.6041; for female k1 = 0.3561, k2 = 0.03308 and k3 = 0.1833). Total blood loss was calculated by multiplying PBV by the change of HCT. Patients with anemia or any other disorder of hemoglobin preoperatively were excluded from this study. Potential factors who may affect operative and hidden blood loss were gender, surgical time, tourniquet time, hemostasis (during surgery with deflating tourniquet). In the group without tourniquet the tourniquet was released before closure of the wound and hemostasis was done and in the group with tourniquet the wound was closed without releasing it.

In all of the patients a typical surgical technique was used. All of the patients were operated under spinal anaesthe-

sia. We used a tourniquet which was inflated 120 mm above the systolic blood pressure. We used the medial parapatellar surgical approach. Cemented cruciate retaining prosthesis was used. Blood loss intraoperatively was measured from the suction device. We put active vacuum drain in every patient. The drain was removed after 48 hours. Hemoglobin and hematocrit levels were measured before and after surgery (after spinal anaesthesia was over, day 2 and day 4 postoperatively). The total blood loss (during the operation and collected from the drain) was compared to the Hb levels on selected days. In patients who received blood transfusion we made correction of the Hb level by 1g/dL for every unit. After that we made the conversion of these numbers to HCT value.

Results

In this study, the mean operative time was 115 minutes (100–190 minutes) and the mean tourniquet time was 107 minutes (80–120 minutes). Intraoperative blood loss of the group with hemostasis using the deflated tourniquet was 155 ml (90–300 ml) and postoperative drain-blood volume was 595±205 ml for that group. Perioperative blood loss was 780±220 ml [(758±243) ml for females and (912±90) ml for males] and hidden blood loss was 280±180 ml [(240±185) ml for females and (410±125) ml for males]. The hidden blood loss was therefore (51 ± 9.3)% of the visible postoperative blood loss (Table 1). The lowest hematocrit levels were measured on the 2-4 postoperative day, and the percentage of the hidden blood loss in both sexes was nearly equivalent. Although male patients had higher levels of hidden blood loss than females (t=-2.022, P=0.049), the proportion volume was nearly equivalent (Table 1). Hidden blood loss might be reduced by hemostasis after deflating tourniquet during the intraoperative period (t=-2.068, P=0.041), but the preoperative blood loss was not affected (t=-1.819 P=0.073) (Table 2).

Table 1. Gender distribution of perioperative blood loss

	Perioperative blood loss (ml)	Hidden blood loss (ml)	Percentage
Female (n = 34)	758 ± 243	240 ± 185	51.1
Male (n = 20)	912 ± 90	410 ± 125	50.7
P value	0.010	0.049	0.372

Table 2. Distribution of blood loss with and without hemostasis

	Perioperative blood loss (ml)	Hidden blood loss (ml)
With tourniquet	780 ± 220	300 ± 105
Without tourniquet	595 ± 205	280 ± 180
P value	0.073	0.041

Discussion

Hidden blood loss (HBL) was usually ignored until year 2000 when it was formally suggested [8]. Several theories were proposed like the idea of Pattison and Faris who suggested that HBL could also be due to hemolysis 9,10. On the opposite, Erskine proposed that the loss went into tissue compartments by using labelled

red cells 11. Other theory suggests that free fatty acids generated from fatty emboli in blood circulation are liable for the hidden blood loss by peroxidation damage of membrane molecules of red blood cells and hemoglobin. Tranexamic acid, closed-suction drainage, body mass index (BMI), gender and anticoagulants can also influence HBL. However, the factors have not been fully clarified 12-20.

Ward et al. revealed the mathematical solution to the hidden blood loss in 1980, and in 1983 the concept was moved forward by Gross PBV = k1 xh3 + k2 xw + k3 (h – height – height (m); w – weight (kg); for male, k1=0.3669, k2 = 0.03219 and k3 = 0.6041; for female, k1 = 0.3561, k2 = 0.03308 and k3 = 0.1833). Total blood loss was calculated by multiplying PBV by the change of HCT 21-23. This new linear formula was projected using patients average hematocrit during the preoperative course. Patients who underwent a surgery were tested by the Gross equation. It had been found that this formula closely followed the logarithmic one unless there was rapid hemorrhage when the formula drifted apart, and thanks to this reason, complicated cases with large losses were excluded from this study. To some extent, Gross equation reflects the actual postoperative blood loss due to individual factors: weight, height, gender and transfusion. This equation does not involve Hb-related factors like anemia and actual blood loss is revealed by the calculated pre-operative blood volume and the changes in HCT, which can limit this method.

Conclusion

No significant differences might be found in hidden blood loss in males compared to females. Hidden blood loss remains the same even after hemostasis during operation with a deflating tourniquet.

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Clinical science

MASTERING THE LEARNING CURVE SIGNIFICANTLY REDUCES OPERATIVE TIME FOR LAPAROSCOPIC TREATMENT OF COMPLICATED APPENDICITIS

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Key words: complicated appendicitis, laparoscopic appendectomy, operative time, learning curve

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Abstract

Laparoscopic appendectomy is the preferred operative method for acute appendicitis treatment. In terms of complicated appendicitis it can be effective in hands of an experienced laparoscopist that overwhelmed the learning curve for the method. Aim: This retrospective study examines whether the operative time for laparoscopic appendectomy for complicated appendicitis is shortened after mastering the learning curve. Material and methods: A total number of 196 patients were operated for the diagnosis of acute appendicitis, of whom 77 were diagnosed with complicated appendicitis. They were subsequently divided in two groups (laparoscopic and open). Operative time in both groups was measured and the conversion and postoperative complications were noted. Results: Conversion rate was 2.3%. Operative time was shorter in the laparoscopic group (67.4 ± 22.9 vs. 77.9 ± 17.9 minutes; p = 0.033). Overall postoperative morbidity was 25.97% with wound infection present only in the open group (p = 0.018). Intraabdominal abscess occurred in one patient from the laparoscopic group (0.38%). Length of hospital stay was shorter in the laparoscopic group (4.3 ± 2.2 vs. 5.7 ± 2.1, p = 0.0052).

Клинички истражувања

СОВЛАДАНАТА КРИВА НА УЧЕЊЕ ЗНАЧИТЕЛНО ГО СКРАТУВА ОПЕРАТИВНОТО ВРЕМЕ ЗА ЛАПАРОСКОПСКИ ТРЕТМАН НА КОМПЛИЦИРАН АПЕНДИЦИТИС

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Клучни зборови: комплициран апендицитис, лапароскопска апендектомија, оперативно време, крива на учење

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Лапароскопската апендектомија е преферирана оперативна метода во третманот на акутен апендицитис. Во услови на комплициран апендицитис таа може да биде ефикасна во рацете на искусен лапароскопист кој ја има совладано кривата на учење за методата. Цел: Оваа ретроспективна студија имаше за цел да испита дали совладаната крива на учење го скратува оперативното време. Материјал и методи: Вкупно беа оперирани 196 пациенти со акутен апендицитис. Од нив, 77 беа дијагностицирани со комплициран апендицитис и беа поделени во две групи (лапароскопска и отворена). Беа мерени оперативното време за двете групи, стапката на оперативни конверзии и постоперативните компликации. Резултати: Стапката на конверзии беше 2,3%. Оперативното време беше пократко во лапароскопската група (67,4 ± 22,9 наспроти 77,9 ± 17,9 минути; p = 0,033).Вкупниот постоперативен морибидет беше 25,97% и притоа инфекција на оперативна рана се јави само во групата оперирана со отворена метода (p = 0.018). Интраабдоминален апсцес беше нотиран кај еден пациент во групата оперирана со лапароскопска метода (0,38%). Бројот на лежечки денови беше пократок во групата оперирана со лапароскопска метода (4,3 ± 2,2 наспроти 5,7 ± 2,1, p = 0,0052).

Introduction

Laparoscopic appendectomy is the current proposed treatment for all grades of complicated appendicitis (CA)[1]. It is well established that laparoscopic appendectomy (LA) has advantages over the open appendectomy (OA) in terms of shorter operative time, low rate of operative conversions, acceptable rate of postoperative complications and shortened length of hospital stay[2-5].

The aim of this study was to examine whether the operative time of the laparoscopic appendectomy in the treatment of CA after mastering the learning curve for the technique was significantly shortened.

Material and methods

Patients

Our retrospective tertiary single center study analyzed patients operated for complicated appendicitis in terms of intraoperative adverse effects, operative time, conversion rate and length of hospital stay. Patients operated for acute appendicitis (AA) in the period of May 2019 – February 2021 were included.

Methods

A standard three-port laparoscopic appendectomy was used for the LA, and Mc Burney muscle-splitting technique for the OA. Operative time for both procedures was measured from incision to the last skin suture at the end of surgery. One surgeon performed the laparoscopic procedure with experience with more than 50 laparoscopic appendectomies and the other two surgeons (with more than 100 open procedures performed) used the open method.

The grades of complicated appendicitis noted intraoperatively were divided into 4 categories:

- Gangrenous appendicitis;
- Perforated appendicitis;
- Periappendicular abscess and
- Secondary diffuse peritonitis.

SPSS for Windows v. 23.0 software was used. Kolmogorov-Smirnov test was used for normality check. The Student and Mann-Whitney tests were used for numerical data and Chi-square test for quantitative variables.

Results

A total number of 196 patients were operated for the diagnosis of acute appendicitis. One hundred and nineteen (60.7%) had simple appendicitis and 77 (39.3%) patients were diagnosed intraoperatively with some grade of complicated appendicitis and only those were subsided for further statistical analysis. Fifty-two of them were males and the rest 25 were females (Table 1).

Table 1. Age of subjects (months)/ Age (in months) at cochlear implantation

n	Simple	Complicated
Male (%)	62 (52.1%)	52 (67.5%)
Female (%)	57 (47.9%)	25 32.5%)
Total	119	77

Patients with complicated appendicitis were subdivided into two groups (laparoscopic – A, open - O). Forty-four were operated laparoscopically and the rest 33 with OA. The most common intraoperative finding in the Group A was perforated appendicitis (18 patients), followed by peritonitis (12), gangrene (8) and abscess (6). In the open group, appendicular perforation was also the most common finding (16 patients) (p = 0.81) (Table 2).

Table 2. Demographic and surgical data

	Group A	Group O	p
Sex Male (%) Female (%)	31 (70.45) 13 (29.55)	21 (63.64) 12 (36.36)	p = 0.53
Age (mean ± SD)	39.4 ± 16.2	41.6 ± 16.3	p = 0.56
ASA (%) 1 2 3	25 (56.82) 12 (27.27) 7 (15.91)	14 (42.42) 14 (42.42) 5 (15.15)	p = 0.36
Intraoperative finding (%) Gangrene Perforation Abscess Peritonitis	8 (18.18) 18 (40.91) 6 (13.64) 12 (27.27)	6 (18.18) 16 (48.48) 5 (15.15) 6 (18.18)	p = 0.81
Operative time (mean ± SD)	67.4 ± 22.9 min.	77.9 ± 17.9 min.	p = 0.033
Length of stay (mean ± SD)	4.3 ± 2.2 days	5.7 ± 2.1 days	p = 0.0052

SD – standard deviation, min. - minutes

The overall range for operative time was 24 – 112 minutes in both groups. The laparoscopic procedures were shorter (67.4 ± 22.9 minutes) than the open ones (77.9 ± 17.9 minutes), which presented with significance (p = 0.033) (Table 2).

In one patient, converted appendectomy was performed (2.3%) due to a significant inflammatory process.

Length of hospital stay was shorter in the laparoscopic group (4.3 ± 2.2 vs. 5.7 ± 2.1, p= 0.0052).

Discussion

More than 90% of the cases with acute appendicitis are treated with appendectomy. Continuous growth in laparoscopy use is reported from 43.4% in 2007 up to 75% in 2011 [3]. Since 2001 when the first series of complicated appendicitis treated laparoscopically was reported, the success of the method was reported in another publication from 2006[6].

One of the factors with direct impact on the postoperative complications rate is the operative time over 90 minutes [7]. Prolonged surgery is expected in terms of any grade of complicated appendicitis due to additional adhesiolysis, partial omental resection, irrigation and suction of the abdominal cavity and the need for additional position changes of the operating ta-

ble[4]. Jeon reported the following factors for prolonged operative time: age over 65 years, body mass index over 25, elevated serum C-reactive protein values, comorbidities and computerized tomography finding in favor of appendicular abscess[8].

Regardless of the intraoperative finding, the surgeons' skills are also an important factor that influences on the operative time. Mastering the learning curve for laparoscopic appendectomy reduces it[2, 4].

The European Association for Endoscopic Surgeons (E. A. E. S.) Consensus Development Conferences on laparoscopic cholecystectomy, appendectomy, and hernia repair recommends performance of at least 20 laparoscopic appendectomies for gaining accreditation[9]. On the other hand, Kim's analysis on the surgical residency reported 30 procedures needed for mastering the learning curve[10].

Different series report differences in the operative time for the examined groups. Li, Biondi, Wang and Takami presented shorter operative time for the open appendectomy procedure[11-14], contrary to Park and Yau that proved significantly shorter operative time in the laparoscopic groups[15, 16].

Our study was conducted on the basis of more than 50 laparoscopic appendectomies performed by the principal investigator, which resulted in a statistically shorter operative time in the laparoscopic group.

Conclusion

Current recommendations and statements on the laparoscopic treatment for complicated appendicitis demand availability of an experienced laparoscopic team in order to provide safe and successful laparoscopic appendectomy on basis of complicated appendicitis. This will result in a positive postoperative outcome in terms of low conversion rate, short operative time and acceptable rate of postoperative morbidity.

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Clinical science

PREDICTIVE POTENTIAL OF THE MELD AND CHILD-TURCOTTE-PUGH II SCORES FOR SBP IN PATIENTS WITH CIRRHOSIS AND ASCITES

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Key words: spontaneous bacterial peritonitis (SBP), Child-Turcotte-PughII score, MELD score

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Abstract

It is very important for patients with spontaneous bacterial peritonitis (SBP) to assess the length of survival and the risk of death, primarily because of the wide range of potential complications that can lead to multisystem organ failure and fatal outcome. The aim of this study was to determine the predictive potential of MELD and Child-Turcotte-Pugh II score for SBP in patients with cirrhosis and ascites. Material and methods: The study was designed as a prospective-analytical-observational and was conducted at the University Clinic for Gastroenterohepatology in Skopje for a period of one year. The study population included 70 hospitalized patients with established liver cirrhosis, regardless of etiology, divided into two groups, 35 patients with SBP and 35 non-SBP. Prognostic scores in patients with liver cirrhosis and ascites: MELD score, according to the formula: MELD = [(0.957 x Ln Creatinin) + (0.378 x Ln Bilirubin) + (1.12 x Ln INR) + (0.643) x 10]. The Child-Turcotte-Pugh II score includes 6 parameters: serum albumin and bilirubin, amount of ascites, degree of encephalopathy (HE), prothrombin time (PT) and serum creatinine, and assessment of the degree of hepatic encephalopathy according to the West Haven criteria. Results: The average value of the MELD score in patients with SBP was 22.6 ± 8.27 and in non-SBP the average value was lower - 17.83±5.87. According to the Mann-Whitney U test, the difference between the mean values was statistically significant for $p < 0.05$ ($z = 2.41$; $p = 0.015$). A score of 30 to 39 was registered in 25.7% of patients with SBP, and only in 2.9% in non-SBP; the percentage difference was statistically significant for $p < 0.05$ (Difference test, $p = 0.0064$). Patients with SBP had an average Child-Pugh score of 13.09 ± 2.48 or 100.0% C-class points. In patients with non-SBP, an average child-Pugh score of 9.63 ± 1.62 was recorded, or class B in 65.7% and class C in 34.3%. The percentage difference was statistically significant for $p < 0.05$ (Difference test, $p = 0.0000000$). According to the Mann-Whitney U test, the difference between the mean values was statistically significant for $p < 0.05$ ($z = -5.44$; $p = 0.00001$). ROC analysis indicated that the Child-Turcotte-Pugh II score contributed to the diagnosis of SBP - 90.7% ($p = 0.000$) (excellent predictor), closer to the ideal value of 1.0 and above the worst value of 0.5. ROC analysis indicated that the MELD score did not contribute to the diagnosis of SBP - 66.7% ($p = 0.017$) (weak predictor), closer to the worst value of 0.5. Conclusion:Our research confirmed that SBP occurs in patients with severe hepatic dysfunction calculated according to the CTP II score and MELD score. Mean value of the MELD score in patients with SBP was higher then in patients with non-SBP. On the other hand all patients with SBP had an average CTP II score, C-class points, while the largest percentage of patients with non-SBP were class B-class points. MELD score is a weak predictor of SBP. The best predictor for predicting SBP is the CTP II score (rank C).

Клинички испитувања

ПРЕДИКТИВЕН ПОТЕНЦИЈАЛ НА MELD И CHILD-TURCOTTE-PUGH II СКОРОТ ЗА СБП КАЈ ПАЦИЕНТИ СО ЦРНОДРОБНА ЦИРОЗА И АСЦИТ

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Клучни зборови: спонтан бактериски перитонитис (СБП), Child-Turcotte-Pugh II скор, MELD скор.

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Печатарски права: ©2021 Фана Личоска Јосифовиќ, Калина Гривчева Стардeлова, Бети Тодоровска, Магдалена Генадиева Димитрова, Лидија Петковска, Мери Трајковска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Поради широкиот спектар на потенцијални компликации кои може да доведат до мултисистемско органско попуштање и смрт, многу е важно кај пациентите со спонтан бактериски перитонитис (СБП) да се направи проценка на должината на преживување и ризикот од смртен исход. Целта на трудот беше да се одреди предиктивниот потенцијал на MELD и Child-Turcotte-Pugh II скорот (CTP II) за СБП кај пациентите со црнодробна цироза и асцит. Материјал и методи: Студијата беше дизајнирана како проспективно-аналитичко-опсервациска и се спроведе на Универзитетската клиника за гастроентерохепатологија во Скопје во период од една година. Студиска популација беа хоспитализирани пациенти со етаблирана црнодробна цироза, без оглед на етиологијата, вкупно 70 пациенти, поделени во две групи, 35 пациенти со СБП и 35 без СБП. Прогностички скорови кај пациенти со црнодробна цироза и асцит: MELD скор, според формулата: MELD = [(0,957 x Ln Creatinin) + (0,378 x Ln Bilirubin) + (1,12 x Ln INR) + (0,643) x 10]. СТП II скор вклучува 6 параметри: албумин и билирубин во серум, количина на асцит, степен на енцефалопатија, протромбинско време (ПВ) и креатинин во серум, а проценка на степенот на хепатална енцефалопатија(НЕ) со West-Haven-овите критериуми. Резултати: Просечната вредност на MELD скорот кај пациентите со СБП изнесуваше 22,6±8,27 а кај оние без СБП просечната вредност беше пониска и изнесуваше 17,83±5,87. Според Mann-Whitney U тестот, разликата помеѓу просечните вредности беше статистички сигнификантна за $p<0,05$ ($z = 2,41$; $p=0,015$). Вредност на скорот од 30 до 39 беше регистрирана кај 25,7% од пациентите со СБП, а само кај 2,9% од оние без СБП; процентуалната разлика беше статистички сигнификантна за $p<0,05$ (Difference тест, $p=0,0064$).Кај пациентите со СБП беше регистрирана просечна вредност на СТР II скорот од 13,09±2,48 или во поени 100,0%, класа С. Кај пациентите без СБП беше регистрирана просечна вредност на СТР II скорот од 9,63±1,62 или класа В кај 65,7% и класа С кај 34,3%. Процентуалната разлика беше статистички сигнификантна за $p<0,05$ (Difference тест, $p=0,000000$). Според Mann-Whitney U тестот, разликата помеѓу просечните вредности беше статистички сигнификантна за $p<0,05$ ($z = -5,44$; $p=0,00001$).ROC-анализата покажа дека СТР II скорот придонесува за дијагностицирање на СБП - 90,7% ($p = 0,000$) (одличен предиктор), поблизу до идеалната вредност од 1,0 и над најлошата вредност од 0,5.ROC-анализата покажа дека MELD скорот не придонесува за дијагностицирање на СБП со 66,7% ($p = 0,017$) (слаб предиктор), поблизу е до најлошата вредност од 0,5. Заклучок:Нашето истражување потврди дека СБП се јавува кај пациенти со тешка хепатална дисфункција пресметана според СТР II и MELD скорот. Средната вредност на MELD скорот кај пациенти со СБП беше поголема отколку кај пациенти со не-СБП. Од друга страна, сите пациенти со СБП имаа просечна вредност на СТР II, С-класа, додека најголем процент од пациентите со не-СБП беа В-класа. MELD скорот е слаб предиктор за СБП. Најдобар предиктор за предвидување на СБП е СТР II (ранг С) скор.

Introduction

It is very important for patients with spontaneous bacterial peritonitis (SBP) to assess the length of survival and the risk of death, primarily because of the wide range of potential complications that can lead to multisystem organ failure and fatal outcome. Prognostic scores, expressed in numerical values, assess the severity of the current condition using mathematical models and are especially important in transplant medicine (priority for hepatic transplantation).

The Child-Turcotte-Pugh score (CTP score) includes five parameters: albumin and bilirubin in the blood, amount of ascites, degree of hepatic encephalopathy, and prothrombin time (PT)[1-3]. The last three decades have shown that this score is a good prognostic indicator for the survival of patients with alcoholic and posthepatic cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis, and Budd-Chiari syndrome [4-7]. According to critics, the disadvantage of this score is the inaccuracy that can occur due to the two descriptive parameters: quantification of ascites and hepatic encephalopathy (HE), which values depend on the experience and personal assessment of the examiner. They also stressed that this score is insufficiently accurate in distinguishing the true clinical significance of category C, not including renal laboratory parameters in the evaluation of patients, primarily due to the development of hepatorenal syndrome in patients with terminal disease as a major factor for lethal outcome[8,9].

In order to overcome these problems, Angermayr et al.10performed remodeling of the CTP score by including a new parameter, serum creatinine level. According to this score, numerical values (points) are added to the baseline values of the CTP score: 0 points for a creatinine value less than 114.92 μolmol / L, 2 points for a creatinine value of 114.92-159.12 μolmol / L and 4 for a creatinine value greater than 159.12 μolmol / L. Analyses showed that the remodeled CTP score was better than the baseline CTP score in predicting HP, but with the same prognostic value in predicting other complications as the baseline CTP score. The significance of the CTP score in terms of survival has been well studied and its grades are: A (5-7 points) - with a median annual survival of 95%, B (7-9 points) - with a median annual survival of 80% and C (10-15 points) - with a median annual survival of 45%[11].

The MELD Score (Model for End Stage Liver Disease) first appeared in 1999 to assess survival in patients with transjugated portosystem shunt (TIPS)[12]. In the following years the MELD score proved to be a good predictor of short-term survival, a major mortality predictor regardless of etiology and has been officially accepted for assessment of patients undergoing potential cadaveric transplantation[13,14]. In the United States and Europe, this model is used to predict the three-month survival of patients waiting on a liver transplant list [15-17]. According to the original formula, the MELD score is a mathematical formula that includes: serum bilirubin, serum creatinine and INR.MELD = 9.57 x ln (creatinine mg / dl) + 3.78 x ln (bilirubin mg / dl) + 11, 2 x ln (INR) + 6.43.

Aim of the paper was to determine the predictive potential of MELD and CTP II score for SBP in patients with cirrhosis and ascites.

Material and methods

The study was designed as a prospective-analytical-observational and was conducted at the University Clinic for Gastroenterohepatology in Skopje for a period of one year. The study population included hospitalized patients with established liver cirrhosis, regardless of etiology; 70 patients, divided into two groups, 35 patients with SBP and 35 non-SBP, with similar demographic characteristics as the SBP group with sterile ascites, in which all variables were examined. as in the study group. The selection of patients who were included in the study was conducted according to pre-determined inclusion and exclusion criteria. Inclusion criteria: patients with cirrhosis of the liver regardless of etiology, age> 18–70 years. Exclusion criteria: age <18 years, acute liver failure, recent abdominal surgery (<3 months), infectious pleural effusion, peritoneal carcinomatosis, haemorrhagic ascites (of any origin), hepatocellular carcinoma, immunocompromised patients and those receiving antibiotics for at least 2 weeks prior to enrollment, patients taking non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives and anticoagulants.

The study included patients with previously signed informed consent (for the examinations they underwent). Polymorphonuclear cells (PMNC) number was determined directly from the non-centrifuged part of the ascites. 3 ml of fluid was placed in an EDTA test tube to assess the total number of cells and PMN cells, counting by using the Sysmex KxN 21 automatic cell counter-model. Paracentesis was performed under aseptic conditions in a patient placed in a supine position and puncture was made in the left or right lower abdomen quadrant, with ultrasound imaging (no patient had complications associated with diagnostic paracentesis). All samples for diagnostic testing were immediately sent to the Central Clinical Laboratory. Five mL of ascites was used for automatic counting of PMNK, and at the same time for the needs of biochemical analysis of blood venipuncture of 10 mL of blood was performed. By ultrasonographic examination of the abdomen (ultrasonographic apparatus Samsung Acuson x 300, CH5-2 MHz convex probe), morphological and circulatory disorders within liver cirrhosis were noted. Quantification of ascites was performed by US examination: no ascites, minimum amount of ascites, medium amount of ascites and large amount of ascites. Prognostic scores in patients with liver cirrhosis and ascites: MELD score, according to the formula: MELD = [(0.957 x Ln Creatinin) + (0.378 x Ln Bilirubin) + (1.12 x Ln INR) + (0.643) x 10]. The CTP II score includes 6 parameters: serum albumin and bilirubin, amount of ascites, degree of encephalopathy, PV and serum creatinine, and assessment of the degree of hepatic encephalopathy according to the West Haven criteria. Quantification of the degree of hepatic encephalopathy was performed using the West-Haven scale: zero degree (minimal encephalopathy without detectable changes in personality, behavior, memory, concentration, intellectual functions and coordination and asterixis absent). Frst degree (hypersomnia, insomnia, changes in affect, euphoria, depression, irritability, confusion, slowness), second degree (lethargy, apathy, disorientation in time, visible asterixis, visible change in personality), third degree (somnolence, disorientation in time and space, amnesia, more severe confusion, unrelated speech), fourth

degree: coma without response to external stimuli.

Criteria for spontaneous bacterial peritonitis: clinical picture, PMNC number in ascites ≥250 / 1 mL and / or PMNC number <250 / in 1 mL ascites fluid, with one bacterial species isolated in microbial culture (CNNA). After prior acquaintance with the structure, content and purpose of the study, as a condition for participation in it, the patients signed the offered informed consent. The study protocol was in line with the ethical principles of the Helsinki Declaration. The protocol and informed consent were submitted for consideration and approved by the Ethics Commission of the Faculty of Medicine at the Ss. Cyril and Methodius Universityin Skopje. The collected data was processed using the statistical program SPSS 20 and Statistica for Windows, version10.

Results

The mean value of the MELD score in patients with SBP was 22.6 ± 8.27 and in non-SBP the mean value was lower at 17.83 ± 5.87. According to the Mann-Whitney U test, the difference between the mean values was statistically significant for p <0.05 (z = 2.41; p = 0.015). A score of 30 to 39 was registered in 25.7% of patients with SBP, and only in 2.9% of non-SBP; the percentage difference was statistically significant for p <0.05 (Difference test, p = 0.0064) (Tab. 1).

Table 1. The prevalence of MELD score in both groups

MELDscore	SBP		Non-SBP	
	N	%	број	%
>40	0		0	
30-39	9	25.7	1	2.9
20-29	12	34.3	13	37.1
10-19	13	37.1	17	48.6
<9	1	2.9	4	11.4
total	35	100.0	35	100.0

Patients with SBP had an average CTP II score of 13.09 ± 2.48 or 100.0% C-class points. In patients with non-SBP, an average CTP II score of 9.63 ± 1.62 was recorded, or class B in 65.7% and class C in 34.3%. The percentage difference was statistically significant for p <0.05 (Difference test, p = 0.000000) (Tab. 2). According to the Mann-Whitney U test, the difference between the mean values was statistically significant for p <0.05 (z = -5.44; p = 0.00001).

Table 2. The prevalence of CTP II score in both groups

points	class	SBP		Non-SBP	
		N	%	број	%
5–6	A				
7–9	B			23	65.7
10–15	C	35	100.0	12	34.3

ROC analysis indicated that the CTP II score contributed to the diagnosis of SBP - 90.7% (p = 0.000) (excellent predictor), closer to the ideal value of 1.0 and above the worst value of 0.5 (Fig. 1).

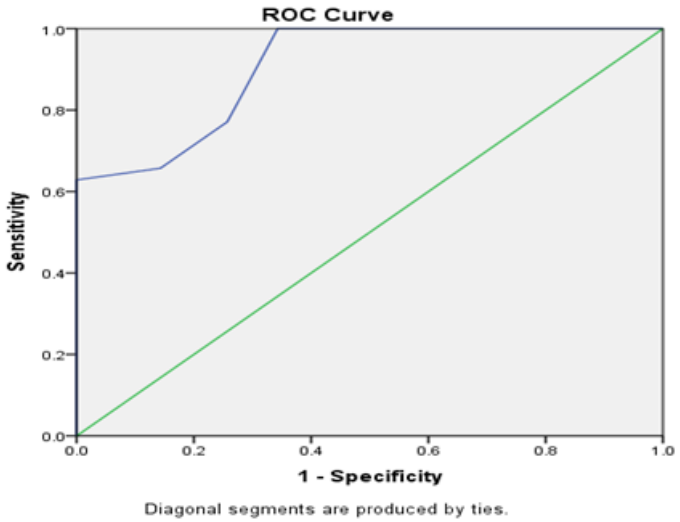


Figure 1. ROC curve of CTP II score as a predictor for SBP

ROC analysis indicated that the MELD score did not contribute to the diagnosis of SBP with 66.7% (p = 0.017) (weak predictor), closer to the worst value of 0.5 (Fig. 2).

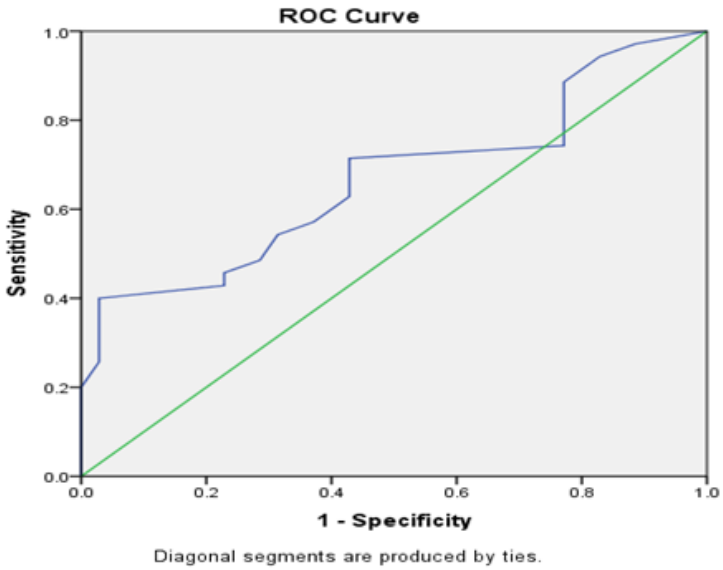


Figure 2. ROC curve of MELD score as a predictor for SBP

Discussion

The study of prognostic scores in the prediction and prognosis of individual complications of cirrhosis has confirmed their role in clinical practice and simplified access to this vulnerable group of patients. Thanopoulou et al.[17] in their study focused on these clinically simple prognostic assessors. The authors encouraged the introduction of diagnostic paracentesis into the daily routine of all patients with ascites, with the aim of early diagnosis of asymptomatic forms of SBP. Significant prognostic factors for SBP in this study were: the number of PMNCs in ascites, serum bilirubin levels, and renal function status, and the recurrence of SBP depended on the value of the CTP score.

In our study all patients with SBP were categorized in class C on CTP II score (100.0%) with a mean value of 13.09 ± 2.40, while in the non-SBP group the mean value was 9.63 ± 1.26 (B score: 65.7% and C score: 34.3% (p = 0.000000). The mean values of the MELD score in patients with SBP were 22.60 ± 8.27 versus 17.83 ± 5.87 in patients with non-SBP (p = 0.0064). The analysis of the results of this segment by our judge can be based on the advantage of the CTP II score over the MELD score in the group of patients with SBP. CTP II contains a calculated amount of ascites and creatinine in serum, and has been shown to be the best predictor of SBP, in contrast to the MELD score which has not been shown to be a good predictor of this condition.According to the ROC analysis, the CTP II score is an excellent predictor of SBP (90.7%) (p = 0.000).

Thus, our study confirmed that the MELD score requires additional data on the amount of ascites to become an accurate predictor of ascites-related conditions and ascites consequences. The prevalence of SBP is higher in patients with severe liver cirrhosis calculated according to the CTP score (class C from 50.3% to 100%), presented in several studies [18-23]. The prospective Haddad 24 study included 148 asymptomatic patients with cirrhosis and refractory ascites. SBP was detected in only 23 patients (3.3%), confirming the low prevalence of SBP in asymptomatic patients with cirrhosis of the liver, while the incidence of SBP was not associated with the severity of liver disease assessed by MELD. Patients on the transplant list have a lower rate of SBP and have significantly higher MELD scores, so the development of SBP is not related to the value of the MELD score but to clinical status and refractory ascites and the need for repetitive paracentesis.

One of the reasons for the low rate of SBP is explained by the fact that in today's conditions, thanks to the appropriate equipment and human resources necessary for proper and successful paracentesis, errors are very rare. Also Zhang et al.[25], who treated a larger population of patients, did not find any score that would be convincing in the SBP prediction. The study only confirmed that patients with SBP had a higher risk of death than non-SBP. In our analysis, the MELD score proved to be a weak predictor for diagnosing SBP with 66.7% (p = 0.017), but several other studies have emphasized its predictive value. Namely, according to them, with each increase of the MELD score, the risk for SBP increases.

Thus, according to Obstein KL. 26 that risk increases by 11%, and according to Gayatri AA. 27by 30.6%. Some authors even suggested that patients with moderate liver cirrhosis

and ascites with MELD score 20 start a preventive antibiotic treatment 28. Desai et al. 29 focused their research on finding the ideal score that would be predictive of persistent STD. The results showed that the MELD score with values greater than 25 had the highest predictive power compared to other prognostic scores.

Conclusion

Our research confirmed that SBP occurs in patients with severe hepatic dysfunction calculated according to the CTP II score and MELD score. Mean value of the MELD score in patients with SBP was higher then in patients with non-SBP. On the other hand all patients with SBP had an average CTP II score, C-class points, while the largest percentage of patients with non-SBP were class B-class points. MELD score is a weak predictor of SBP. The best predictor for predicting SBP is the CTP II score (rank C).

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Clinical science

INDICATIONS FOR OPERATION AND RESULTS FROM SURGICAL TREATMENT OF VESICOURETERAL REFLUX

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Key words: vesicoureteral reflux, open surgery, uropathy, pediatric urology

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Abstract

The main objective of this retrospective study was to evaluate the value of surgical approach in the treatment of children with vesicoureteral reflux (VUR). Material and method: The study was conducted in the period from January 2006 to December 2014, and included children with symptomatic VUR, who were surgically treated. A total of 72 children were treated, of whom 56 were females and 16 were males, aged between 2 and 16 years. They were treated with IV and V grade reflux ureters. Thirty-two of the unilateral refluxes were left-sided, 18 right-sided and 22 both-sided. VUR was diagnosed with Voiding cystourethrography (VCUG). Cohen technique was performed in 64 (90%) patients, Politano-Lead better technique in 4 (5%) patients and Lich-Gregoir technique in 4 (5%) patients. Results: Out of the 72 treated patients, 69 had a postoperative negative finding of VUR on the performed VCUG, indicating a high 95% success rate. In three girls, persistent postoperative reflux was found in postoperative VCUG. In the first patient persistent VUR was unilateral, of V grade. In the second patient, a third-degree VUR was found and the third patient was diagnosed with II grade VUR. Postoperatively, non-febrile UTIs (urinary tract infections) were diagnosed in 23 patients (20 female children and 3 male children) out of 72 patients in total. One female child was hospitalized with febrile UTI and 8 patients or 10% developed febrile UTI within one year of the operative treatment. Conclusion: Open surgery, despite excellent results, is used for more complicated cases, VUR grade IV – V or in previously failed cases, and it does not appear to provide definitive correction of VUR in all patients and does not prevent certain low incidence of UTI postoperatively. Non-febrile UTIs can occur several years after a surgical correction. Endoscopic treatment is an alternative treatment for VUR.

Клинички истражувања

ИНДИКАЦИИ И РЕЗУЛТАТИ ОД ХИРУРШКИ ТРЕТМАН НА ВЕЗИКОУРЕТЕРАЛЕН РЕФЛУКС

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Клучни зборови: везикуретерален рефлукс, отворена операција, уропатија, детска урологија

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Печатарски права: ©2021 Гани Чеку, Миле Петровски, Шабан Мемети, Нецми Хисени, Сејди Статовци, Блерим Бериша. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитира-ат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Главната цел на оваа ретроспективна студија беше да се оцени вредноста на хируршкиот пристап во третманот на деца со везикоуретерален рефлукс (ВУР). Материјали и методи: Студијата беше спроведена во периодот од јануари 2006та до декември 2014та година, и вклучуваше деца со симптоматски ВУР, кои беа хируршки третирани. Вкупно биле третирани 72 деца, од кои 56 биле женски и 16 мажи, на возраст помеѓу 2 и 16 години. Тие беа третирани со IV и V степен рефлуксни уретери. Триесет и два од едностраните рефлукси беа лево, 18 десно и 22 обострани. ВУР беше дијагностициран со Voiding-ова цистоуретрографија на (VCUG). Коенова техника беше применета кај 64 (90%) пациенти, Политано-Лидова техника кај 4 (5%) пациенти и Лих-Грегоарова техника кај 4 (5%) пациенти. Резултати: Од 72 третирани пациенти, 69 имале постоперативен негативен наод на ВУР по извршениот VCUG, што укажува на висока успешност од 95%. Кај три девојчиња е утврден постоперативен рефлукс. Кај првиот пациент перзистирачкиот ВУР беше едностран, од V степен. Кај вториот пациент, беше пронајден ВУР од трет степен, а на третиот пациент му беше дијагностициран ВУР од II степен. Постоперативно, не-фебрилни инфекции на уринарниот тракт (ИУТ) биле дијагностицирани кај 23 пациенти (20 женски деца и 3 машки деца) од вкупно 72 пациенти. Едно женско дете беше хоспитализирано со фебрилна ИУТ и 8 пациенти (10%) развиле фебрилна ИУТ во рок од една година по оперативниот третман. Заклучок: Отворената операција, и покрај одличните резултати, се користи за посложени случаи, ВУР IV - V степен или во претходно неуспешни случаи, и се чини дека не обезбедува конечна корекција на VUR кај сите пациенти и не спречува одредена ниска инциденца на ИУТ постоперативно. Не-фебрилни ИУТ може да се појават неколку години по хируршката корекција. Ендоскопскиот третман е алтернативен третман за ВУР.

Introduction

VUR is significant in the siblings of patients with VUR (46%), children with urinary tract infections (UTI) (30%), infants with prenatal diagnosed hydronephrosis (16%) and urogenital abnormalities: posterior urethra valve (PUV) (60%), cloaca (60%), and duplex kidney (46%)[1]. Primary VUR may be due to either abnormal position or integrity of the ureterovesical junction (UVJ) (60%), and duplex kidney (46%)[2,3,4].The risk for primary VUR varies based on ethnicity, age and gender. Reflux is usually a congenital defect. Spontaneous resolution of primary reflux is common. This is thought to be multi-factorial, in part due to remodeling of the UVJ, elongation of the intravesical ureter, and stabilization of bladder voiding dynamics over time. At birth, the likelihood of spontaneous resolution is inversely proportional to the initial grade of reflux; approximately 80% of low-grade (I and II) reflux will resolve spontaneously vs. about 50% of grade III reflux. Few or approximately 20% of high-grade (IV and V)[5].

VUR is defined as active if it occurs during a micturition, while VUR is passive if it is manifested during bladder filling. There are two forms of VUR: primary and secondary.

Primary VUR as the most common form of reflux is due to incompetent or inadequate closure of the ureterovesical junction (UVJ), which contains a segment of the ureter within the bladder wall (intravesical ureter). Normally, reflux is prevented during bladder contraction by fully compressing the intravesical ureter and sealing it off with the surrounding bladder muscles.

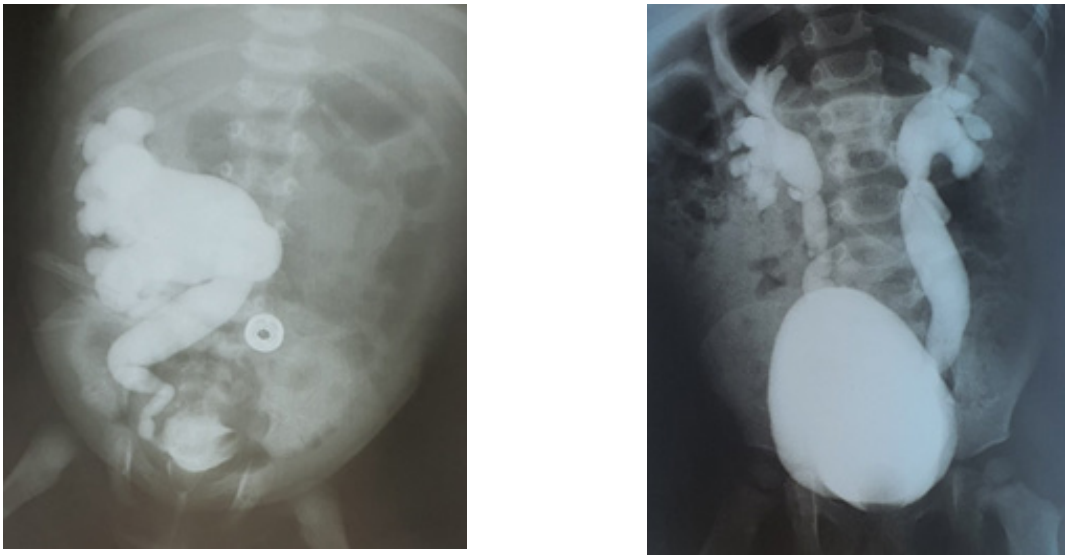


Figure 1. Unilateral and bilateral VUR (MCUG)

Secondary VUR is a result of abnormally high voiding pressure in the bladder that results in failure of the closure of the UVJ during bladder contraction. Secondary VUR is often associated with anatomic (e.g. posterior urethral valves) or functional bladder obstruction (e.g. bladder bowel dysfunction - BBD) and neurogenic bladder [6].

In the majority of cases, UTI is diagnosed when evaluating a urinary tract infection. Reflux in children is often hidden behind the symptoms of acute,

chronic or recurrent urinary infection. In some cases, VUR is "accidentally" diagnosed when screening patients at risk (those with a parent, brother or sister with reflux, polycystic kidney or hydronephrosis). Visualization after the first urinary tract infection is indicated in all children younger than 5 years with urinary tract infection, children of any age with febrile urinary tract infection, as well as children with pre-identified hydronephrosis.

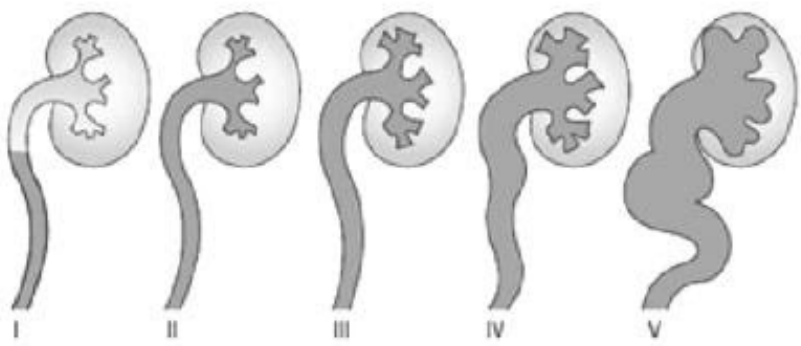
A routine renal and bladder ultrasound is obtained in all children after an initial UTI to assess the size and shape of the kidneys, and to detect any renal anatomical abnormality.

Laboratory examination: urine culture, blood counts, serum C-reactive protein, and other hematological tests are routinely determined[7].

VCUG is the gold standard for diagnosing VUR, giving accurate anatomical details and gradation of reflux (Fig. 1). Radionuclide cystography (RNC) is also used to detect reflux. Radioisotope methods: static (DMSA) and dynamic (DTPA) renal scan for visualization of scar changes, renal function assessment and urine transport dynamics[8,9]. Dimercaptosuccinic acid (DMSA) renal scan is superior in detecting renal cortical abnormalities compared to other imaging modalities and should be obtained in patients who are at risk for scarring or appear to have loss of renal parenchyma on renal ultrasound.

A grading system for reflux was established by the International Reflux Study Committee established in 1981 to aid with clinical management and prognostication. Five grades are defined based on the extent of reflux and degree of dilation of the upper tract on imaging[10,11].

a



b

Grade	Description
I	Into a nondilated ureter
II	Into the pelvis and calyces without dilatation
III	Mild to moderate dilatation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices
IV	Moderate ureteral tortuosity and dilatation of the pelvis and calyces
V	Gross dilatation of the ureter, pelvis, and calyces; loss of papillary impressions; and ureteral tortuosity

Figure 2. International classification of Vesicoureteral reflux11

Material and Methods

This retrospective study was realized in the period between January 2006 and December 2014, and included children with symptomatic VUR who were surgically treated at the University Clinical Center, Department of Pediatric Surgery in Prishtina, Kosovo. Grading of the severity of reflux

in all patients was made according to the International Reflux Study committees in 5 groups. The degree of reflux was estimated based on VCUG. Generally accepted indications for surgical treatment were the following: low probability of spontaneous resolution, after unsuccessful endoscopic treatment, high-grade reflux, renal scarring, recurrent pyelonephritis, breakthrough febrile UTI while on continuous antibiotic prophylaxis, parental preference[10].

A total of 72 children were treated, of whom 56 were females and 16 were males, aged between two and 16 years. The ureters reflux of grade IV and V were treated. VUR was diagnosed with VCUG. The operation was performed under general endotracheal anesthesia.

Open repairs prevent reflux by increasing the length of the intravesical ureter, facilitating compression of the ureter against the detrusor muscle during bladder filling (Table 1). These procedures generally require inpatient hospitalization for management of postoperative pain as well as temporary urinary catheter drainage. The average time of the intervention was about 80 minutes in unilateral reflux and about 110 minutes in bilateral reflux. During the operation, only 5% of patients received 1 unit of blood or blood derivate. After the open surgical operation, all patients received double antibiotic therapy (ceftriaxone and aminoglycoside). All patients received pain therapy for 2 days. Hematuria was noted in all children in duration from 2 to 3 days. The majority of children had no need of blood transfusion. Urinary catheter was extracted at the 7th postoperative day and control ultrasonography was performed. Retrovesical catheter was present only in few of them and it was removed after 2 days. Ureteric stent was placed in only 2 cases. Complete blood count, urine sediment, urea and creatinine level were analyzed every third day.

The postoperative evaluation protocol included renal echo and VCUG after 3 - 6 months. If VCUG and renal ultrasound were normal, prophylaxis with antibiotics was discontinued. Follow-up lasted 4 years on average.

Procedure	Illustration	Advantages	Disadvantages
Extravesical			
Lich-Gregoir 1961, 1964	 (24)	Bladder is not opened Decreased postoperative hematuria/bladder spasm	Increased risk of urinary retention due to damage to pelvic nerves in bilateral repairs
Intravesical			
Politano-Leadbetter 1958	 (26)	Creation of longer tunnel	Ureteral kinking/obstruction
Glenn-Anderson 1967	 (27)	Avoids ureteral kinking	Limited tunnel length
Cohen 1975	 (30)	Avoids ureteral kinking Longer tunnel length	Difficult retrograde catheterization

Table 2. Open Surgery

The illustrations used in this table are from the references [12.13,17,19]

Hutch in 1952 initially described the technique of elongating the intravesical ureter to create an anti-reflux valve in paraplegic patients with VUR[14]. Since then, multiple additional techniques have been described.

Extravesical

Lich-Gregoir (1961, 1964): The juxtavesical ureter is dissected and a submucosal groove is created extending laterally from the ureteral hiatus along the course of the ureter. The ureter is placed in the groove and the detrusor is closed over the ureter[15,16,17].

Intravesical

Politano-Leadbetter (1958): The ureter is mobilized intravesically and then brought through a new muscular hiatus located superior and lateral to the original mucosal orifice[18,19].

Cohen (1975): The ureter is advanced through a submucosal tunnel across the trigone to the contralateral bladder wall with the new mucosal orifice located superior to the contralateral orifice[13,20].

Results

Out of the 72 surgically treated patients due to VUR, 56 were females and 16 were males (Fig. 2) aged between 2 and 16 years. Thirty-two of the unilateral refluxes were left-sided, 18 right-sided, and 22 two sided. A total of 94 ureters were treated (Table 2, Fig. 4). VUR was diagnosed with VCUG. Sixty-four patients or 90% of cases used the Cohen technique, 5% patients used the Politano-Leadbetter technique and 5% patients the Lich-Gregoir technique (Fig. 5).

Indications for surgical intervention were pronounced grade of UTI (patients with grade IV and V). The postoperative evaluation protocol included renal ultrasound and VCUG after 3 - 6 months. If VCUG and renal ultrasound were normal, prophylaxis with antibiotics was discontinued. Follow-up lasted 4 years on average.

Sixty-nine patients had normal postoperative VCUG, representing a 95% success rate. No patient had significant postoperative hydronephrosis on postoperative renal ultrasound. Persistent postoperative reflux was found in three patients. One was a female child with unilateral VUR grade V, and the other girl had grade III reflux. In the third patient, also a female child, a grade II VUR was found, which we expect to spontaneously recede. This study also included cases of postoperative urinary tract infections (UTIs). Non-febrile UTIs were found in 23 patients (20 female and 3 male children) out of a total of 72 patients. One patient, a female child, was hospitalized due to febrile UTI, and the other 8 patients or 10% had febrile UTI. These UTIs were diagnosed up to one year after surgery.

The average time of hospitalization of these patients was 7 days (from 5 to 9 days).

One-sided surgery was used in 50 patients with VUR of the left or right ureter, and bilateral surgery due to VUR was performed in 22 patients.

Desired results represented the achievement of proportion for the length of the submucosal tunnel of the ureter to the ureter 4-5:1.

Table 2. Characteristics of the study group

	Male	Female	Male	Female
Number and percentage of patients	16	56	22%	78%
Total number of ureters	94		100%	
Left-sided refluxes	32		34%	
Right-sided refluxes	18		19%	
Two-sided refluxes	22		47%	
Patients treated with Cohen method	64		90%	
Patients treated with Politano-Leadbetter method	4		5%	
Patients treated with Lich-Gregoir method	4		5%	

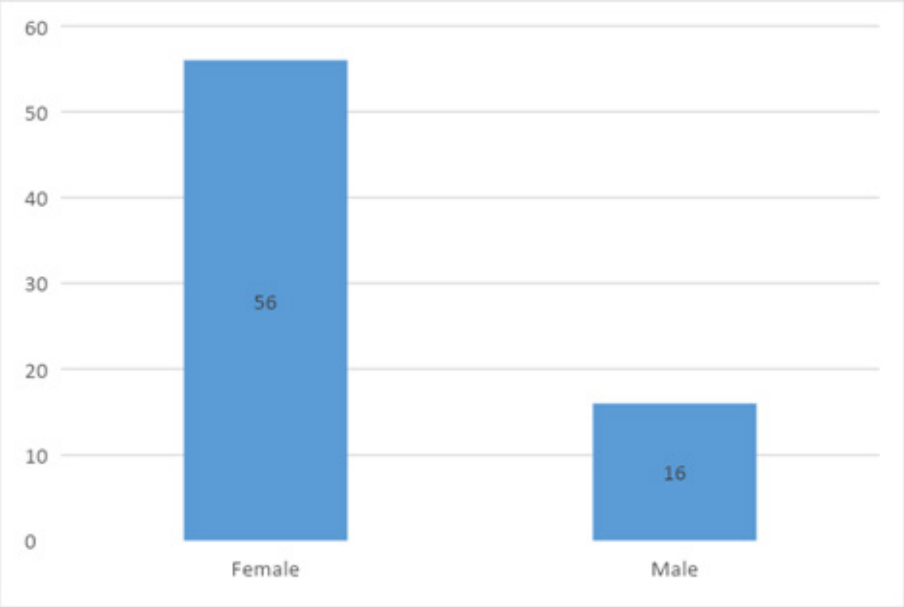


Figure 3. Number of male and female patients with VUR

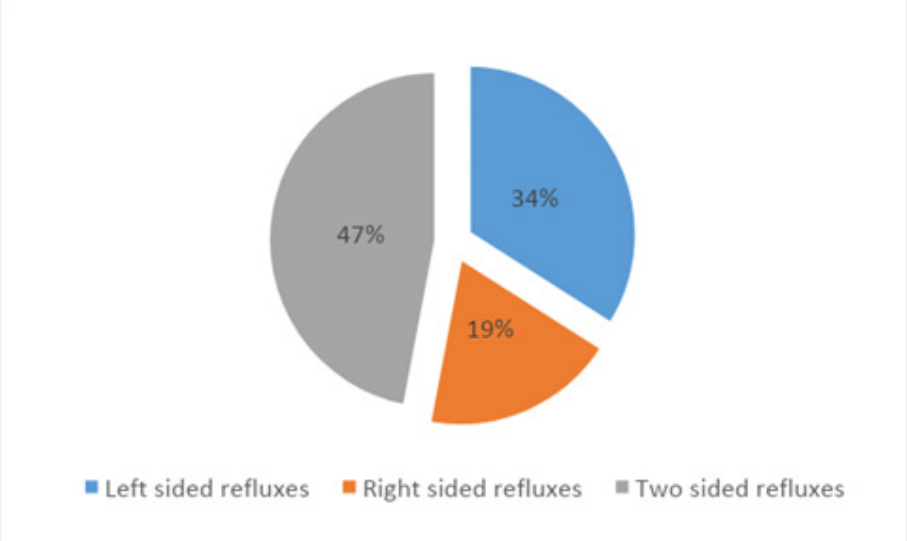


Figure 4. Percentage of the side of ureter affected

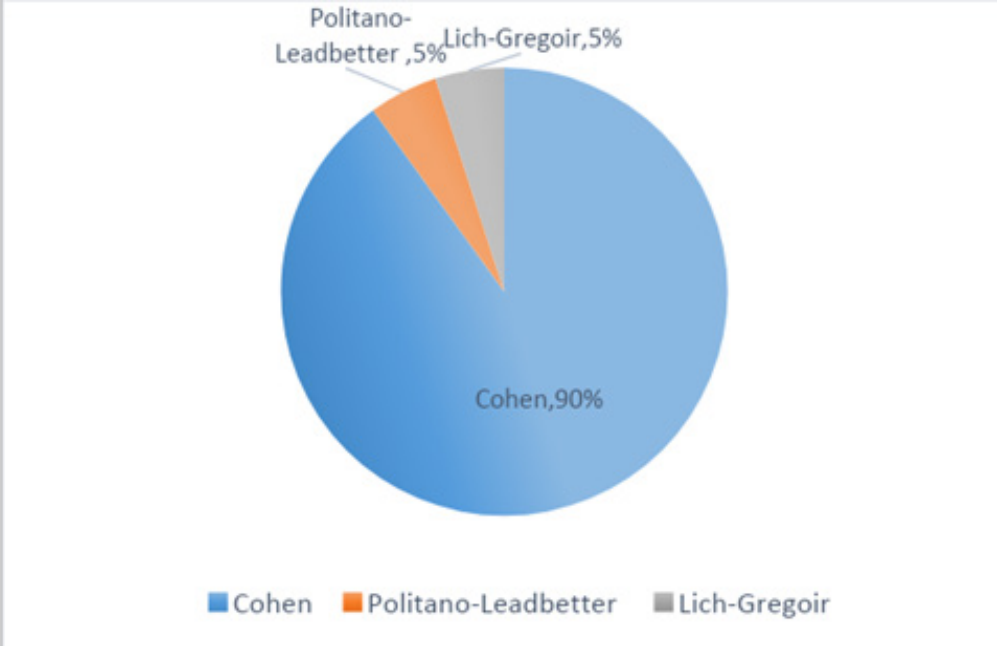


Figure 3. Percentage of surgical methods used for VUR treatment

Discussion

VUR is the most common uropathy in children. Treatment of children with reflux tend to prevent kidney infection, kidney damage and complications caused by kidney damage. The treatment includes: pharmacotherapy, surgical treatment and monitoring. Although spontaneous resolution in primary reflux is about 70%, it is common in children younger than 5 years old and in lower grade of reflux (gr I, gr II). It is considered that Grade III reflux has spontaneous resolution of 50%, and the resolution is less likely in children over 5 years. It is unlikely that expressed reflux will spontaneously withdraw. Sterile reflux usually does not lead to reflux nephropathy. Long-term antibiotic prophylaxis in children is considered safe, and surgery used to correct the VUR is highly successful [21,22]. Antibiotic prophylaxis is considered successful if a child does not get urinary infection; does not develop kidney damage, and scaring in parenchyma and the VUR spontaneously resolves[23].

Anticholinergic and bladder treating can reduce symptoms of dysfunctional voiding and risk of infection.

Depending on sex, age of the patient, grade of reflux, the changes in the renal parenchyma, systemic changes that can note in the presence of VUR will decide which type of treatment would be appropriate choice for the particular patient. Each treatment is indicated in varying degrees of development of the disease[24].

Open surgery involves modification of dysfunctional ureter – vesical circuit, which creates a ratio of 4:1 to 5:1 in the length for intramural ureter to the diameter of ureter[25].

Surgical correction of VUR has had excellent results. The success rate has been about 95%. Urinary tract infections have been reported in the postoperative period. The risk of anesthesia as well as the general surgical risks of open surgery should not be neglected[26].

Open surgery, despite its excellent results, does not seem to promise a definitive correction of VUR by eliminating the possibility of UTIs. Non-fe-

brile UTIs can also occur several years after the surgery.

The International Reflux Study demonstrated the incidence of UTI and febrile UTI in a 10-year study in patients undergoing open surgery. Some of the operated children in this series with pyelonephritis had early surgical complications with ureteral obstruction[27].

Recurrent reflux was rare, and other factors such as urinary diffusion were the main causes of these recurrences. Most patients were not febrile and were not accompanied by VUR.

Although statistics show that open surgical technique is superior to endoscopic procedure, however endoscopy proved better in terms of time of verticalization of the patients, the need to receive additional drug therapy, blood loss during operation and the duration of the operation[28]. But we cannot favor any surgical method because we believe that both methods have their indicational area in appropriate developmental stage of VUR[21].

Conclusions

Open surgical procedure is reserved for more complicated VUR cases (grade IV-V) and for patients with previously failed endoscopic procedure. This surgical method is superior in terms of satisfactory end results. This is relatively inexpensive method, but the time of verticalization of the patients, the need to receive additional drug therapy, long duration of the operation and anesthesia increase the cost.

Summary points

- Children with VUR are more likely to develop acute pyelonephritis and renal scarring compared to children without VUR.
- Surgical correction of VUR reduces the occurrence of febrile UTIs.
- The 2010 AUA guidelines recommend consideration of surgical (open or endoscopic) correction of VUR in patients receiving continuous antibiotic prophylaxis with a febrile breakthrough UTI.
- Preoperative reflux grade is the single most important factor affecting the success rate of endoscopic injection.
- Patients with febrile UTI following treatment with endoscopic injection should be evaluated with VCUG to rule out recurrent VUR.

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Clinical science

THE MOST COMMON DISORDERS OF THE HAND ASSOCIATED WITH CARPAL TUNNEL SYNDROME IN ADULTS

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Key words: carpal tunnel syndrome, trigger finger, de Quervain's disease

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Abstract

Carpal tunnel syndrome (CTS) is one of the most common peripheral neuropathies caused by chronic compression of the median nerve in the area of the carpal tunnel and its etiology is multifactorial. Trigger fingers and de Quervain's disease are common disorders of the hand related to CTS in adults. The aim of this study was to present the most common disorders of the hand such as stenosing tenosynovitis in adults with surgically treated CTS and to evaluate their demographic data. Material and methods: A total of 116 surgically treated patients with established diagnosis of CTS (clinically and by electrophysiological examination) were included in this prospective study, which was conducted at the University Clinic for Orthopedic Diseases in Skopje. Demographic data, findings of history of the disease and clinical examination were recorded and analyzed. Results: Participants with CTS included in the study were with a mean age of 55.41 ± 10.7 years (age range 29-75). 75% of them were female. 63.8% of participants suffered from one or more comorbid chronic diseases. On admission to hospital, disorders such as trigger fingers and de Quervain's disease were concomitantly diagnosed in 15.51% on ipsilateral hand with CTS. All disorders were surgically treated following open carpal tunnel release, as "one stage procedure", under local anesthesia. Conclusion: Our findings have determined concomitant existence of CTS and stenosing tenosynovitis (trigger fingers and de Quervain's disease) on ipsilateral hand, which suggests common etiological factors. Female gender and age range 40-60 years are major common factors related to these three disorders.

Клинички истражувања

НАЈЧЕСТИ НАРУШУВАЊА НА РАКАТА КАЈ ВОЗРАСНИ ПАЦИЕНТИ ПОВРЗАНИ СО СИНДРОМ НА КАРПАЛЕН ТУНЕЛ

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Клучни зборови: синдром на карпален тунел, закочени прсти, де Куервенова болест

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Печатарски права: ©2021 Душанка Грујоска-Вета, Даниела Георгиева, Ненад Атанасов, Илир Шабани, Лилјана Ангелеска, Антонио Георгиев, Јасна Богданска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Синдром на карпалниот тунел (СКТ) е состојба на периферна невропатија предизвикана од хронична компресија на n. medianus во предел на карпалниот тунел, и има мултифакториска етиологија. Често пати овој синдром кај возрасни лица е поврзан и со состојби на закочени прсти и де Куервенова болест. Целта на овој труд беше да ги прикаже поврзаните состојби на стенозирачки теносиновити на раката кај оперативно лекуваните возрасни пациенти со СКТ и нивните демографски карактеристики. Материјал и методи: Оваа проспективна клиничка студија на 116 возрасни оперирани пациенти со дијагноза СКТ (потврдена со клинички и електрофизиолошки испитувања) беше изведена на Клиниката за ортопедски болести - Скопје. Релевантни демографски податоци, наоди од историја на болеста и клиничките испитувања беа регистрирани и статистички обработени според утврдени критериуми за вклучување на испитаниците со СКТ. Резултати: Испитаниците беа на возраст од 29 до 75 години, со просечна возраст од 55,41 ± 10,7 години и доминантност на пациентите од женски пол (75%). 63,8% од пациентите со СКТ имаа една или повеќе придружни болести. Кај 15,51% пациенти беа истовремено дијагностицирани состојби на закочени прсти и де Куервенова болест на истата рака и тие беа оперативно третирани во еден акт со отворената декомпресија на n. medianus. Заклучок: Истовременото постоење на СКТ и стенозирачки теносиновити (закочени прсти и де Куервенова болест) со различно време на појавување упатуваат на заеднички етиолошки фактори. Најглавни заеднички ризик-фактори за појава на овие состојби е женскиот пол кај пациентите и возраст од 40-60 години.

Introduction

Carpal tunnel syndrome (CTS) is one of the most common non-traumatic disorders of the hand in adult patients and the most common reason for visiting orthopaedic surgeons. This syndrome is often associated with trigger fingers and de Quervain's disease in adults. These disorders might exist separately, but also might be concomitantly present on the same hand or appear after surgical procedures of one of them.

Carpal tunnel syndrome (CTS) is a peripheral neuropathy caused by chronic compression of the median nerve in the area of the carpal tunnel and its etiology is multifactorial. The clinical picture depends on the duration and intensity of pressure on median nerve, which is a mixed type of nerve with sensitive and motor nerve fibers. At the beginning, the discomfort is in the form of sensory disturbances (numbness, paresthesia and/or pain in the fingers - from the thumb to the radial side of the ring finger, tingling and burning pain even radiating to the elbow or shoulder, nocturnal pains). Later, in more severe cases, when motor component of the median nerve is involved, clumsiness during everyday activities and hypotrophy of tenor muscles, are observed.[1] Nocturnal pains are typical due to the additional pressure on median nerve because of the prolonged flexion position of the wrist during sleeping. Shaking of the hand during nights is a typical act in patients with CTS in order to relieve pain.

The exact incidence and prevalence vary depending on the diagnostic criterion. The highest incidence is in patients aged 50-60 years and more often in females.[2] The exact prevalence of people with complaints is from 13.0% to 15.8% in the general population, and according to the clinical picture and confirmed by ENMG examinations varies from 2.7% to 5.8%.[3] Surgical carpal tunnel release is a treatment of choice in cases where conservative therapy for CTS failed.

Trigger finger is a disorder characterized by an impaired smooth sliding of the flexor tendons of the fingers due to the mechanical entrapment usually at the level of the first annular pulley, caused by multifactorial etiology. Chronic discrepancy between the flexor tendons with tenosynovitis and the first annular pulley is the cause of morphological and functional disorders. According to the Green classification, complaints might be pain and discomfort, painful tenderness on palpation at the level of the metacarpophalangeal joint on palmar side, locking of fingers in flexion/extension or inability of passive extension of fingers due to flexion contracture of proximal interphalangeal joint.[4] Prevalence of 2.6% is frequent in the general population aged 40-60 years.[5]

Morbus de Quervain (mother's wrist, mommy thumb) is a disorder characterized by an impaired smooth sliding of the tendons of m. abductor pollicis longus (m.APL) and m. extensor pollicis brevis (m.EPB) due to the mechanical entrapment at the level of the first dorsal compartment. Tenosynovitis of those tendons, caused by multifactorial etiology, is a reason for pain and burning sensation in the radial area of the wrist during thumb movements. Complaints are more often in females, especially after delivering a baby.[6] Most of the patients have positive provocative Finkelstein's test (pain in the area of radial styloid during passive ulnarward deviation of the wrist). Wolf reported rate of

de Quervain's disease in 2.8 casesper 1000 persons/year in females and 0.6 cases per 1000 persons/year in males, in a study conducted from 1998-2006 on United States military personnel.[7]

Surgical release of A1 pulley and first dorsal compartment release are done in cases where conservative therapy is ineffective.

Occupations that include repetitive movements, packing, counting money, clothing industry, use of vibrating machines are main risk factors for development of these disorders.[8]

Although the etiology is multifactorial, coexistence of several diseases (diabetes, rheumatoid arthritis, and hypothyroidism, overweight) in the same person is noticeable.[9]

The aim of this paper was to present the most commonly associated disorders of the hand in surgically treated adult patients with CTS and by evaluating the demographic data of these patients to identify possible risk factors for the coexistence of these three disorders.

Material and methods

One handred and sixteen surgically treated patients with CTS were included in our prospective clinical study that was conducted at the University Clinic for Traumatology, Orthopedic Diseases, Anesthesiology, Reanimation and Intensive Care Medicine and Emergency Department, Clinical Center Mother Theresa, Skopje, RNM during a three-year- period. Patients were with clinical diagnosis of CTS and confirmed by electroneuromyographic examination (ENMG). Data from surgically treated hands were analyzed, and in cases with bilateral involvement, only data from the first treated hands were included.

Inclusion criteria:

- persons aged 25-75 years
- anamnestic data on tingling and/or pain in the thumb, second, third and radial part of the fourth finger, nocturnal paresthesia, clumsiness with the fingers of the affected hand
- positive provocative tests
- confirmed diagnosis of CTS by ENMG

Exclusion criteria:

- persons under 25 years of age and older than 75 years
- pregnant women
- people with reduced cognitive abilities
- detainees and prisoners
- previous hand surgery
- soft-tissue injuries or fractures of the bones of the forearm and wrist
- polyneuropathy, hereditary neuropathy

The following data of interest for the study were recorded:

- personal and family medical history, occupation, education, comorbidities and demographic characteristics (age, sex, dominant hand, height, weight, body mass index (BMI), nationality, place of residence),
- complaints and their duration until surgery,
- findings of clinical examination of symptomatic hand (thenar hypotrophy, positive provocative tests of Phalen and Finkelstein, signs of trigger fingers).

The clinical study was approved by the Ethics Committee for Human Research at the Faculty of Medicine in Skopje, Ss. Cyril and Methodius University in Skopje, R N Macedonia (Approval No. 03-2895/7). All the partic-

ipants were informed and gave their written consent for the examination and surgical procedures.

Statistical analysis

A descriptive-analytical statistical method was used for the statistical processing of the results obtained in the clinical study. Statistical analysis was made with the software SPSS, version 22.0. Descriptive data are presented as mean± standard deviation (SD), or as median. Percentages are given for categorical variables. The threshold for statistical significance was set at $p<0.05$.

Results

One hundred and sixteen patients surgically treated at the University Clinic for Orthopedic Diseases in Skopje were enrolled in this study according to the inclusion criteria. They were examined with ENMG prior to the surgical procedure. 74.14% (86) of patients were from Skopje. In the distribution according to the level of education, most of the patients had completed secondary education - 62.9% (73). 86.2% (100) of CTS patients were of Macedonian ethnicity, followed by patients of Albanian - 6% (7), and Serbian ethnicity - 4.3% (5). Two patients were of Turkish and one patient was of Roma ethnicity.

Eighty-seven patients were female and twenty-nine male, with a mean age of 55.41±10.7 years (age range 29-75). Female patients with CTS were younger than male patients, but the mean age was not statistically significant (p=0.16). The mean age of female patients was 54.6±10.4 and of male patients 57.83 ± 10.9 years.

The body mass index (BMI) had an average value of 27.7 ± 5.6 kg/m² and ranged from 27.7 to 46.5 kg/m². 33.6% of patients had normal weight and 30.2% patients were obese. The body mass index did not differ significantly between patients according to their gender (p=0.71).

36.2% of patients smoke more than 20 cigarettes per day.

Table 1 shows the percentage of comorbidities in operated patients. 63.8% of patients with CTS had one or more comorbidities, mainly joint diseases (polyarthritis), tenosynovitis and diabetes mellitus - 24.1%, 19% and 18,1%, respectively. (Table 1)

Table 1. Comorbidities in patients with CTS

Other diseases	**n** (%)
absent	42 (36.21)
present	74 (63.79)
1. Hypothireosis	3 (2.59)
2. Diabetes mellitus	21 (18.1)
3. Matebolic diseases	4 (3.45)
4. Rheumatic diseases	6 (5.17)
5. Thenosynovitis	22 (18.96)
6. Chronic renal failure	8 (6.9)
7. Osteoporosis	5 (4.31)
8. Joint diseases (Polyarthritis)	28 (24.14)
9. Malignant diseases	3 (2.59)
10. Cardiovascular diseases	11 (9.48)
11. Discopathy (cervical or lumbal)	13 (11.21)
12. Psychic diseases	3 (2.59)

CTS – carpal tunnel syndrome

The type and duration of the complaints and the clinical findings in the patients were examined. Table 2 presents the most common symptoms and duration of symptoms by gender. The results obtained showed that

all patients complained on tingling and numbness in the thumb, second, third and radial side of the fourth finger. 17.2% of CTS patients had pain during daytime. Nocturnal pains and sleep disturbance were predominant symptoms in 47.4% of patients. Sleep disturbance and clumsiness of the hands were positive in 35.35% patients, who also had hypotrophy of thenar and muscle weakness. The symptomatology was significantly dependent on the gender of the patients, (p=0.034), meaning that 55.2% male patients complained more on tingling, nocturnal pains, sleep disturbances and clumsiness compared to 28.7% female patients. Duration of characteristic symptoms of more than 2 years was noted in 50.9% (59) of CTS patients. Male patients had longer duration of symptoms but without statistically significant difference (p=0.13) (Table 2).

62.1% of patients had a positive provocative test of Phalen on clinical examination and 37.93% of patients had hypotrophy of thenar preoperatively. 95.69% of patients were right-handed. Open carpal tunnel release (OCTR) under local anesthesia was performed in all patients. Of them, 56.9% were on the right hand and 43.1% on the left hand.

Table 3 presents the percentage of concomitant disorders in 116 surgically treated patients for CTS. Duration of symptoms due to these disorders was from 2-6 months. 18% of these patients underwent additional surgical procedures. 15.51% of these patients were diagnosed with trigger fingers and de Quervain's disease upon admittance for OCTR. All trigger fingers and thumbs were in the third stage of Green's classification (locking in flexion and assisted extension). They were surgically treated following OCTR as "one-stage procedure" under local anesthesia. 2.58% of female patients were diagnosed with tumor-like lesions and they were surgically treated 3 months after OCTR (Table 3).

Table 2. Distribution of patients with CTS according to symptomatology and gender

Variables	n	gender		p-level
		Female n (%)	Male n (%)	
Main complaints				
Tingling	116	87 (75%)	29 (25%)	
Tingling, pains,	20	17 (19.54)	3 (10.34)	$\chi^2 = 6.73$
Tingling, pains, sleep disturbance	55	45 (51.72)	10 (34.48)	p = 0.034 sig
Tingling, pains, sleep disturbance clumsiness with hands	41	25 (28.74)	16 (55.17)	
Duration of symptoms				
6 – 12 months	15	10 (11.49)	5 (17.24)	$\chi^2 = 4.08$
12 – 24 months	42	36 (41.38)	6 (20.69)	p = 0.13 ns
> 24 months	59	41 (47.13)	18 (62.07)	

p (Pearson Chi-square), CTS-carpal tunnel syndrome

Table 3. Percentage of patients with CTS and additional concomitant disorder on the same hand

Concomitant disorder		gender	
	n (%)	Female	Male
none	95 (81.89)		
Trigger thumb	11 (9.48)	8	3
Trigger fingers (third and fourth)	6 (5.17)	3	2
De Quervain's disease	1 (0.86)	1	
TLL	3 (2.58)	3	

TLL–tumor-like lesions (1 Ganglioma, 2 benign giant-cell tumors of tendon sheet), CTS –carpal tunnel syndrome

Discussion

CTS, trigger fingers and de Quervain's disease are so called "disorders of entrapped nerves and tendons". They are a result of special anatomy of the hand adjusted for fulfillment of precisely coordinated movements. Special anatomy of tunnels with bone floors and soft-tissue roofs allows the passage and facilitates movements of nerves and tendons. Mutual existence of CTS and stenotic tenosynovitis (trigger finger and de Quervain's disease) with different times of occurrence refer to common etiological factors that act on a similar anatomical structure and lead to inadequacy of the space in the bone-fibrous tunnel and its contents (nerve and tendon), resulting in morphological and functional changes of both of them. The clinical picture depends on the duration of chronic pressure on the median nerve or tendons. In the beginning symptoms are similar, while in later stages, when more changes develop due to prolonged pressure, the differentiation of these disorders becomes clearer.

Our results presented in Table 1 show that about 63% of patients with CTS had one or more comorbidities. 33% of respondents suffered from cardiovascular, metabolic and hormonal diseases, which are possible causes for the microvascular changes expressed mostly in nerves located in narrow bone-fibrous tunnels such as the median nerve.[10, 11]

Other comorbidities (rheumatic diseases, tenosynovitis, arthritic changes and chronic renal failure) may also be responsible for the increased chronic pressure of the median nerve at the level of the carpal tunnel. It is assumed that this leads to many alterations, especially intraneural circulation that cause morphological changes of the nerve in the form of swelling and change shape, with progressive demyelination, eventual axonal degeneration and fibrosis.[12]

Histopathological studies of stenotic tenosynovitis have shown that noninflammatory hypertrophy and fibrosis of tendon sheath are biggest at the level of the first annular pulley and there is deposition of an abundant extracellular matrix with chondroid in the deep parts of the pulley. These changes lead to difficult movement, i.e. sliding of the flexor tendons in the inner lining.[13]

A similar process develops in de Quervain's disease. Thickening of the tendon sheath due to mucopolysaccharide deposition and myxoid degeneration corresponding to chronic

degenerative changes, rather than an inflammatory reaction, was demonstrated in a study conducted in England by examining histopathological specimens taken from 23 operatively treated patients with de Quervain's disease.[14]

Some of the comorbidities listed in this paper were: diabetes, cardiovascular and metabolic diseases, hypothyroidism, chronic renal failure, rheumatic diseases.[15,16,17,18,19]

The results obtained in our study have shown that majority of participants (75%) were of female gender. Female patients in our study were younger than male patients, but the mean age was not found to be statistically significant (p=0.16). This finding was consistent with other studies.[20, 21]

According to the results in Table 2, the duration of symptoms in female patients until surgery was shorter and the functional discomfort was smaller compared to male patients

The symptoms (pain, insomnia, clumsiness and hypotrophy of thenar) as signs of more advanced damage of the median nerve were statistically more common (p=0.034) in males than in females, 55.2% vs 28.7%. The reason for delayed surgery was mostly due to the refusal of the operation, fear of it, reduced funds due to sick leave and the fear of losing a job (as obtained from our talks with the participants).

Overall, more women suffer CTS from than men and it has been reported in a large number of epidemiological studies.[22, 23] In a retrospective study done in New Zealand including 2,313 patients who underwent CTR, 61% were female and 39% were male.[22] In another study conducted by Farioli et.al. in Italy between 1997 and 2000, an almost 4-fold increase in the risk of surgically treated CTS was observed in women compared to men among non-manual workers.[23] In a study of Nosewicz et al. 60.3% of 967 participants with CTS were females.[24]

The mean age of female participants in our study was 54.6±10.4, implicating that they were in the reproductive and menopausal period and the hormonal changes during these periods might be responsible for the onset of tissue edema and an increased pressure on the median nerve and tendons.[25] Our clinical study confirmed a concomitant presence of CTS, trigger fingers and de Quervain's disease in 15.51% of patients at admittance for CTR. The majority of them were also females, which could be explained by increased work in postpartum period, repetitive movements in taking care of small children and during housework.[26] The research by Rottgers also showed concomitant presence of CTS and trigger fingers, even in higher percentage of 61%.[27] In other prospective study of 211 patients with trigger finger, 43% were diagnosed with CTS, too.[28]

Many authors report an increased incidence of trigger fingers on the same hand following CTR. Lin et al. in a retrospective study conducted on 10,420 patients with CTS and 2,605 patients with CTR reported a 6.71% incidence of trigger fingers, while after open decompression of the median nerve, the overall risk of trigger fingers was 3.63 times higher in the operated patients in the first 6 months after the intervention.[29] In another study comprising patients with CTS, where 66.7% were female, prevalence of trigger fingers after CTR was 26.3%.[30] According to Acar et al., the incidence of occurrence of trigger fingers after open decompression of the median nerve was 13.9%, and if the distal fascia of

the forearm was also released, the incidence was up to 31.3% in patients with more severe EMG findings.[31]

The trigger thumb was the most common finger (9.48%), followed by ring and middle finger (5.17%) in our study. These findings are consistent with data from a study conducted on 497 patients with CTR, of which in 229 patients with postoperatively developed trigger fingers, the thumb was registered in 42.22% after 3.5 months of intervention, and the fourth and third trigger finger were registered in 46.66% after 7.5 months.[32] The thumb and the ring finger were the most common trigger fingers in another study.[33] Some authors explain the more common occurrence of trigger fingers after surgical decompression of the median nerve by the displacement of the tendons of the superficial flexors of the fingers towards the volar, which leads to a mechanical irritation of the tendon sheath and its hypertrophy, usually at the level of the A1 pulley.[34, 35] However, the existence of trigger fingers without CTS or CTR suggests other, still unknown etiological factors.

Disadvantages of our clinical study were the small number of patients, their inhomogeneity in terms of occupation and comorbidities, and the lack of a control group.

The importance of this paper is that this is the first research in our country, according to the available data, which deals with the association of CTS with simultaneous coexistence of de Quervain's disease and trigger fingers according to precisely defined inclusion and exclusion criteria. The results determined the prevalence of the females at the age of 40-60 years. The research findings can be the basis for further investigation of other risk factors, and thus the detection of possible preventive measures and appropriate treatment.

Conclusion

Our study showed a simultaneous coexistence of CTS and stenotic tenosynovitis -trigger fingers and de Quervain's disease with different time of onset. Our results also indicated that common risk factors were the female gender in patients and the age of 40-60 years. It might be assumed that common etiological factors, which act on a similar anatomical structure and lead to inadequacy of the space in the bone-fibrous tunnel and its contents (nerve and tendon), result in morphological and functional changes. In order to conduct a more significant statistical analysis and reach valid statistical conclusions, it would be necessary to perform research in the future on large groups of patients with CTS according to certain inclusion criteria in terms of comorbidities, physiological conditions and occupation.

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Clinical science

C-REACTIVE PROTEIN AND NEUTROPHIL-LYMPHOCYTE RATIO AS PREDICTORS OF CLINICAL SEVERITY OF COVID-19

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Abstract

COVID-19 is an infectious disease that can manifest quite differently. In this study we examined the relationship between the value of serum CRP(C-reactive protein) andneutrophil-lymphocyte ratio (NLR) as predictor factors for the development of a severe clinical manifestation in COVID19 patients. Materials and methods: We followed 95 COVID-19 positive patients who were hospitalized at the University Clinic for Eye Diseases - COVID Center. We analyzed the initial laboratory parameters of white blood cells and CRP on admission of the patients and the results of laboratory analyses performed before they left the Clinic, or the last parameters before the lethal outcome in those patients who died. Several models of logistic regression were tested to analyze the predictive value of these markers of inflammation for lethal outcome in patients hospitalized for COVID-19. Results: Bivariate analysis demonstrated that the length of hospital stay was significantly shorter in patients with lethal outcome (p=0.001). The NLR was significantly higher in patients with lethal outcome at both times (p=0.005; and p=0.017). Leukocyte's count (p=0.046, and p<0.001) and CRP (p=0.013,and p=0.005) were also significantly higher in patients with lethal outcome at both times. The increase on the NLR scale both at hospitalization and at discharge (or the last analysis before death) leads to increase in the odds of lethal outcome (T1:40.4% increased odds; T2:36% increased odds). Conclusion: CRP and NLR are laboratory parameters that can predict the severity of the clinical manifestation in patients with COVID-19.

Клинички испитувања

Ц-РЕАКТИВЕН ПРОТЕИН И СООДНОСОТ НА НЕУТРОФИЛИ-ЛИМФОЦИТИ КАКО ФАКТОРИ ЗА ПРЕДИКТИВНОСТ НА ТЕЖИНАТА НА КЛИНИЧКАТА СЛИКА КАЈ COVID-19

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Печатарски права: ©2021 Стефан Пандилов, Сузана Кленкоски, Елена Јовановска-Јанева, Газменд Мехмети, Драган Мијакоски, Сашо Столески, Христиан Дума, Дејан Докиќ.. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

COVID-19 е инфективно заболување кое може да се манифестира доста различно. Во оваа студија ние ја испитувавме поврзаноста помеѓу вредностите на CRP (Ц-реактивен протеин) и соодносот неутрофили-лимфоцити (NLR) како предиктивни фактори за развој на тешка клиничка слика кај пациентите со COVID-19. Материјали и методи:Следевме 95 COVID-19 позитивни пациенти кои беа хоспитализирани во УК за очни болести - COVID центар во Скопје. Ги анализиравме лабораториските параметри на леукоцитите и CRP при прием на пациентите во Клиниката и резултатите од лабораториските анализи изведени пред пациентите да ја напуштат Клиниката или пред нивниот летален исход, кај оние што починаа. Беа тестирани неколку модели на логистичка регресија со цел да се утврди предиктивната вредност на овие маркери на инфламација за летален исход кај пациенти хоспитализирани од COVID-19. Резултати: Анализата покажа дека должината на престој во болница беше значително пократка кај пациентите со летален исход (=0,001). NLR беше значително повисок кај пациенти со летален исход и во двете времиња (p = 0,005; и p = 0,017). Бројот на леукоцитите (p = 0,046, и p <0.001) и CRP (p = 0,013, и p = 0,005), исто така, беа значително повисоки кај пациенти со летален исход во двете времиња. Повисоки вредности на NLR и при хоспитализација и при отпуштање (или последна анализа пред настапување на смртта) доведува до зголемување на шансите за летален исход (T1: 40,4% зголемени шанси; T2: 36% зголемени шанси). Заклучок: CRP и NLR се лабораториски параметри кои можат да ја предвидат сериозноста на клиничката слика кај пациенти со COVID-19.

Introduction

COVID-19 is a highly infectious disease that has spread throughout the world. The disease is caused by SARS-CoV-2, an RNA virus that has been known to science since 1937 when it was first isolated in chicken embryos.[1] There is almost no country in the world that has not described at least one case of this disease in the past year. In this way, the disease has affected public health around the world. The clinical picture in patients with COVID-19 is quite different, ranging from asymptomatic to life-threatening. Many patients who initially have mild symptoms, mostly from the upper respiratory tract, develop a severe clinical picture within a few days. So far, it has been shown that patients with a severe clinical picture have a poor chance of survival. The most common causes of death in COVID-19 patients are ARDS, thromboembolic events, acute renal failure, sepsis and septic shock, and acute liver failure.[2] Therefore, the detection of biological markers in patients who will predict the severity of the clinical picture is crucial to timely indicate appropriate health care. For these reasons, monitoring of vital parameters and laboratory findings have been shown to be predictors of the possibility of developing a severe clinical picture in COVID-19 patients. A few laboratory markers are used as predictors of clinical severity in patients with COVID-19 and for fatal outcome including: CRP (C-reactive protein), the ratio between neutrophils and lymphocytes (NLR), LDH and elevated D-dimer values.[3,4]

Serum CRP (C-reactive protein) is known as one of the acute phase proteins. This protein is produced in the liver in response to infection or inflammation.[5] It starts to increase rapidly in 6-8 hours after the onset of the inflammatory response by the host and reaches maximum values in 48h after the onset of inflammation.6 Its half-life is 19th, and it begins to decrease as the inflammation subsides and returns to normal values when the body recovers.[7] Normal values of this laboratory parameter are lower than 6mg/l. Once created, CRP travels through the bloodstream to the areas of the body where inflammation takes place. It attaches to phosphocholine on the surface of damaged cells and thus activates the classical complement pathway of the immune system, resulting in phagocytosis of damaged cells and bacteria by phagocytic cells.[8,9]

The ratio between neutrophils and lymphocytes (NLR) is another biological marker that can be easily calculated from a standard blood count and can serve as a predictor of the severity of a clinical picture in a variety of conditions. Normal NLR is between 0.78 and 3.53. A value greater than 6 indicates stress in the body.[10] So far, a lot of data have been published linking NLR as a survival factor in cancer patients, COPD patients and patients with cardiovascular disease. 11-14With the advent of COVID-19, this biomarker (NLR) has been used to assess the possibility of developing a severe clinical picture in patients with COVID-19.15

In this study we examined the relationship between the value of serum CRP and NLR as predictor factors for the development of a severe clinical manifestation in patients with COVID-19.

Material and methods

For that purpose, in the period from 19.11.2020 to 18.01.2021 we followed

95 COVID-19 positive patients who were admitted for hospital treatment at the University Clinic for Eye Diseases - COVID Center, at the University Clinic Mother Theresa in Skopje.

Blood samples and laboratory parameters were taken during the hospitalization. In this study, we analyzed the initial laboratory parameters obtained on admission of a patient to our Clinic (T1), and the last laboratory parameters obtained before leaving the Clinic, or the last parameters before the lethal outcome (T2) in those patients who died. Blood was collected (3 ml) in an EDTA-counting tube to determine neutrophil and lymphocyte counts, and a tube without additives to determine CRP as an immune marker. The determination of CRP was performed using turbidimetry. The normal ranges in our laboratory are: for neutrophils 1.2-8.0 x 109 / L (35-80%), for lymphocytes 0.5-5.0 x 109 / L (15-50%), and for CRP up to 6mg / L. Normal NLR is between 0.78 and 3.53.

Statistical analysis

Independent samples t-test was used to compare data obtained for patients who remained alive and patients with lethal outcome. Several models of logistic regression were tested to analyze the predictive value of white blood cells and CRP, the marker of inflammation, for lethal outcome in patients hospitalized for COVID-19. The models were tested while controlling for age, gender, and length of hospital stay. The factors were entered in a single block and the Enter method was used. The variables related to white blood cells and CRP at both times (T1 and T2) were included in the models. The percentages of neutrophils and lymphocytes were included in each model since they did not demonstrate significant associations with patient outcome within the bivariate analyses and they were used as control variables. However, we tested the predictive value of neutrophils/lymphocytes ratio, absolute count of leukocytes, and CRP for lethal outcome in this group of patients.

P values < 0.05 were considered statistically significant, and the main results are given with 95% confidence intervals (CI). The Statistical Package for the Social Sciences (SPSS) statistics (Chicago USA 2011, version 20) was used for the statistical analyses.

Results

Out of the total number of patients (95), 56 (59%) patients were male and the remaining 39 (41%) were female. The youngest hospitalized patient was 25 years old, and the oldest 87 years. The average age of alivepatients was 60.59±13.75 years and the mean of hospital stay in days was 9.68 ± 4.72.

In a period of two months, 21 (22%) of the hospitalized patients died at the Clinic,some of them in the Clinic itself and some in intensive care, after they were transferred due to general health deterioration. Of all those who died, 15 patients were maleand the remaining 6 were female. The average age of the deceased patients was 66.95 ± 13.9 years, and the mean of hospital stay in days was 5.33 ± 5.06.

Bivariate analysis (Table 1) demonstrated that the length of hospital stay was significantly shorter in patients with lethal outcome (5.33 ± 5.06 vs. 9.68 ± 4.72, t=-3.662, p=0.001). Neutrophils/lymphocytes ratio was significantly higher in patients with lethal outcome at both times (T1:

12.05 ± 7.53 vs. 6.47 ± 4.64, t=3.082, p=0.005; T2: 13.05 ± 8.31 vs. 5.81 ± 4.46, t=2.823, p=0.017). Leukocytes count (T1: 10.63 ± 7.5 vs. 6.98 ± 2.98, t=-2.125, p=0.046; T2: 14.71 ± 6.33 vs. 9.52 ± 4.03, t=-3.743, p<0.001) and CRP (T1: 129.27 ± 111.21 vs. 78.73 ± 67.54, t=-2.529, p=0.013; T2: 89.4 ± 76.97 vs. 12.74 ± 28.82, t=-3.407, p=0.005) were also significantly higher in patients with lethal outcome at both times. Age, gender, as well as relative counts (i.e., their percentages) of neutrophils and lymphocytes did not show significant associations with patient outcome.

Table 1. Bivariate analysis of associations between patient outcome and other variables of interest.

	Alive (N=74)	Dead (N=21)	Statistic, *p* value
Age (years) (mean ± SD)	60.59 ± 13.75	66.95 ± 13.9	*t*=-1.866 *p*=0.065
Gender - n (%) Male (n=56) Female (n=39)	 41 (73.2) 33 (84.6)	 15 (26.8) 6 (15.4)	$\chi 2$=1.735, p=0.188
Length of hospital stay (days) (mean ± SD)	9.68 ± 4.72	5.33 ± 5.06	t=3.662 p=0.001
Neutrophils T1 (%) (mean ± SD)	76.45 ± 11.46	75.11 ± 28.31	t=0.201 p=0.843
Neutrophils T2 (%) (mean ± SD)	73.44 ± 13.82	79.17 ± 27.12	t=-1.087 p=0.28
Lymphocytes T1 (%) (mean ± SD)	17.06 ± 9.65	12.97 ± 19.27	t=1.291 p=0.2
Lymphocytes T2 (%) (mean ± SD)	19.29 ± 11.12	15.65 ± 26.11	t=0.798 p=0.427
Neutrophils/Lymphocytes Ratio T1 (mean ± SD)	6.47 ± 4.64	12.05 ± 7.53	t=-3.082 p=0.005
Neutrophils/Lymphocytes Ratio T2 (mean ± SD)	5.81 ± 4.46	13.05 ± 8.31	t=-2.823 p=0.017
Leucocytes T1 ($x10^9$/L) (mean ± SD)	6.98 ± 2.98	10.63 ± 7.5	t=-2.125 p=0.046
Leucocytes T2 ($x10^9$/L) (mean ± SD)	9.52 ± 4.03	14.71 ± 6.33	t=-3.743 p<0.001
CRP T1 (mg/L) (mean ± SD)	78.73 ± 67.54	129.27 ± 111.21	t=-2.529 p=0.013
CRP T2 (mg/L) (mean ± SD)	12.74 ± 28.82	89.4 ± 76.97	t=-3.407 p=0.005

*T1 - values at hospitalization; T2 - values at discharge (or the last analysis before death)

Table 2. Logistic regression model for lethal outcome that includes the factor neutrophils/lymphocytes ratio in hospitalized patients with COVID-19.

Dependent variable	Covariates	B (SE)	exp ^{b} (95% CI)	Cox & Snell R^2; Nagelkerke R^2	χ^2 of the Model (p)
Lethal outcome	Constant	17.38 (24.31)		.343; .617	32.81 (<0.001)
	Age	0.03 (0.04)	1.03 (0.96-1.11)		
	Gender	-0.67 (1.52)	0.51 (0.03-10.03)		
	Length of hospital stay	-0.37 (0.16)	0.69* (0.51-0.96)		
	Neutrophils T1	0.02 (0.18)	1.02 (0.71-1.46)		
	Neutrophils T2	-0.29 (0.22)	0.75 (0.49-1.15)		
	Lymphocytes T1	0.23 (0.23)	1.26 (0.8-1.98)		
	Lymphocytes T2	-0.37 (0.29)	0.69 (0.39-1.22)		
	Neu/Lymph Ratio T1	0.34 (0.16)	1.404* (1.03-1.92)		
	Neu/Lymph Ratio T2	0.31 (0.16)	1.36* (1.001-1.85)		

Neu/Lymph Ratio - Neutrophils/Lymphocytes Ratio
*p<0.05

Table 2 shows that the increase on the Neutrophils/lymphocytes ratio scale both at hospitalization and at discharge (or the last analysis before death) leads to increase in the odds of lethal outcome (T1: 100*[1.404-1] = 40.4% increased odds; T2: 100*[1.36-1] = 36% increased odds). The increase on the Length of hospital stay scale leads to decrease in the odds of lethal outcome (100*[0.69-1] = -31% decreased odds).

Table 3 shows the logistic regression model for lethal outcome that includes the factor leukocytes count in hospitalized patients with COVID-19.

Table 3. Logistic regression model for lethal outcome that includes the factor leukocytes count in hospitalized patients with COVID-19

Dependent variable	Covariates	B (SE)	exp [b] (95% CI)	Cox & Snell R^2; Nagelkerke R^2	χ^2 of the Model (p)
Lethal outcome	Constant	-2.16 (23.54)		.296; .532	27.38 (0.001)
	Age	0.04 (0.04)	1.04 (0.96-1.13)		
	Gender	-0.44 (1.66)	0.64 (0.03-16.48)		
	Length of hospital stay	-0.32 (0.13)	0.73* (0.56-0.94)		
	Neutrophils T1	0.14 (0.17)	1.15 (0.83-1.59)		
	Neutrophils T2	-0.17 (0.22)	0.85 (0.55-1.3)		
	Lymphocytes T1	0.17 (0.2)	1.18 (0.8-1.74)		
	Lymphocytes T2	-0.31 (0.28)	0.73 (0.42-1.27)		
	Leukocytes T1	0.34 (0.15)	1.403* (1.04-1.89)		
	Leukocytes T2	0.22 (0.11)	1.24* (1.001-1.55)		

*p<0.05

Table 3 shows that increase on the Leukocytes count scale both at hospitalization and at discharge (or the last analysis before death) leads to increase in the odds of lethal outcome (T1: 100*[1.403-1] = 40.3% increased odds; T2: 100*[1.24-1] = 24% increased odds). The increase on the Length of hospital stay scale leads to decrease in the odds of lethal outcome (100*[0.73-1] = -27% decreased odds).

Table 4 shows the logistic regression model for lethal outcome that includes the factor CRP count in hospitalized patients with COVID-19.

Table 4. Logistic regression model for lethal outcome that includes the factor CRP in hospitalized patients with COVID-19

Dependent variable	Covariates	B (SE)	exp [b] (95% CI)	Cox & Snell R^2; Nagelkerke R^2	χ^2 of the Model (p)
Lethal outcome	Constant	-5.36 (20.99)		.286; .512	25.99 (0.001)
	Age	0.04 (0.04)	1.04 (0.97-1.11)		
	Gender	-0.73 (1.28)	0.48 (0.04-5.84)		
	Length of hospital stay	-0.2 (0.12)	0.82 (0.64-1.04)		
	Neutrophils T1	0.01 (0.16)	1.01 (0.74-1.38)		
	Neutrophils T2	0.01 (0.17)	1.01 (0.72-1.4)		
	Lymphocytes T1	0.06 (0.19)	1.07 (0.73-1.56)		
	Lymphocytes T2	-0.03 (0.21)	0.97 (0.64-1.46)		
	CRP T1	0.01 (0.01)	1.01* (1.001-1.02)		
	CRP T2	0.02 (0.01)	1.02* (1.002-1.04)		

*p<0.05

Table 4 shows that increase on the CRP scale both at hospitalization and at discharge (or the last analysis before death) leads to slight increase in the odds of lethal outcome (T1: 100*[1.01-1] = 1% increased odds; T2: 100*[1.02-1] = 2% increased odds).

Discussion

Continuous monitoring of relevant laboratory and clinical parameters will assist in the detection of those patients who are at risk of developing severe COVID-19. With the help of these parameters, appropriate therapy will be started at time, which can change the course of this disease. A routine blood tests are possible in almost every medical laboratory and hospital. Some blood count parameters, such as NEU or LY, may indicate good distinction between patients who will develop mild and those who will develop severe clinical picture with COVID-19. Previous studies have shown16,17 that the ratio between NEU and LY, known as NLR, provides even more accurate results on the severity of the clinical picture that may develop in patients with viral infections. These

studies also saw the importance of NLR as a parameter that can predict the course of the disease. According to them, the value of 5 was a limit reference value, and 80% of patients who had a value above or below this corresponded to the type of the clinical picture they later developed during hospitalization. During the past year, many studies have emphasized the values of CRP, PCT, FIB, LDH and D-D as acute-phase reaction proteins that are closely related to the progression of COVID-19.[18,19]

Similar to previous studies[20-23], our study has shown the importance of NLR as a parameter in monitoring the course of the disease in patients with COVID-19. The study also showed the association of this parameter with other pivotal laboratory parameters used to diagnose this disease. This result further suggests that the NLR can be used as a parameter to assess the severity of a patient developing a severe clinical picture, which may be explained by the increased number of Neu and the decreased Ly in patients with severe COVID-19, as a consequence of complex immune responses in the body.[24]

The conclusions reached so far related to this issue say that patients with severe COVID-19 have dysregulation in the immune response that leads to the development of a hyperinflammatory response to the virus.21 As it is well known, elevated NLR values in peripheral blood are commonly associated with a systemic inflammatory response. The increased value so far has been prognostic for many diseases such as: cardiovascular, autoimmune infectious and malignant diseases.[26,27]Therefore, determining the laboratory parameters that suggest this hyper-inflammatory response of the organism are of crucial importance in the monitoring of patients to reduce mortality from this disease. Such biomarkers that may indicate a hyper-inflammatory response from the body, as mentioned earlier, and are available in all laboratories are the ratio between neutrophils and lymphocytes (NLR), as well as the ratio between lymphocytes and C-reactive protein (LCR). In the study, a meta-analysis was performed to assess the possibility of NLR and LCR to serve as predictors of the severity of the clinical picture that would develop in patients.

Meta-analysis was performed, calculating the standardized mean difference (SMD) and the 95% confidence interval (95% CI) of the NLR and LCR values in patients with COVID-19 with or without severe disease. All studies included in this meta-analysis were conducted in China. A total of 825 patients were included, of whom 407 (49.15%) had a severe clinical picture, and the sample size from study to study varied from 48 to 452 patients. The NLR values were found to be significantly increased (SMD = 2.404, 95% CI = 0.98-3.82) in COVID-19, patients with severe clinical picture, and the LCR value was significantly reduced (SMD = −0.912, 95% CI = −1.275 to −0.550), compared to COVID-patients with mild clinical picture. Although there are studies showing that COVID-19 patients have an increase in neutrophil and C-reactive protein and a decrease in lymphocyte counts, few studies have considered effective NLR and LCR markers as predictors of complications of COVID19.[21, 27-31] From all this, it can be concluded that the increased value of NLR and the decreased LCR in patients with COVID-19 lead to an enhanced inflammatory response,

which indicates a poor prognosis.

The ratio between neutrophils and lymphocytes (NLR), alone, but also in combination with other parameters, has been shown to determine a patient's risk of whether it is a mild / moderate or severe clinical case. Also, its increased value is associated with higher COVID-19 mortality.[15, 32-37]

However, still little is known about its value as a predictor of the patient's clinical picture as well as the outcome of the disease. Determining NLR when a patient is admitted to hospital has a high value in predicting deteriorating health, shock, or death, with areas under the curve of 0.801, 0.830, and 0.828, respectively, and a cutoff value of 2.6937. The sensitivity of the ≥2.6937 NLR cutoff for predicting the subsequent presence of disease deterioration, shock and death was 82.0%, 93.3%, and 92.9%, respectively, and the corresponding negative predictive values were 95.7%, 99.5% and 99.5%, respectively. Compared with patients who had an NLR of < 2.6937, the adjusted hazard ratios for disease deterioration, shock and death were 4.1, 13.1 and 11.3, respectively, among those with an NLR of ≥2.6937. The cumulative risk of the clinical outcome was significantly higher in patients with an NLR of ≥2.6937 than in those with an NLR of < 2.6937. Early detection of patients who are at risk of developing a severe clinical condition can help in providing appropriate care, as well as appropriate management of resources that are quite limited during a pandemic.[38]

For patients with COVID-19 the elevated NLR values are due to both the damage that occurs in the lung parenchyma and the prominent derangement of the lymph hematopoietic system. Elevated NLR levels may indicate the severity of the condition in COVID-19 patients as well as the patient's immune status. Recently, several studies have shown the importance of elevated levels of this marker in assessing the severity of the clinical picture in patients with COVID-19 as well as the possibility of a fatal outcome.[15, 25, 32-38] The NLR was also included as a variable in a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19.[38] This finding can be extremely helpful in the accurate and precise triage of patients on admission to a hospital where COVID-19 patients are treated, especially in areas where there are many patients and limited medical resources.

Different studies have so far reported different NLR thresholds. Therefore, in practice, it is not precise which threshold should be considered when categorizing the severity of the clinical picture that a patient may develop. The study demonstrated not only the ability of this biomarker to predict the severity of the clinical condition that may develop in a patient with COVID-19, but also the likelihood of a fatal outcome. In laboratory examination of peripheral blood in COVID-19patients, it has been noted that the absolute value of white blood cells is normal or slightly reduced, but lymphopenia has been expressed.[39] Also, in patients with severe clinical condition or patients with fatal outcome, a rapid decrease in the number of lymphocytes and a gradual increase in the number of neutrophils has been observed. This is probably due to the highly pronounced inflammatory response on one hand, and the immune sup-

pression by SARSCoV-2 on the other. Specifically, neutrophils, as proinflammatory cells with pronounced antimicrobial potential, are activated by proinflammatory mediators associated with viral infection, such as interleukin-6 and interleukin-8.40 At the same time SARSCoV-2 exerts immune suppression, leading to a reduction in CD3 + T cells, CD4 + T cells and CD8 + T cells.[41,42]

Having in mind these observations, NLR is an important marker that may be associated with progression of the clinical picture in patients with COVID-19 and can be relatively easily determined by routine peripheral blood laboratory tests. To date, four meta-analyses have indicated that this marker is elevated in patients with a severe clinical picture compared to those with mild, but none of them assessed the predictive value of NLR for the severity and mortality of COVID-19. [43-46]

Recent meta-analysis has shown that lymphopenia is a good biomarker indicating an increased risk of severe COVID-19 infection.[47] Regarding our results, a higher lymphopenia level was found in the severe cases, but the assessment of the prognosis value of the biological parameters in correlation with the severity of the disease demonstrated that CRP level was more relevant. C-reactive protein has been shown to be a good biomarker for predicting poor outcome in patients with COVID-19.These results were in line with the results obtained in a study conducted in Wuhan by Luo et al. In the study, the sensitivity was 65% and the specificity 83.7%, with a positive predictive value (PPV) of 81.6% and a negative predictive value (NPV) of 68.2%.48 The findings have been consistent with recent publications stating that the value of CRP on admission is a sensitive and early indicator for COVID19 severity.[48-50] Studies have also shown that the level of C-reactive protein correlates with the extent of the lesion in the lung on a tomographic scan.[51] At the time of admission, detailed laboratory tests are sometimes difficult to perform, but determining CRP is a routine procedure that can predict the severity of the clinical picture that would develop in a patient with COVID-19.

Conclusion

Analyzing the obtained laboratory parameters in patients in our study as well as in several other studies, showed that CRP and NLR are two laboratory parameters that can be used as markers to predict the severity of the clinical manifestationin COVID-19patients, certainly complemented by other pivotal laboratory indicators. The most important part in the managing of COVID-19 is early and accurate diagnosis, identification of severe patients and active and timely treatment as soon as possible.

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Case report

ASSOCIATION OF POLAND SYNDROME AND HYPERTRICHOSIS IN PUBERTAL GIRL - CASE REPORT

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Abstract

Poland syndrome (PS) is a rare congenital malformation, most commonly characterized by absence of chest wall muscles on one side of the body. It may be accompanied with other deformities of the extremities. We present the case of a 10-year-old girl with Poland syndrome and hypertrichosis of the back of the trunk and extremities. The clinical examination did not reveal the etiology of the syndrome, such as familial predisposition or some event that led to interrupted blood flow during the early embionic growth. The pregnancy was concieved with in vitro fertilization (IVF); triplets were born and our patient is one of these three girls. The hypertrychosis appeared at 8 years of life, without evidence of previous familial occurance, medications or hormonal disbalance. Other malformations that were found were: a mild form of kyphoscoliosis and mitral valve prolapse. The child was evaluated using a multidisciplinary approach, with further follow-up planned with surgical correction of the chest wall and breast augmentation.

Приказ на случај

ПОВРЗАНОСТ НА POLAND-ОВ СИНДРОМ И ХИПЕРТИРЕОЗА КАЈ ЖЕНСКО ДЕТЕ ВО ПУБЕРТЕТ – ПРИКАЗ НА СЛУЧАЈ

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***Кореспонденција:** Марина Крстевска -Константинова, Универзитетска клиника за детски болести – Скопје, E-mail: mkrstevskakonstantinova@yahoo.com

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Печатарски права: ©2021 Марина Крстевска-Константинова; Константина Кузевска-Манева; Христијан Несторов; Даниела Георгиева. . Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Поландовиот синдром е ретка конгенитална малформација, која најчесто се карактеризира со отсуство на мускули на градниот кош на една страна на телото. Може да биде придружена и со други деформитети на екстремитетите. Нашиот приказ на случај е женско дете старо 10 години со Поландов синдром, здружен со појава на хипертрихоза на грбот и екстремитетите. Направените иследувања кај детето не ја откриј етиологијата на синдромот, како генетска предиспозиција или настан за време на бременоста на мајката кој довел до намалена циркулација за време на раниот ембрионален раст на плодот. Кај мајката е спроведена in vitro фертилизација (IVF) и ова е едно од трите женски деца кои се родени. Хипертрихозата се појавила на 8-годишна возраст, без податок за претходна фамилијарна појава, медикаментозна терапија или хормонален дисбаланс. Додатни малформации кои се најдени беа: лесна форма на кифосколиоза и пролапс на митрална валвула. Детето е водено мултидисциплинарно со план за понатамошна хируршка корекција на градниот кош и неразвиената града.

Introduction

Poland syndrome (PS) is a rare congenital malformation, most commonly characterized by absence of chest wall muscles on one side of the body. The pectoralis major muscle is absent or underdeveloped, and may be associated with thoracic anomalies, upper limb anomalies, anomalies of fingers (syndactyly and brachydactyly), ipsilateral underdeveloped breast and subcutaneous fat tissue, and rarely other organ involvement[1].

Hypertrichosis, which may be congenital or acquired, is characterized by excessive hair growth anywhere across the body[2].

Case presentation

A 10-year-old girl presented at the Pediatric Endocrinology Department due to unilateral breast development and hypertrichosis. The child was born from in vitro fertilization (IVF); the pregnancy was uneventful and resulted in triplets, all of them were female. The clinical examination did not reveal the etiology of the syndrome, such as familial patterns or some event leading to interrupted blood flow during the early embionic growth. The birth parameters were as follow: birth weight was 2,250 gr, birth length was 48 cm. The other two babies, also girls had a normal appearance.

At the time of admission, the puberty has started and left breast was M33, while the right breast was absent, although a small nipple was present. Chest wall deformity of the right thoracic cage was noted as well as a mild kyphoscoliosis (Figure 1). The deformity had been noticed at birth, although further clinical examinations or hospital visits were not preformed. The hair was pigmented, long and soft. Teeth and nails were normal without gingival hypertrophy. There was excessive hair growth on the extremities and the back of the trunk (Figure 2).

Figure 1. Chest wall deformity in our patient

Figure 2. Hypertrichosis in the arm



Hypertrichosis started at the age of 8 years and it became more noticeable, leading to a conclusion it was acquired.

The height was 135 cm (50‰ on growth chart) and the weight was 29 kg (25‰). Pubertal stage was M33 (on the left side), P2A13 and the menstrual cycle was still absent (Pubertal

stage by Tanner and Whitehouse).

From the laboratory findings, sex chromatin was 5%. Routine blood investigations were normal. Hormonal study was within normal limits for her age. Chest X-ray showed absent rib deformities, and normal lung transparency. Medistinal structures were centrally placed (Figure 3).

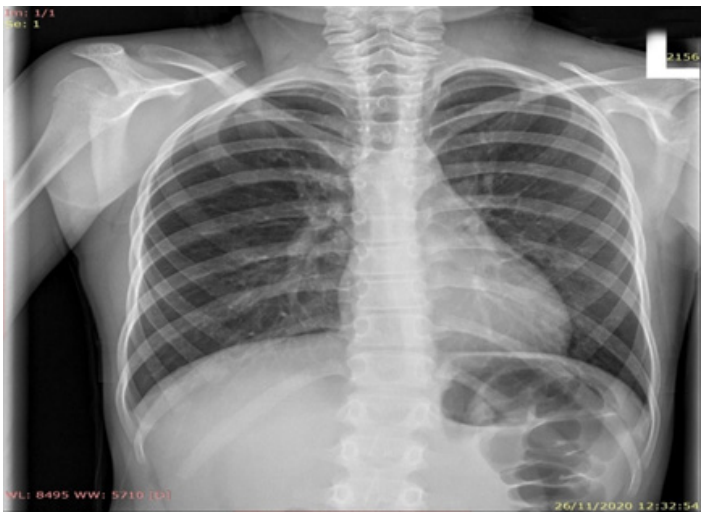


Figure 3. Chest X-ray

Echocardiogarphy revealed mitral valve prolapse without mitral regurgitation.

Evaluation was made by plastic and orthopedic surgeons revealing a mild kyphoscoliosis and physiotherapy was started. Clinical follow-up was suggested until reconstruction and breast augmentation can be performed in late adolescence or adulthood.

Discussion

This is the second case of Poland syndrome in our practice (although 4 more were seen by colleagues). The first was a 3-year-old girl who also had unilateral premature thelarche. Unfortunately, the patient was lost from follow-up, due to migration abroad.

The incidence of PS has been estimated from 1:30 000 to 1:80 000 live births4 and it is more frequent in males, more commonly seen on the right side of the thorax, as in our case. Familial cases have been described, with different inheritance patterns, suggesting a genetic background including gene mutations on different chromosomes[5]. Yet, the most common theory is impairment of embryonic blood supply induced by hypoplasia of the ipsilateral subclavial artery, due to prenatal exposure to teratogens that interfere with vascular development6. Other theories include disruption of the lateral mesodermal plate after fertilization[7.] Also, there have been alternative diagnoses proposed in patients with congenital pectoral muscle deficiency. In a large study by Baas et al., 627 patients were described, using 136 articles, where ten different definitions of PS were utilized. In 58% of the cases, an upper extremity deformity was found, 43% had an associated deformity, 57% had a pectoral malformation, hand malformation and another deformity that matched an alternative syndrome. Twenty-nine percentage had classical PS. The authors concluded that differentiating PS from other syndromes had serious consequences for the patients and their families

in terms of inheritance and possible related anomalies[8,9].

The clinical presentation of PS may be subtle, so the diagnosis can be made by radiological studies using standard mammograms in adulthood[10,11]. Identifying PS is important for better care and avoiding potential clinical mismanagement and possible litigation in cases of incidental trauma[12].

A study of 72 patients with PS in Italy revealed the need of specific national diagnostic and therapeutic guidelines, which will guarantee patients complete and appropriate health services that will improve the quality of life of people living with rare diseases[13].

The treatment of PS is surgical, meanning surgical reconstruction of the thoracic wall anomaly and hand anomaly if present. Surgical treatment options include reconstruction of the chest wall with myocutaneous flap coverage and breast augmentation procedure as needed. Preoperative angiography and chest computed tomography or MRI should be preformed to evaluate the blood supply of potential flaps and the extent of the anomaly[14,15]. For children with more severe thoracic deformities and if the patient is more than 3 years old, Nuss procedure should be preformed as early as possible, as it is done without high rate of complications[16,17]. Other methods include muscle transfer with or without implants. Young patients with PS in their adolescence may be psychologically concerned regarding their body image and early surgical procedures may have positive benefits on their quality of life.

Hypertrichosis, which was also present in our patient, did not point to any specific syndrome associated with this condition, medication, hormonal etiology or inheritance. Low birth weight may have been a contributing factor. Some authors have described premature adrenarcha in babies born small for gestational age 18, although the girls pubic and axillary hair was absent. The association between PS and hypertrichosis was not found.

Conclusion

PS is a rare syndrome which needs early recognition, correct diagnosis and multidisciplinary approach. Surgical intervention should be planned on basis of the severity of disease and/or accompanying malformations. The finding of hypertrichosis in our patient is also interesting, but seems to be sporadic and not associated with the syndrome.

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