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KLINIČKI CENTAR UNIVERZITETA SARAJEVO

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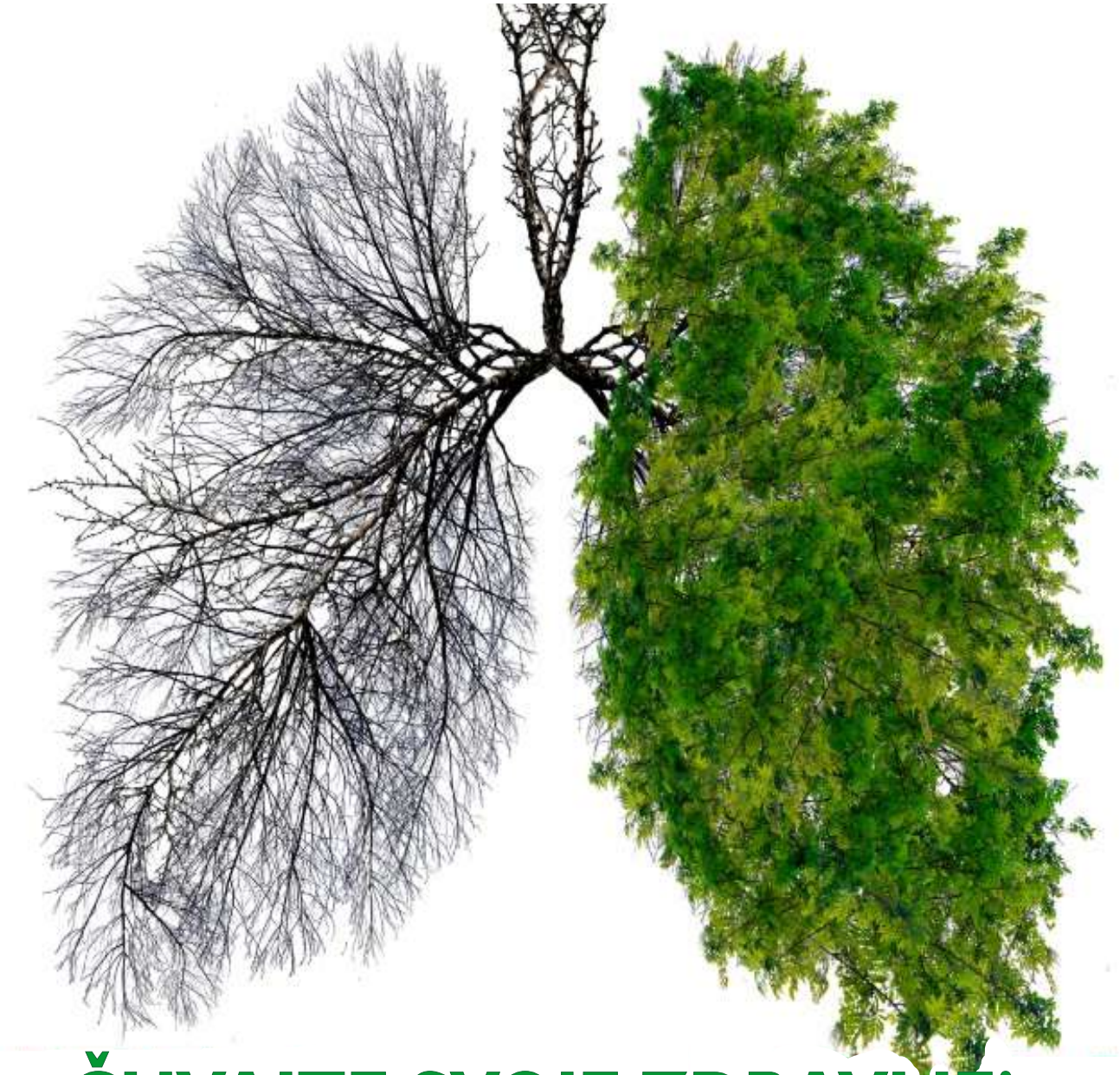

ČUVAJTE SVOJE ZDRAVLJE!

31. maj
Svjetski dan nepušenja

KLINIČKI CENTAR UNIVERZITETA SARAJEVO

Bosnia and Herzegovina was the fourth country in Europe that developed National version of HeartScore program !

Bosna i Hercegovina je bila četvrta zemlja u Evropi koja je razvila Nacionalnu verziju HeartScore programa !

Bosnia and Herzegovina version of HeartScore is developed on the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Serbian and Croatian! Program is easy to use and accessible at www.heartscore.org/eu !

Verzija za Bosnu i Hercegovinu razvijena je na jezicima naroda Bosne i Hercegovine, bosanskom, srpskom i hrvatskom! Program je jednostavan za upotrebu preko web stranice www.heartscore.org/eu !

Bosnia Herzegovina	France	Russian Federation
Croatia	Germany *	Spain *
Cyprus *	Greece *	Sweden *
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Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu
New Central Medical Building - Clinical Center University of Sarajevo

Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

CHA_2DS_2-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

Risk factor-based point-based scoring system - CHA_2DS_2 -VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

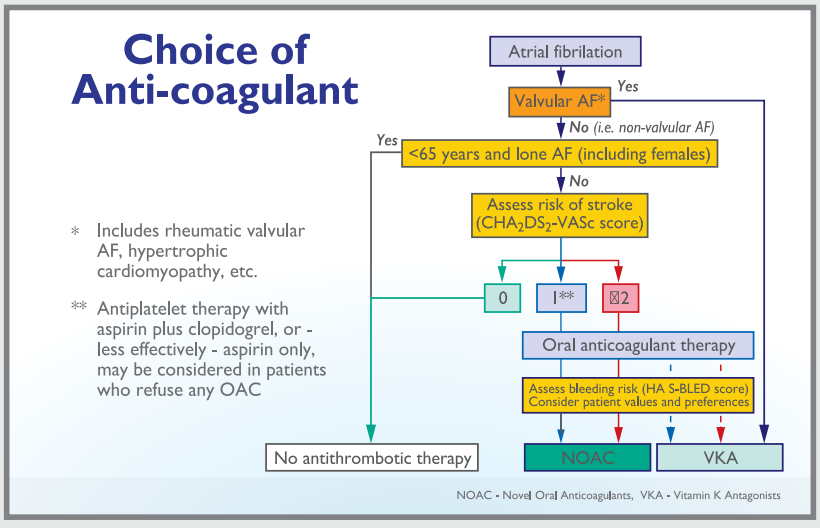
Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

Risk factors for stroke and thrombo-embolism in non-valvular AF

Major risk factors	Clinically relevant non-major risk factors
Previous stroke	CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ⊠ 40%]
TIA or systemic embolism	Hypertension
Age ⊠75 years	Diabetes mellitus
	Age 65-74 years
	Female sex
	Vascular disease

AF = atrial fibrilation; EF = ejection fraction (as documented by echocardiography, radio nudide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left venticular; TIA = trasient ischaemic attack.

Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!



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AIMS AND SCOPE

The Medical Journal is the official quarterly journal of the Discipline for Research and Development of the Clinical Center University of Sarajevo and has been published regularly since 1994. It is published in the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Croatian and Serbian as well as in English.

The Medical Journal aims to publish the highest quality materials, both clinical and scientific, on all aspects of clinical medicine. It offers the reader a collection of contemporary, original, peer-reviewed papers, professional articles, review articles, editorials, along with special articles and case reports.

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Original articles

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Case reports

Women's reasons for artificial abortion

Najčešći razlozi žena za arteficijalni (namjerni) abortus

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ABSTRACT

Introduction: artificial abortion is an abortion in which a pregnancy is intentionally, violently and artificially terminated. Termination of pregnancy older than 10 weeks will be allowed if there are certain reasons. These indications are: medical - the existence of a disease that could seriously threaten the health and life of the woman; ethical indications are pregnancy caused by rape or rape of a weak or minor person, rape by abuse of official position, incest, poor financial condition, large number of children, pregnancy out of wedlock; eugenics refer to the existence of biological-genetic factors that damage the fetus, the mother's disease in the first trimester of pregnancy from rubella, the use of tetracycline, incompatibility of blood groups. Aim: to analyze reasons of women for artificial abortion. Materials and methods: the research was conducted with the questionnaire which was conducted by the authors of Ratovoson and others (2020) was used in a study approved by the Ethics Committee of the Ministry of Public Health of Madagascar. The respondents consisted of 60 women who reported to the Clinic of Gynecology and Obstetrics of the Clinical Center Universty of Sarajevo (CCUS). The research is descriptive on a representative sample. The results were processed in Excell and frequencies and percentages were used, as well as statistical significance testing via chi-square. Spearman's correlation test and ANOVA test were also used. Results: the average age of the surveyed women was from 18 to 45 years. The largest number of surveyed women cited education/career (40%) and age (30%) as the reason for artificial abortion. Their socio-economic position was average. A history of abortion was significantly more common among younger women (< 20 years compared to 35+ years). The proportion of women who used misoprostol alone (oral, vaginal or both) at 50.0%, while 25.0% were on contraceptive pills. The surveyed women did not do prenatal tests during pregnancy (95%). Conclusion: the most common reasons given by women for artificial abortion in the sample of women who came to the CCUS were education, that is, career and age, and socio-economic status.

Keywords: artificial abortion, women, prenatal test, pregnancy, birth, reason

SAŽETAK

Uvod: arteficijalni abortus je pobačaj kod koga se namjerno, na zahtjev trudnice, vještački prekida trudnoća. Prekid trudnoće koja je starija od 10 sedmica će se dozvoliti ako postoje određeni razlozi. Te indikacije su: medicinske - postojanje oboljenja koje bi moglo ozbiljno ugroziti zdravlje i život žene; etičke indikacije su trudnoća nastala silovanjem ili obljubom nad nemoćnom ili maloljetnom osobom, obljuba zloupotrebom službenog položaja, incest, loše materijalno stanje, veći broj djece, vanbračna trudnoća; eugeničke se odnose na postojanje biološko-genetskih faktora koji oštećuju plod, oboljenje majke u prvom tromjesečju trudnoće od rubeole, upotreba tetraciklina, nepodudarnost krvnih grupa. Cilj: analizirati razloge žena za arteficijalnim abortusom. Materijali i metode: Istraživanje je provedeno upitnikom koji su proveli autori Ratovoson i drugi (2020) koji je korišten u studiji koju je odobrilo Etičko povjerenstvo Ministarstva javnog zdravstva Madagaskara. Ispitanice su bile 60 žena koje su se javile na Kliniku za ginekologiju i akušerstvo Kliničkog centra Univerziteta u Sarajevu (KCUS). Rezultati su obrađeni u Excell-u i iskorištene su frekvencije i procentualni prikazi, te testiranje statističke značajnosti putem hi-kvadrat testa. Korišten je i Spearmanov test korelacije i ANOVA test. Rezultati: prosječna dob ispitanih žena bila je od 18 do 45 godina. Najveći broj ispitanih žena kao razlog za umjetni pobačaj navodi obrazovanje/karijeru (40%) i dob (30%). Njihov društveno-ekonomski položaj bio je prosječan. Povijest pobačaja bila je znatno češća među mlađim ženama (< 20 godina u usporedbi s 35+ godina). Udio žena koje su koristile samo misoprostol (oralno, vaginalno ili oboje) iznosi 50,0%, dok je 25,0% uzimalo kontracepcijske pilule. Ispitanice nisu radile prenatalne testove tijekom trudnoće (95%). Zaključak: najčešći razlozi žena za arteficijalni abortus na uzorku žena koje su se javile u KCUS su obrazovanje, odnosno karijera i godine, te socio-ekonomski status.

Ključne riječi: arteficijalni abortus, žene, prenatalni test, trudnoća, porod, razlog

INTRODUCTION

An artificial abortion is an abortion in which a pregnancy is intentionally, violently and artificially terminated. Instruments for artificial termination of pregnancy existed as far back as the ancient Greeks and Romans (1).

The history of induced abortion can be traced back to ancient times. There is evidence to suggest that pregnancies were terminated in a variety of ways, including the use of abortifacient plants, the use of sharp instruments, the application of pressure on the abdomen, and other methods (2). The reasons why women decide to terminate a pregnancy are: postponement or interruption of raising a child, concern about the interruption of work or education, issues related to financial stability or stability in a relationship, perceived immaturity (3).

Today, every pregnant, able -bodied woman has the right to submit a request for termination of pregnancy. The request is submitted to the appropriate health institution (gynecology and obstetrics departments and clinics) with evidence that the pregnancy has not exceeded 10 weeks and that the termination of the pregnancy will not directly endanger the health of the woman. Termination of pregnancy older than 10 weeks will be allowed if there are certain reasons.

These indications are: medical - the existence of a disease that could seriously threaten the health and life of the woman; ethical indications are pregnancy caused by rape or rape of a weak or minor person, rape by abuse of official position, incest, poor financial condition, large number of children, pregnancy out of wedlock; eugenics refer to the existence of biological-genetic factors that damage the fetus, the mother's disease in the first trimester of pregnancy from rubella, the use of tetracycline, incompatibility of blood groups. Some women underwent abortion due to socio-economic circumstances. These may include stigmatization of the disabled, preference for children of a certain gender, disapproval of single motherhood, insufficient economic support for families, lack of access to or refusal of contraception or population control methods (such as China's one-child policy). These factors can sometimes result in forced abo rtion or sex-selective abortion of a child (4). The use of the term 'safe' or 'unsafe' in relation to induced abortion is important because legal abortion in certain regions of the world does not always mean safe abortion (5).

Induced (artificial) abortion is made possible by law for about 2/3 of women worldwide. In the USA, abortion is legally allowed in the 1st trimester (≤12 i.e.); after that, it depends on the law of the individual state (federal, op. trans.). In the US, about 1/2 of pregnancies are accidental; about 1/2 of them end in an elective abortion, of which 90% in the 1st trimester (6).

Annually, 55.7 million abortions take place in the world, of which an estimated 30.6 million are safe abortions, performed by a trained professional in an appropriate medical environment. The share of unsafe abortions, that is, the share of pregnancy terminations by people without the necessary skills or in an unsuitable environment, is significantly higher in developing countries than in developed countries (49.5% vs. 12.5%) (7).

In the last few decades, abortion has been a much-discussed topic in the world. This is a question that is often manipulated in daily political discussions, which creates an environment in which it is difficult to think seriously about the very essence of the matter and argue with arguments (8). Abortion is one of the current bioethical issues in modern society because it concerns the life of both the woman and the future child, and as soon as life is concerned, it is a bioethical issue (9). The issue of abortion is controversial not only because certain people believe that it violates the (human) rights of embryos and fetuses, but also because it is "a symbol of historical conflicts over sexual morality, the birth rate and the social role of women" (10).

MATERIALS AND METHODS

The research was conducted at the Clinic of Gynecology and Obstetrics of the Clinical Center University of Sarajevo, in the period from 20 May to 20 September 2022. The survey included 40 women aged 18 to 45, who came to perform an artificial abortion service. It is a cross-sectional study, the questionnaire which was conducted by the authors of Ratovoson and others (2020) was used in a study approved by the Ethics Committee of the Ministry of Public Health of Madagascar (n°051-MSANP/CE - 05.05.2015).

Adults who voluntarily agreed to participate in the research were included in the research, while minors were excluded. The survey questionnaire contained questions about general information, about the reasons for artificial abortion, data about the number of abortions and children, and knowledge about artificial abortion.

The research was conducted prospectively, according to the type of longitudinal non-control study, where with the help of the original author's (non-standardized) research instrument (survey questionnaire) we obtained results. The results of the research were processed in the Microsoft Excel software system. The data were presented through frequencies and a percentage presentation of the results in a tabular form. Among the methods of inferential statistics, Spearman's rank correlation coefficient and ANOVA test were used. The level of significance was $p<0.05$.

RESULTS

The results of the research showed that the largest number of women surveyed were from the age group of 18 to 25 years, 42% of them, and 12 of them out of a total of 40 had an artificial abortion. On the basis of the chi-square test, it was established that there was a statistically significant difference between women who did and did not undergo artificial abortion, where the chi-square value was $\chi 2=6.4$, at a significance level of $p<0.05$.

Using this framework, we tested sequentially the following individual-level variables for any possible association with history of abortion (Table 1): age, highest level of education attained, religion, civil status, socioeconomic status (based on quintiles of all interviewed women), history of transactional sex (whether the woman reported ever receiving money/gifts/favors in exchange for sex), history of live births, desired number of children (below the median of 4 or not), and ever having used contraception (ever used potentially ineffective methods, ever used effective methods only, or never used).

A history of abortion was significantly more common among younger women (< 20 years compared to 35+ years, with higher odds ratios for lower age groups), women with less education (those with at least a secondary level of education compared with those with a higher level of education). Induced abortion was significantly lower among women who (at the time of the interview) were partnered, widowed, or divorced than among those who were single (never married), and among those who

wanted fewer than four children than among those who wanted more than four children. However, these associations were not statistically significant in the multivariate model. History of abortion is not significantly associated with SES or number of live births.

Women who reported ever using contraceptive methods were also more likely to report a history of miscarriage compared to those who did not. The association was similar for more effective and less effective methods, and was strongest for women who reported a history of both.

Table 1 **Categorization of independent variables included in analysis of risk factors for history of abortion.**

Variable	Values	12
Age	≥35 years	1 (8.3%)
	25 to <35 years	2 (16.7%)
	20 to <25 years	2 (16.7%)
	<20 years	7 (58.3%)
Maximum Education	Primary school or less	2 (16.7%)
	Middle school	8 (66.7%)
	High school or more	2 (16.7%)
Civil Status	Single (never married)	7 (58,3%)
	Married or living with a partner	4 (48.0%)
	Other (widowed, divorced)	1 (8.3%)
Socioeconomic status, according to socioeconomic index developed based on assets and amenities	Quintile 1	1 (8.3%)
	Quintile 2	2 (16.7%)
	Quintile 3	6 (50.0%)
	Quintile 4	2 (16.7%)
	Quintile 5	1 (8.3%)
Transactional Sex	No (never received money/gifts/favors in exchange for sex)	12 (100.0%)
	Yes (ever received money/gifts/favors in exchange for sex)	0 (0.0%)
Number of Previous Live Births	0 previous live births	7 (58.3%)
	≥1 previous live births	5 (41.7%)
Ideal Number of Children	<4	10 (83.3%)
	≥4	2 (16.7%)
Contraceptive Use	No history of contraceptive use	2 (16.7%)
	History of using less effective methods only	8 (66.7%)
	History of using more effective methods only	1 (8.3%)
	History of using both more and less effective methods	1 (8.3%)

Table 2 presents the methods of service that women described for each induced abortion listed in the study. Many women reported multiple methods for the same abortion. We estimated the proportion of women who used misoprostol alone (oral, vaginal or both) at 50.0%, while 25.0% were on contraceptive pills.

Table 2 **Methods of abortion.**

Method Percentage of Abortions	
Oral misoprostol	1 (8.3%)
Vaginal misoprostol	5 (41.7%)
Contraceptive pills	3 (25.0%)
Curettagea	1 (8.3%)
Insertion of a tube or plant stem into the genital tract	0 (0.0%)
Ingestion of a herbal decoction (tambavy)	0 (0.0%)

We estimated that 83.3% of abortions resulted in at least one symptom or complication (Table 3). The most common symptom reported was hemorrhage or blood clots (33,3%), then dizziness or confusion (25,0%) and abdominal pain (25,0%).

Table 3 **Symptoms and complications of induced abortion in women.**

Symptoms	
Hemorrhage or blood clots	4 (33.3%)
Dizziness or confusion	3 (25.0%)
Abdominal pain	3 (25.0%)
Foul smelling vaginal discharge	0 (0.0%)
Fever or chills	0 (0.0%)
Possible infection (fever, chills, or foul smelling vaginal discharge)	0 (0.0%)

The largest number of respondents who had an artificial abortion cited education or career as the reason (83.33%). A total of 21 women who did not have an abortion stated that education was not the reason for the abortion (75%). Based on the correlation test, there was a medium strong connection between education and the frequency of abortions. Based on the ANOVA test, there was no statistically significant difference in the connection between education as a reason for abortion and performing an artificial abortion, with the value of $F=0.63$; $p=0.473$, and $p>0.05$.

Table 4 **Education of respondents as a reason for artificial abortion.**

		Frequency of access to artificial abortion			
Education/career reason for abortion.			**Yes**	**No**	**Total**
	Yes	N	10	6	16
		%	83.33	21.43	40.00
	No	N	2	21	23
		%	16.67	75.00	57.50
	I am not sure	N	0	1	1
		%	0	3,57	2,50
Total		N	12	28	40
		%	100.00	100.00	100.00

r=0.943; p=0.01
F=0.63, p=0.473

The largest number of respondents who had an artificial abortion suffered from certain disease that endangers their pregnancy, 10 of them (83.33%), while 2 respondents who did not suffer from any disease had an artificial abortion (16.67%). Out of the respondents who did not have an artificial abortion, 6 suffered from a disease that could endanger pregnancy, and 22 respondents did not suffer from any disease (78.57%). Based on the correlation test, there was a strong connection between the frequency of access to artificial abortion and the disease that threatens their pregnancy. Based on the ANOVA test, there was no statistically significant difference in the comparison of the correlation between the disease the subject suffered from as a reason for abortion and the frequency of artificial abortion, where F=0.8; p=0.465, and p>0.05.

Table 5 **Illness of the subject as a reason for artificial abortion.**

		Frequency of access to artificial abortion			
Do you suffer from any disease that endangers your pregnancy?			**Yes**	**No**	**Total**
	Yes	N	10	6	16
		%	83.33	21.43	40.00
	No	N	2	22	24
		%	16.67	78.57	60.00
Total		N	12	28	40
		%	100.00	100.00	100.00

ro=0.80; p=0.503
F=0.8; p=0.465

Out of the total number of respondents who had an artificial abortion, 5 gave a statement that the child would be born with a birth defect (41.67%), while 7 of them did not have the previously mentioned statement (58.33%) about the birth of a defect in the child. Based on the correlation test, there was a strong connection between the finding that the child would be born with a birth defect and the frequency of access to artificial abortion. Based on the ANOVA test, there was no statistically significant difference in the incidence of abortion with the statement that the child would be born with a birth defect (F=0.376; p=0.602, p>0.05).

Table 6 **Correlations of the statement that the child will be born with a birth defect as a reason for abortion with the frequency of artificial abortion.**

		Frequency of access to artificial abortion			
Finding that the child will be born with a birth defect.			**Yes**	**No**	**Total**
	Yes	N	5	1	6
		%	41.67	3.57	15.00
	No	N	7	27	34
		%	58.33	96.43	85.00
Total		N	12	28	40
		%	100.00	100.00	100.00

r=1, p=0.005
F=0.376; p=0.602

DISCUSSION

According to United Nations data, the abortion rate in Bosnia and Herzegovina is low and amounts to 1.4 abortions per 1,000 women of reproductive age. This number is lower than in neighboring countries: Croatia (4.7), Montenegro (6.3) and Serbia (10.7) and corresponds to the abortion rate in Austria (1.4). The average number of abortions in Europe is 202 per 1,000 live births. In the countries of Southeast Europe, including Bosnia and Herzegovina, the average number is 298. The average number of abortions in 2017 per 1000 women of reproductive age (15-49) was 7.4 in the Republic of Srpska and 4.3 in the Federation of Bosnia and Herzegovina. About half of all abortions were medically induced and the percentage of abortions among women under the age of 20 was low and amounted to 2.1% in the Republika Srpska (11).

One of the reasons why women decide to have an abortion is that they feel abandoned by their partners. This is the result of research by the Institute for Psychosomatic Medicine, Psychotherapy and Medical Psychology of the Technical University of Munich. 130 couples who were tormented by internal conflicts related to pregnancy took part in the study. For the most part, the abortion brought relief to the men, but they did not want to take responsibility for it. They claimed that they were completely unaware of the consequences of the procedure for the woman and wanted to forget the whole incident as soon as possible (12).

Various studies show that the number of pregnancies caused by sexual violence is quite small, lower than expected. In Czechoslovakia, for example, out of 86,000 abortions, only 22 were performed due to violence. Different authors talk about a percentage that varies between 2% and 5% of rape cases. R. Alcorn presents the results of the Guttmacher Institute according to which "16000 abortions occur annually as a result of sexual violence or incest, which represents 1% of all abortions" (13).

A history of abortion was significantly more common among younger women (< 20 years compared to 35+ years. Women who reported ever using contraceptive methods were also more likely to report a history of miscarriage compared to those who did not. The association was similar for more effective and less effective methods, and was strongest for women who reported a history of both. We estimated the proportion of women who used misoprostol alone (oral, vaginal or both) at 50.0%, while 25.0% were on contraceptive pills.

We concluded that there was a strong connection between socio-economic of the status of the respondents with the frequency of abortions, as well as the connection between the employment status. There was also a strong support for women from their families or partners when having an abortion. There was a connection between education as a reason for abortion and the frequency of abortion.

CONCLUSION

The most common reasons of the observed women for having artificial abortion was their education, age and socio-economic status. A program of preventive measures to reduce artificial abortions that should be implemented could include educating young people about risky sexual behavior, familiarizing them with contraceptive methods, and measures to protect reproductive health, short-term and long-term potential complications of artificial abortion.

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Burnout syndrome among anesthesiologists

Sindrom izgaranja među anesteziolozima

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ABSTRACT

Introduction: burnout syndrome reflects public health crises with negative impacts on doctors, patients, and healthcare organizations. Several medical disciplines are considered to be at high risk for psychological stress, and anesthesiology is certainly one of them. Aim: to analyze the occurrence of burnout syndrome in anaesthesiology and possibly establish the characteristics of the syndrome in relation to the workplace, career, and promotion status, as well as the personal characteristics of the doctors. Materials and methods: the total number of respondents who participated in the study was 72. The study involved members of the Association of Doctors of Medicine and Anesthesiologists-Reanimatologists of the Federation of Bosnia and Herzegovina. The tool used for research was the Maslach questionnaire. Results: a total of 72 respondents took part in the study, and descriptive statistical analysis revealed that female gender dominated with 57, or (79.2%). A statistically significant difference was found at the level of burnout rate of depersonalization in 8% between resident doctors and specialist doctors. The average burnout rate in the field of personal accomplishment differs significantly among resident doctors and specialist doctors at a 5% risk of error and type. The group with the most emotional exhaustion among respondents was the divorced group. An analysis of the burnout rate of personal performance with regard to marital status found an 8% difference in mistake rate that was statistically significant. In the area of personal achievement, divorced and single persons typically experienced the highest levels of burnout. Conclusion: in this study, anesthesiologists were at high risk of burnout. In addition to the above, we found that the following characteristics affect the same marital status, divorced or single, resident versus specialist doctor, on-call hours and partially female gender.

Keywords: anaesthesiologists, burnout syndrome, risk factors

SAŽETAK

Uvod: sindrom izgaranja predstavlja krizu javnog zdravstva sa negativnim uticajima na ljekare, pacijente i zdravstvene organizacije. Nekoliko medicinskih disciplina se smatra pod visokim rizikom od psihičkog stresa, a anesteziologija je svakako jedna od njih. Cilj: analiza pojave izgaranja u anesteziologiji i eventualno utvrđivanje karakteristika izgaranja u odnosu na radno mjesto, stanje u karijeri i napredovanju, kao i ličnim karakteristikama ljekara. Materijali i metode: ukupan broj ispitanika koji je učestvovao u istraživanju je 72. U istraživanju su učestvovali ljekari članovi "Udruženja doktora medicine anesteziologa-reanimatologa FBiH". Kao instrument istraživanja poslužio je Maslach upitnik. Rezultati: u istraživanju je učestvovalo ukupno 72 ispitanika, a deskripitivna statistička analiza je pokazala da u ukupnom uzorku dominira ženski spol sa 57 (79,2%). Ustanovljena je statistički značajna razlika u nivou izgaranja depersonalizacije na nivou od 8% između specijalizanata i specijalista. Na nivou od 5% rizika greške i vrste, postoji statistički značajna razlika u prosječnom nivou izgaranja na polju ličnog postignuća između specijalizanata i specijalista. Razvedeni ispitanici imaju najviši nivo emocionalnog izgaranja. Analizom stepena izgaranja ličnih postignuća u odnosu na bračni status ustanovljeno je da postoji statistički značajna razlika na nivou greške i vrste od 8%. Na tom nivou, razvedeni i samci imaju u prosjeku najviši nivo izgaranja od ličnog postignuća. Zaključak: u ovom istraživanju anesteziolozi su u visokom riziku od izgaranja. Pored navedenog utvrdili smo da sljedeće karakteristike podjednako utiču na bračni status razveden ili samac, specijalizant u odnosu na ljekara specijalistu, dežurstva i djelimično ženski spol.

Ključne riječi: sindrom izgaranja, anesteziolozi, faktori rizika

INTRODUCTION

Despite the fact that burnout syndrome was firstly described almost sixty years ago, it has yet to be classified as a health disorder. A wide range of clinical signs and etiopathogenic theories undoubtedly contributed to the current situation. There are various clinical forms of burns in addition to variety of therapeutic strategies (1).

High emotional exhaustion (the subjective sense of fatigue), depersonalization (defense mechanism in an attempt to detach from work), and low satisfaction with personal accomplishments are generally accepted as the three main components of burnout syndrome (feeling of frustration at work). Burnout syndrome differs from depression, it is specific to the work environment and the factor of determination varies. Burnout syndrome is associated with deteriorated collegial relationships and reduced work ability,

resulting in a decline of the quality of health care provided as well as potential increases in health care costs (2).

Burnout syndrome can affect healthcare professionals at any stage of their careers. The occurrence of burnout syndrome among healthcare workers has increased in recent years, differing by country and based on different areas of specialization and working units (3). This syndrome had also reached epidemic levels in the medical profession, with a prevalence of around or higher than 50% (2).

Several medical disciplines are considered to be particularly susceptible to emotional anxiety. Anesthesiology is unquestionably one of the most stressful medical disciplines, subjecting doctors to high responsibilities and stressful situations on a daily basis, such as dealing with life-threatening situations. Furthermore, the work hours may be considered more stressful compared to other medical disciplines, as duties include overnight shifts, weekend hours, and holidays (2).

The burnout symptoms are associated with a public health crisis, with negative consequences for individual doctors, patients, health organizations, and the system itself. Burdening, ineffective work processes, indignities that management roles carry, a conflict between work and home, a lack of contributions or control of doctors with regard to issues affecting their work, and organizational structure of support and management are the main drivers of this epidemic.

Individually focused solutions such as the reduction of consciousness-based stress and programmes in small groups to promote the community, connectivity and the introduction of protocols have also proved effective. Regardless of specific approach, the problem with burnout amongst doctors is best addressed when viewed as a shared responsibility of health care system and individual doctors (4).

AIM

The aim of this study was to analyse the incidence of burn out among anaesthetists and possibly to determine the characteristics of burnout syndrome in conjunction with workplace, career status, promotion and personal characteristics of doctors in order to provide an overall perspective of burnout syndrome (anaesthetists).

MATERIALS AND METHODS

The study was a prospective, comparative cross-sectional research study which included a total of 72 respondents.

Doctors from the Federation of Bosnia and Herzegovina's Association of Doctors of Medicine and Anesthesiologists-Reanimatologists (UDMAR) also took part in the research.

The research was conducted from February to April 2022. The small sample was due to the small number of anaesthesiologists in the Federation of Bosnia and Herzegovina.

The Maslach Burnout Inventory (MBI), as the most used self-assessment tool, was used exploring three components of burnout syndrome: fatigue, depersonalization, and personal achievement (with permission of the author) (5).

The questionnaire was used as a research tool and was distributed via online platform. After verifying the integrity of the data, a statistical analysis was performed in IBM SPSS Statistics v.20.0 for Windows. The questionnaires were distributed online (via web page and e-mail) in the form of a Google document (Google form) and they also included explanations of the importance and significance of the research, the method to fill out forms, and the required voluntary consent for participation.

After verifying the integrity of the data, a statistical analysis was performed in SPSS Statistics.

For statistical analyses, the NP test, the Mann-Whitney test, and the Kruskal-Wallis test were used.

The statistical significance level was set to the industry standard of α=0.05.

RESULTS

The study included 72 respondents, 57 (79.2%) female and 15 male (20.8%) respondents. They were divided into two groups based on their age: the first group (aged 28-44), included 46 (63.9%) respondents, and the second group (aged 45 and over), included 26 (36.1%) respondents. Analysis of the respondents' marital status showed that 57 (79.2%) of the respondents were married, 6.9 % were divorced, and 10 (13.9%) were single.

Households were also divided into two groups: Group I (1-3 members) included 34 (47.2%) respondents, and Group II (four and more household members), consisted of 38 (52.8%) respondents.

In the overall sample, there were 62 (86.1%) specialists in anesthesiology and 10 (13.9%) anaesthesiology trainees. In the intensive care unit, all doctors were specialists, i.e. 62 (86.1%).

The respondents were also divided into two test groups based on their work experience: Group I (1-20 years of work experience), included 51 (70.8%) respondents and Group II (21- more years of work experience), consisted of 21 (29.2%) respondents. In the anesthetic unit, 47 (65.3%) respondents had from 1 to 15 years of work experience, and 25 (34.7%) had over 16 years of work experience.

Statistical tests of the differences in levels of three types of burnout (emotional burnout, depersonalization and level of personal accomplishment) between the groups were as follows:

The analysis of the level of emotional burnout in relation to gender revealed that with 5% of the level of error and type there was no statistically significant difference in the average burnout level of emotional fatigue between male and female respondents ($p=0.65 > 0.05$).

The modes of the dependent variable (emotional burnout level/caused by exhaustion) were marked as low level 1, medium level 2 and high level 3, meaning that higher average rank of the taken variable caused higher burnout from emotional exhaustinon.

According to the available data, the average response rate was higher for women (38.63) than for men (28.40). However, this difference was not statistically significant, 5%. The observed difference of 10.23 (38.63-28.40) was random, not systematic; it was caused by sample fluctuation, meaning that if we had had another sample of the same size, we would have got some other difference determined as statistically significant, 5%. Such a difference only existed with 7% error and level type. With 5% error rate and type, no statistically significant difference in the average rate of burnout from depersonalization was found between male and female respondents ($p=0.917 > 0.05$).

There was no statistically significant difference in terms of emotional exhaustion, depersonalization, and level of burnout related to personal achievement with regard to age, employment, number of household members, work in intensive care unit, and length of work in aesthesia unit.

There was a statistically significant difference (8%), in the burnout rate of depersonalization between doctors in practice and doctors in training. On average, residents had higher levels of burnout than specialists.

There was a statistically significant difference in the average burnout rate in the field of personal achievement between residents and specialists with 5% of risk error and type. Based on average levels (49.40 versus 34.42) (p=0.0250.05), the burnout was significantly higher in residents than in specialists.

Based on the analysis, the overnight duty (night shifts) did not have any effect on burnout rates at the 5% level. There was a statistically significant difference (9%) regarding the average level of burnout in a field of personal achievement, which was significantly higher in respondents who did not have overnight shifts.

According to burnout analysis related to marital status there was a statistically significant difference (5%) in the average level of burnout between respondents from different marital status. Recently divorced respondents had the highest level of burnout. The average level of burnout within and between married respondents was the lowest.

There was a statistically significant difference (6%) in the average burn rate between married and divorced respondents. On average, divorcees had higher burnout rate than married respondents. There was also a statistically significant difference (7%) in the average burn rate between married and single respondents. On average, single men had higher burn rates than married men.

There was no difference between divorced and single men and there was no statistically significant difference in depersonalization based on marital status. An evaluation of the burning rate of personal achievement versus marital status showed a statistically significant difference in error rate and type of 8%. Divorced and single respondents had the highest level of burnout regarding personal achievement at this level.

DISCUSSION

At work, burnout syndrome is common in medicine and it has been linked to lower quality of life for doctors and lower health-care quality. Data analysis in available databases disclosed that there was a lack of data on the prevalence and risk factors of burnout among anesthesiologists. According to some authors, anesthesia ranks among the highest rates of combustion of any branch of medicine, with rates approaching 40% (6,7).

In this study, the female gender was dominant with 79.2%, the largest number of respondents belonged to 28 to 45 age group. There was statistically significant difference in marital status, with married respondents accounting for 79.2% of the total sample. The majority of the respondents (86.1%) were specialists, whereas 13.9% were residents.

In the study of Vergas M, et al., 58.1% of respondents were over 40 years of age, women dominated with 53.8%, and 60.8% of respondents were married, which was in line with the findings of this study (8). In the study of Barbosa FT, et al., male gender was slightly dominated (51.16%), and the average age was 49, 82 ±12, 05 years. A high level of burnout rate in at least one of three dimensions was determined by 67, 44% of anesthesiologists (9).

In this study, the analysis showed that regarding the level of emotional burnout and gender there was no significant difference in the average level of burnout from the emotional fatigue between male and female respondents (p=0.065, gt; 0.05), even though it was recorded that the female population was at a higher level. No statistically significant difference was found in the average level of burnout from depersonalization between male and female respondents (p=0.232>0.05). Also, there was no statistically significant difference in the average burnout level in a field of personal accomplishment between male and female respondents (p=0.197>0.05). In the study of Vergas M, et al., higher level of depersonalization was shown by male gender; which was not correlated with this study (8).

In the study conducted by Abut YC, et al., female anaesthesiologists showed higher level of burnout syndrome in personal accomplishments, but lower depersonalization results from the male anaesthesiologists. There was no statistical correlation between marital status and burnout syndrome, which was not correlated with the results of this study (10).

The average burnout level of emotional exhaustion among the respondents of this study in relation to diverse marital statuses differed in a statistically significant way. The highest level of burnout was found in divorced people. The average level of this burnout was lowest among the married respondents. Additionally, compared to married people, single people generally have higher level of burnout. No difference was found when compared divorced people and single. There was no significant statistical difference in depersonalization and relationship status.

The investigation of the degree of burnout in personal accomplishments compared to marital status discovered a statistically significant difference at the level of error and kind in 8%. In that regard, divorced and unmarried people on average had the highest level of burnout in a field of personal accomplishment. In an observation study conducted by the author Eslav-Schmalbach J, et al., 19,2% of data respondents were categorized as burningout under the first criterion (high emotional fatigue, followed by a high depersonalization or reduced personal accomplishment), and 9.2 % under second criterion (high emotional exhaustion combine with high depersonalization and reduced personal accomplishment). The findings of this study revealed that married respondents faced higher risks than those who were not married, which was contrary to the results/findings of this study (11).

A statistically significant difference in the burnout syndrome of depersonalization was found in this study at a level of 8% between residents and specialists. Residents had a higher level of burnout syndrome than specialists. There was also a statistically significant difference in the average burnout level in the field of personal achievement between residents and specialists. The average level of this burnout syndrome was significantly higher in residents than in specialist (49, 40 versus 34, 42) (p=0.025, < 0.05), which can partly be justified by greater pressure on residents with their specialisations as well as lack of professional experience.

The overall score of burnout syndrom from the personal achievement was also found to be significantly higher in non-standby (night duties) respondents. Vargas M, et al., (8) burnout study showed that working in an intensive care unit and being less than 40 years old causes a significant increase in burnout syndrome potential.

In the section study, which used an appropriate sample of resident doctors and anesthesiologists from the Federal District of Portugal, by Goveia CS, et al., male (57,69%) were annihilated, an anesthesiologist's average age was 42 ±97 years and residents' average age was 30±2.9 years. The burnout syndrome was identified in 2.43% amongst anesthesiologists and slightly higher (2.70%) among residents, while the high risk for its appearance was found at 21.5% between anesthesiologists and 29.72% specialists in

anesthesiology, which was consistent with the results of this study (12).

The results that correlated with this research were also pointed by Looseley A, et al. In fact, there is more evidence that residents of anaesthesia experience greater stress and can be particularly vulnerable to high stress at work, burnout and depression. They conducted an anonymous electronic survey to determine the prevalence of perceived stress, the risk of burning/depression and the satisfaction of work among trainees of anaesthesia in south-western England and Wales, and examined in detail the impact of key basic characteristics, lifestyle and variables in specialization for anaesthesia. They identified 619 eligible participants and received 397 responses, a response rate of 64%. They detected a high prevalence of perceived stress; 37%, the risk of burning 25% and the risk of depression 18%, and found that these problems often occur at the same time. Some of the predictors of a bad psychological outcome were: respondents without children subject > 3 days absences due to illness in the previous year, and >7. 5 hours of seven additional non-clinical work. Although female respondents reported greater stress, the risk of burnout was more likely among male respondents (13).

In the study of Magalhães E, et al., 134 anaesthesiologists of male gender were outnumbered with (65.6%) at the age of 30-50 (67.9%). Significantly lower levels of satisfaction with job were found (47.7%), depersonalization (28.3%) and emotional exhaustion (23.1%). The burnout syndrome showed a prevalence of 10.4%, mainly in men (64.2%), aged 30-50 (64.2%), with over ten years of experience (71.4%), a sedentary lifestyle (57.1%), which was not correlated with the results of this research given the dominant male population involved in the study (14).

In a cross-sectional study conducted in 2020 on a sample of 300 anesthesiologists recruited from AAROs-EMAC subscribers in Italy, by author Vittori A, et al., 29% of individuals were assessed as having a high risk of emotional exaustion and 36% as having a moderately high risk. Depersonalization of high and moderately high risk was marked by 18.7% and 34.3% individuals respectively. The burnout in reduced personal accomplishment was evaluated in 34.7% respondents. The highest average burnout dimensions were related to job dissatisfaction, conflict situations with surgeons, and last but not least important finding hard in explaning their work to patients (15).

CONCLUSION

Based on the results of this study, it can be conclude that anesthesiologists are at a high risk of developing burnout syndrome. Various risk factors were presented in our sample and the most common were divorced or single, residents versus specialists, no on call shifts and partially female gender. The effects of burnout syndrome at work in medical profession are inexhaustible and intolerable; therefor it is assumed that prevention is an important step in reducing incidence rate of the burnout syndrome for anesthesiologists. Also a well-organized institutional strategy to mitigate the professional requirements of anesthesiologist can decrease stress and burnout rate.

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Therapeutic hypothermia and effect on blood glucose, urea and creatinine values

Terapijska hipotermija i uticaj na vrijednosti glukoze u krvi, uree i kreatinina

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ABSTRACT

Introduction: therapeutic hypothermia is a controlled lowering of body temperature for therapeutic reasons, a method of neuroprotection aimed at saving the brain tissue from irreversible damage by controlled lowering of body temperature. Hypothermia reduces the destructive processes caused by hypoxic damage by reducing the release of free radicals, stabilizing the lipid membrane, reducing the tissue's need for oxygen, reducing the release of neurotransmitters and inhibiting harmful enzymatic processes. For each degree of reduction in body temperature, the metabolic activity of the brain decreases by 6%-7%. Also, hypothermia improves the oxygenation of ischemic parts of the brain due to a decrease in cellular metabolism and lowers intracranial pressure. Aim: to determine the influence of therapeutic hypothermia on blood glucose, urea and creatinine values and to examine the outcomes of the neuroprotective effect at the cellular level, and the level of preservation of brain tissue. Materials and methods: a randomized, prospective, descriptive-analytical study was conducted at the Clinic of Anesthesia and Reanimation and the Clinic of Neurology of the Clinical Center University of Sarajevo (CCUS). The research consisted of 101 respondents divided into two groups. The first group of 40 patients was treated at the Clinic of Anesthesia and Reanimation and the second group of 61 patients at the Clinic of Neurology of the CCUS. The Clinic of Anesthesia and Resuscitation treated the patients applying the method of intensive resuscitation, including therapeutic hypothermia, and the Clinic of Neurology the method of conventional treatment. Mild systemic hypothermia and cooling of the body to a target body temperature of 34°C to 35°C was carried out from 12 to 24 hours, using the Arctic Sun hypothermia machine. Periods of hypothermia longer than 24 hours were associated with a higher risk of complications, which was the reason why hypothermia for a maximum of 24 hours was chosen for the purpose of this research. Results: a non-invasive t-test in the group of respondents who underwent hypothermia established that the values of blood glucose increased; they decreased from admission to discharge, and that decrease was statistically significant (p=0.003), while urea values from admission to discharge varied, but were not statistically significant (p=0.371). Creatinine values from admission to discharge decreased, which was not statistically significant (p=0.371). Conclusion: values of glucose, urea and creatinine on admission correlated with the level of brain cell damage. Therapeutic hypothermia has a neuroprotective effect so it is necessary to approach the acute phase of treatment as soon as possible, to prevent complications and damage at the cellular level.

Keywords: hypothermia, stroke, metabolism, therapy

SAŽETAK

Uvod: terapijska hipotermija je kontrolirano snižavanje tjelesne temperature iz terapijskih razloga i metoda je neuroprotekcije koja pokušava spasiti moždano tkivo od ireverzibilnog oštećenja kontroliranim snižavanjem tjelesne temperature. Hipotermija smanjuje destruktivne procese uzrokovane hipoksičnim oštećenjem tako što smanjuje oslobađanje slobodnih radikala, stabilizira lipidnu membranu, smanjuje potrebu tkiva za kisikom, smanjuje oslobađanje neurotransmitera i inhibira štetne enzimske procese. Za svaki stepen smanjenja tjelesne temperature, metabolička aktivnost mozga se smanjuje za 6%-7%. Također, hipotermija poboljšava oksigenaciju ishemijskih dijelova mozga zbog smanjenja staničnog metabolizma i snižava intrakranijalni tlak. Cilj: utvrditi uticaj terapijske hipotermije na vrijednosti glukoze u krvi, uree i keratinina i spitati ishode neuroprotektivnog efekta na nivou ćelije, i očuvanja moždanog tkiva. Materijali i metode: provedeno je randomizirano, prospektivno, deskriptivno-analitičko istraživanje, na Klinici za anesteziju i reanimaciju i Klinici za neurologiju Kliničkog centra Univerziteta u Sarajevu. Istraživanje je uključilo 101 ispitanika podijeljenih u dvije grupe. Prva grupa od 40 pacijenata je bila liječena na Klinici za anesteziju i reanimaciju, a druga od 61 pacijenta je bila liječena na Klinici za neurologiju KCUS-a. Na Klinici za anesteziju i reanimaciju primjenjivala se metoda intenzivnog reanimacionog liječenja uključujući terapijsku hipotermiju, a na Klinici za neurologiju metoda konvencionalnog liječenja. Blaga sistemska hipotermija i hlađenje tijela na ciljanu tjelesnu temperature od 34°C do 35°C se provodila od 12 do 24 sata, pomoću Arctic Sun mašine

za hipotermiju. Periodi hipotermije duži od 24 sata udruženi su sa većim rizikom od komplikacija, te je zbog toga za ovo istraživanje izabrana hipotermija u trajanju od maksimalno 24 sata. Rezultati: neinvazivnim t-testom u grupi ispitanika koji su podvrgnuti hipotermiji utvrđeno je da su vrijednosti ŠUK-a bile povišene; od prijema do otpusta su padale, i taj pad je statistički značajan (p=0,003), dok su se vrijednosti ureae od prijema do otpusta mjenjale, a promjena nije bila statistički značajna (p=0,371). Vrijednosti kretinina od prijema do otpusta su padale što nije bilo statistički značajno (p=0,371). Zaključak: vrijednosti glukoze, uree kreatinina pri prijemu koreliraju sa nivom oštećenja moždane ćelije. Terapijska hipotermija djeluje neuroprotektivno i neophodno je što prije pristupiti akutnoj fazi liječenja, spriječiti komplikacije i oštećenja na ćelijskom nivou.

Ključne riječi: hipotermija, moždani udar, metabolizam, terapija

INTRODUCTION

Stroke (cerebrovascular insult) is a focal or global disorder of brain function which occurs suddenly, as a result of cerebral circulation disorders and changes in blood vessels, when blood flow is not sufficient to meet the brain's metabolic needs for oxygen and glucose. Interruption of blood flow leads to disruption of brain metabolism and disruption of neuron function (1).

There are two types of stroke; ischemic and hemorrhagic. Ischemic stroke occurs as a result of occlusion of a blood vessel by thrombus or embolus, it is more common, has better prognosis and occurs in 80% to 85% of cases.

By its type hemorrhagic stroke can be of intracerebral or subarachnoid, it is more severe than ischemic stroke, has a higher mortality rate and occurs in 15 to 20% of cases.

In a stroke, blood flow to a certain part of the brain is reduced or interrupted, resulting in dysfunction of the brain tissue in the affected area (2).

Progressive cell destruction occurs which includes ischemic neural cascade and the process of apoptosis, specifically the brain cell death. The brain uses glucose and oxygen for its functioning. With the brain damage of any etiology, there is not enough oxygen supply to the brain, and the glucose that was dissolved in the process of aerobic glycolysis is now dissolved in the process of anaerobic glycolysis resulting in progressive cell destruction, ischemic neural cascade and the process of apoptosis, specifically the brain cell death (3).

Therapeutic hypothermia as a modern method of treatment has the basic function of improving the metabolism of those cells that are in the immediate vicinity of the focus, which represents a controlled decrease in body temperature for therapeutic reasons. It has become increasingly frequent as a therapeutic option and is one of the most challenging treatments that improve the neurological recovery and treatment outcome of patients with acute stroke (4).

With the progress of medicine, there are also new fundamental discoveries of neuroprotective treatments in the acute stroke cure, which could be of great importance for understanding its pathogenesis and the treatment of patients. Therapeutic hypothermia is a controlled lowering of body temperature for therapeutic reasons, a method of neuroprotection attempting to save the brain tissue from irreversible damage by controlled lowering of body temperature (5).

There are no energy reserves in the brain, except for a small amount of glycogen in astrocytes, thus the cessation of blood flow in the brain leads to brain function damage. In aerobic conditions, when there is enough oxygen, glucose is oxidized to water and CO2, creating ATP as a product of aerobic glucose metabolism. Oxidation of one molecule of glucose produces 6 molecules of CO2 and 6 molecules of water, with the consumption of 6 molecules of oxygen.

Ischemic brain damage is the result of a complex series of events caused by a temporary or permanent reduction in blood flow to the brain. Cerebral ischemia occurs due to interruption of circulation at least in one part and to such an extent that the supply of oxygen and glucose to the brain is inadequate, whereby the cell becomes dependent on the anaerobic production of ATP. Cerebral ischemia triggers a series of events that ultimately lead to cell death, including ATP consumption, changes in sodium, potassium, and calcium ion concentrations, increased lactate, acidosis, accumulation of free radicals, intracellular water accumulation, and activation of proteolytic processes (6).

Any acute circulatory failure that causes insufficient supply of oxygen and glucose to the brain leads to brain damage. Ischemia causes a cascade of events including depletion of energy phosphate compounds i.e. ATP, dysfunction of the Na/K ion pump, release of free radicals, glutamate and calcium (7).

These harmful processes are more expressed if the body temperature rises, given that the production of free radicals and glutamate is proportional to the body temperature. Hypothermia reduces the destructive processes caused by hypoxic damage by reducing the release of free radicals, stabilizing the lipid membrane, reducing tissue demand for oxygen, reducing the release of neurotransmitters, and inhibiting harmful enzymatic processes. For each degree of Celsius reduction in body temperature, the metabolic activity of the brain decreases by 6%-7%. Furthermore, hypothermia improves oxygenation of ischemic parts of the brain due to a decrease in cellular metabolism, and lowers intracranial pressure. There are numerous favorable hemodynamic effects of hypothermia: pulse frequency decreases, systemic vascular resistance increases, stroke volume and arterial pressure are stabilized. Reduced metabolism requires a reduced need for oxygenation and facilitates patient ventilation.

Therapeutic hypothermia after ischemia should be started as soon as possible, given that longer periods of hypothermia are better than shorter ones.

Mitochondria within the cell are in a constant dynamic state, constant fission and fusion, thus creating mitochondrial networks that help maintain cell function and cell survival (8,9). Therapeutic hypothermia attenuates ischemia-induced mitochondrial dysfunction.

MATERIALS AND METHODS

This was a randomized, prospective, descriptive-analytical study conducted at the Clinic of Anesthesia and Reanimation and the Clinic of Neurology of the Clinical Center University of Sarajevo (CCUS).

The research was conducted on two groups of respondents. The first group of 40 patients was treated at the Clinic of

Anesthesia and Reanimation, and the second group of 61 patients at the Clinic of Neurology of the CCUS. The Clinic of Anesthesia and Resuscitation treated the patients applying the method of intensive resuscitation, including therapeutic hypothermia, and the Clinic of Neurology used conventional treatment.

Mild systemic hypothermia and body cooling to a targeted body temperature from 34°C to 35°C was carried out from 12 to 24 hours, using the Arctic Sun hypothermia machine. Periods of hypothermia longer than 24 hours were associated with a higher risk of complications, which was why hypothermia for a maximum duration of 24 hours was chosen for this study. In order to speed up the onset of hypothermia, cold infusion solutions of 0.9% NaCl or Ringer's lactate at a temperature from 4°C to 12 degrees, were prescribed immediately during the first hour. In the first 60 minutes solutions for infusion at 4°C were given to intubated patients and up to 12°C to non-intubated patients. This fluid volume is well tolerated in both cardiac arrest and ICV patients.

Vital parameters were monitored in all stroke patients subjected to hypothermia: blood pressure values, pulse, oxygen saturation SaO2, acid-base status ABS, blood sugar, urea creatinine, respiratory rate with continuous ECG monitoring. Patients treated with hypothermia had a continuous transesophageal temperature measurement using an esophageal probe, before prescribed therapy, every 15 minutes for the first three hours, and then every 60 minutes. Following the treatment phase, the temperature was measured every 8 hours until discharge.

The Arctic Sun® device is used for therapeutic hypothermia. It is an advanced, non-invasive technique that allows chilled water to circulate in external cooling systems - pads - lowering the patient's body temperature to between 34°C and 35°C, inducing mild hypothermia.

It is intended for use in adults with the aim of inducing mild hypothermia in order to reduce brain damage and improve neurological outcomes. As recommended by the European Resuscitation Council and the guidelines of the European Society for Intensive Care, mild hypothermia is induced as soon as possible after the patient's admission. The Actic Sun device has three operation phases: induction or introduction to hypothermia, maintenance of hypothermia, gradual warming up to 36°C.

RESULTS

In the study of patients with acute stroke, 44 of them were male and 57 female.

Out of the total number of respondents with acute stroke, 91 had ischemic and 10 respondents had hemorrhagic stroke.

Out of the total number of patients hospitalized for acute stroke, 40 were treated with therapeutic hypothermia in addition to standard therapy at the Clinic of Anesthesia and Reanimation, while 61 patients were treated at the Clinic of Neurology of the CCUS, using a standard protocol without hypothermia.

Table1 **Average blood glucose, urea and creatinine values in relation to the examined groups.**

Biochemical findings	Hypothermia	Mean	Std. D.	Std. Error Mean	p
Blood glucose mmol/l	YES	10.99	5.56	0.94	0.149
	NO	9.35	5.07	0.67	
Urea mmol/l	YES	9.07	6.02	1.02	0.792
	NO	8.79	4.49	0.58	
Cr mmol/l	YES	143.11	39.46	13.57	0.059
	NO	95.17	34.81	7.14	

An independent t-test showed that there was no difference in the values of blood glucose on admission in respect of the relevant group, regardless of hypothermia, p=0.149.

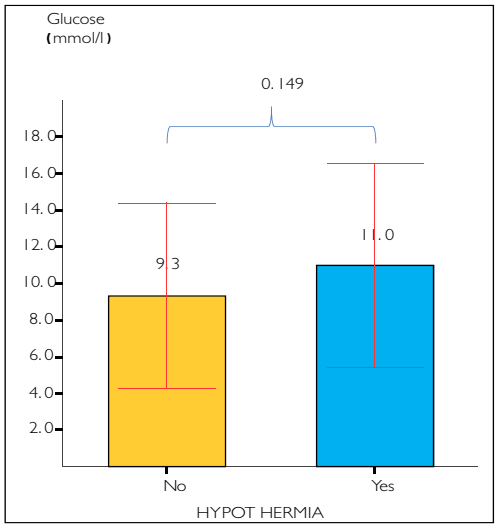

Figure 1 **Blood glucose values in relation to the examined group.**

In the group with hypothermia, the respondents had an average blood glucose level of 10.99±5.66 mmol/L on admission. In the group of respondents treated without hypothermia the blood glucose level was 9.35±5.07mmol/L. Respondents in both groups had hyperglycemia on admission. On admission hyperglycemia was present in both groups of patients, increased blood sugar values were present in both patients who underwent hypothermia and in those who did not.

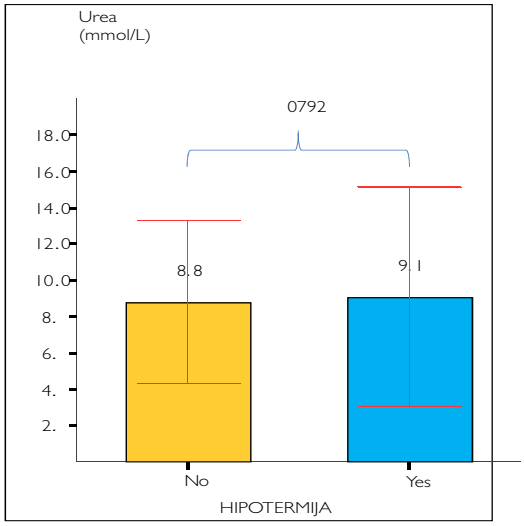

Figure 2 **Urea values in relation to the examined group.**

An independent t-test showed that there was no difference in the values of urea in the respondents on admission in relation to the relevant group, regardless of hypothermia, p=0.792. In the group with hypothermia, the respondents had an average urea value of 9.07±6.02 mmol/L on admission. In the group of respondents without hypothermia the average value of urea was 8.79±4.49 mmol/L. The value of urea was slightly increased in both groups of patients on admission.

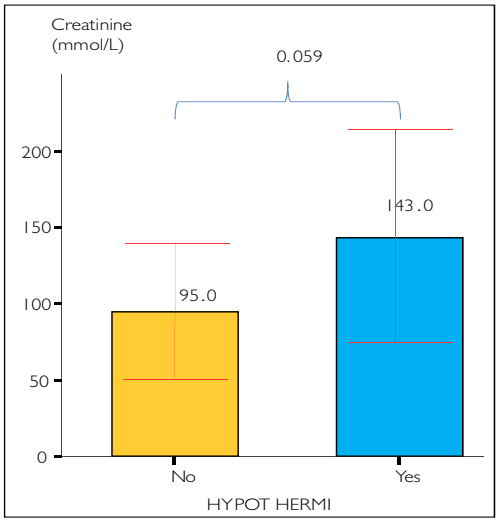

Figure 3 **Creatinine values in relation to the examined group.**

In the group treated with hypothermia, the average creatinine values in respondents on admission were above the reference values, 143.11±139.43 mmol/L. In the group of respondents treated without hypothermia the average values of creatinine were 95.17±54.81 mmol/L. On admission, creatinine values were increased in the group of respondents exposed to hypothermia.

Table 2 **Blood glucose levels in respondents with acute stroke with and without hypothermia, on admission, after 24 hours and on discharge.**

					Percentiles		Friedman (χ^2)
Hypothermia NO	Time	Min.	Max.	25th	50th (Median)	75th	p
Blood glucose mmol/L	On admission	2.50	28.60	6.00	7.60	10.80	
	First check-up	6.00	6.50	6.08	6.40	6.50	0.333
	On discharge	4.50	14.10	5.98	7.10	8.08	
Hypothermia YES							
Blood glucose mmol/L	On admission	4.80	28.30	6.50	9.00	14.20	
	First check-up	3.10	15.10	5.15	6.55	9.45	0.003
	On discharge	3.70	11.60	4.38	5.00	7.13	

In the group of respondents who underwent hypothermia, the values of blood glucose decreased from admission to discharge, but the decrease was not statistically significant, p=0.333

Average blood glucose values on admission were 7.6 (6.0-108) mmol/l, 6.4 (6,08-6,5) mmol/l at first check-up and 7.1 (5.98-8.08) mmol/l on discharge.

In the group of respondents who underwent hypothermia the values of blood glucose decreased from admission to discharge, and the decrease was statistically significant, p=0.003.

In this group of respondents the average blood glucose values on admission were 9.0 (6.5-14.20) mmol/l, 6.54 (5.15-9.45) mmol/l at first check-up and 5.0 (4.38-7.16) mmol/l on discharge. Therapeutic hypothermia lowered increased blood sugar values, from admission to discharge, which was statistically significant.

Table 3 **Urea values in respondents with acute stroke with or without hypothermia, on admission, after 24 hours and on discharge.**

					Percentiles		Friedman (χ^2)
Hypothermia NO	Time	Min.	Max.	25th	50th (Median)	75th	p
Urea mmol/l	On admission	3.3	25.0	5.800	8.00	10.60	
	First check-up	7.0	28	6.80	11.10	27.80	0.564
	On discharge	2.5	25.2	4.725	6.65	9.52	
Hypothermia YES							
Urea mmol/L	On admission	0.6	24.0	4.300	6.60	11.70	
	First check-up	3.0	33	5.20	11.30	14.50	0.371
	On discharge	2.6	33.0	3.90	5.10	12.90	

In the group of respondents who did not undergo hypothermia, the values of urea from admission to discharge varied, but the change was not statistically significant, p=0.564.

Average urea values on admission were 8 (5.8-10.6) mmol/l, on the rise at the first check-up11.10 (6.8-27.8) mmol/l, and in referent values on discharge, 6.65 (4.72-9.52) mmol/l.

In the group of respondents subjected to hypothermia, values of urea varied from admission to discharge, but the that change was not statistically significant, p=0.371.

In this group of respondents, the average urea values on admission were 6.6 (4.3-11.7) mmol/l, on rise at the first check-up, 11.3 (15.2-14.5) mmol/l, and in referent values on discharge 5.1 (3.9-12.9) mmol/l. Urea values were slightly increased in both groups of respondents on admission, whereas they were within the reference values at discharge.

Table 4 **Creatinine values in respondents with acute stroke with or without hypothermia, on admission, after 24 hours and on discharge.**

					Percentiles		Friedman (χ^2)
Hypothermia NO	Time	Min.	Max.	25th	50th (Median)	75th	p
Creatinine mmol/l	On admission	45	400	60.00	83.00	115.00	0.564
	First check-up	84	222	84.00	92.00	222.00	
	On discharge	41	97	54.00	63.00	85.75	
Hypothermia YES							
Creatinine mmol/l	On admission	41	705	65.00	101.00	152.00	0.371
	First check-up	44	852	60.00	77.00	147.00	
	On discharge	24	603	46.00	71.00	145.00	

In the group of respondents who did not undergo hypothermia the values of creatinine from admission to discharge varied, but the change (increase-decrease) was not statistically significant, p=0.564.

Average creatinine values on admission were 83.0 (60-115) mmol/l, 92.0 (84.0-222.0.5) mmol/l at first check-up, and within reference values on discharge, 63.0 (54.0-85.75) mmol/l.

In the group of respondents who underwent hypothermia, creatinine values decreased from admission to discharge.

In this group of respondents the average creatinine values on admission were 101.0 (65.0-52.0) mmol/l. On second check-up, the creatinine values decreased to 77.0 (60.0-147.0) mmol/l, and at the time of discharge, the average values were 71.0 (46.0-145) mmol/l. Patients who underwent hypothermia had increased creatinine values on admission, which were brought to reference values on discharge.

DISCUSSION

Despite the application of modern therapy and the extremely rapid development of medical science, it is necessary to continue working on neuroprotective clinical research.

The research consisted of 101 respondents divided into two groups. The first group of 40 patients was treated at the Clinic of Anesthesia and Reanimation and the second group of 61 patients at the Clinic of Neurology of the CCUS. The Clinic of Anesthesia and Reanimation treated the patients applying the method of intensive resuscitation, including therapeutic hypothermia, and the Clinic of Neurology the method of conventional treatment. Out of the total number of respondents with acute stroke 40 respondents were subjected to therapeutic hypothermia at the Clinic of Anesthesia and Reanimation whereas 61 patients were treated at the Clinic of Neurology applying standard protocol without therapeutic hypothermia.

According to the Framingham study (10), ischemic stroke accounts for 75% of cases. In our study, there were 90% of patients with ischemic stroke. Our results were consistent with the research of Nahlae, et al. from 2018, who stated that about 87% of strokes occured as a result of ischemic cerebral infarction, and 13% of strokes as a result of hemorrhage (6). Patients from both groups had hyperglycemia. Diabetes mellitus is also one of the major risk factors for the development of a stroke, but hyperglycemia can also be explained by the state of body stress during the stroke development.

According to the study of Arboix A from 2015 (11), high blood pressure and diabetes are the main risk factors for the recurrence of lacunar infarction. That study describes that lacunar infarcts account for 20-25% of all acute strokes. Hypothermia affects the metabolism of glucose and insulin. Therapeutic hypothermia reduces insulin secretion causing insulin resistance in tissues. Consequently, in order to maintain normoglycemia in diabetics, higher doses of insulin are required during hypothermia. When warming up the patient, the reverse process is possible, therefore insulin doses should be reduced as a preventive measure in avoid hypoglycemia.

In our study, hyperglycemia was present in both groups, glycemic values in patients subjected to hypothermia decreased from admission to discharge, which could be explained by intensive glycemic control and the timely inclusion of crystalline insulin in cases of higher increases in glycemia. During hypothermia, larger doses of crystalline insulin were given to correct glycemia, and during warming up, the dose was reduced by half. The drop in sugar values was statistically significant in subjects exposed to hypothermia.

Creatinine values on admission were on average higher in patients exposed to hypothermia compared to patients not exposed to hypothermia, from which it can be concluded that patients subjected to hypothermia had a more severe general condition, more severe kidney damage and more expressed generalized atherosclerotic changes in blood vessels. Creatinine values were increased on admission in the group of patients exposed to hypothermia, but values dropped from admission to discharge to reference values. Urea values were slightly elevated in both groups, and they decreased from admission to discharge

Therapeutic hypothermia using various methods of superficial and complete cooling helps with brain ischemia, including cerebral ischemia due to cardiac arrest and hypoxic ischemic encephalopathy. Understanding the protective role of therapeutic hypothermia may improve efforts to reduce brain damage after stroke.

Hypothermia initiated during acute stroke reduces infarct size and alleviates functional damage and is one of the most promising stroke therapies. Numerous studies have clarified its mechanisms and proved its strong neuroprotection. A multiple mechanism of action is considered to contribute to the powerful therapeutic effect (5). Therapeutic hypothermia has a beneficial effect on metabolism, on cell metabolism, and it lowers increased values of blood sugar, urea and creatinine. It is necessary to apply therapeutic hypothermia as early as possible, in the acute phase of the disease.

CONCLUSION

Therapeutic hypothermia and intensive resuscitation therapy will have a better treatment outcome, reduction of irreversible damage to brain structures and acute stroke. The basic aim and contribution of therapeutic hypothermia is its application to brain cell metabolism. The protective action is reflected in the preservation of brain function and degree of brain tissue damage. It is necessary to approach the acute phase of stroke treatment as soon as possible using therapeutic hypothermia as the most comprehensive treatment method in preventing brain damage and preserving brain functions. The beneficial effect of hypothermia on cell metabolism is of great importance for the patient's recovery, and it should be applied in the acute phase of the disease.

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Predictors of re-amputation after major lower limb amputations in patients with peripheral arterial disease

Prediktori reamputacije nakon „major“ amputacija kod pacijenata sa perifernom arterijskom bolešću

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ABSTRACT

Introduction: amputation of the lower limb is an unwanted, but not the final outcome of treatment in patients with peripheral arterial disease. Unfortunately, a certain number of patients have local complications that indicate re-amputation, which significantly increases morbidity and mortality. Until some time ago, it was considered that a wrong assessment in planning the level of amputation was the only reason for re-amputation, but in practice it is shown that there are additional risk factors that can be marked as predictors of re-amputation. Aim: to determine risk factors that have a direct or indirect impact on the occurrence of local complications, which will ultimately result in re-amputation. Materials and methods: research was designed as prospective collection of variables, and subsequently, according to the model of a cohort study, a retrospective analysis of the data of patients hospitalized in the Clinical Center of the University of Sarajevo between January 2021 and December 2022 was performed. Results: the sample consisted of 165 patients who underwent below-the-knee or above-the-knee amputation. Out of that number, 65 (39.4%) patients were female and 100 (60.6%) were male patients. The average age was 70.92 (±10.95) years. The age range was 29-90 years. Re-amputation was performed in a total of 54 (32.7%) subjects, namely in 36 (32.4%) subjects who underwent below-the-knee amputations, and in 18 (33.3%) patients who underwent above-the-knee amputations. Conclusion: as predictors that carry the significantly highest risk of re-amputation are records of diabetes (p=0.012), hyperlipidemia (p=0.001), smoking addiction (p=0.001), and stump trauma (p=0.045).

Keywords: lower limb amputations, re-amputations, PAD

SAŽETAK

Uvod: amputacija donjeg ekstremiteta je neželjeni, ali ne i konačni ishod liječenja kod pacijenata s perifernom arterijskom bolešću. Nažalost, određeni broj pacijenata ima lokalne komplikacije koje ukazuju na reamputaciju, što značajno povećava morbiditet i mortalitet. Do prije izvjesnog vremena se smatralo da je pogrešna procjena u planiranju nivoa amputacije jedini razlog za reamputaciju, ali se u praksi pokazuje da postoje dodatni faktori rizika koji se mogu označiti kao prediktori reamputacije. Cilj: utvrditi faktore rizika koji imaju direktan ili indirektan uticaj na nastanak lokalnih komplikacija, što će u konačnici rezultirati reamputacijom. Materijali i metode: istraživanje je osmišljeno kao prospektivno prikupljanje varijabli, a zatim, prema modelu kohortne studije, provedena je retrospektivna analiza podataka pacijenata koji su bili hospitalizirani u Kliničkom centru Univerziteta u Sarajevu u periodu od januara 2021. do decembra 2022. Uzorak se sastojao od 165 pacijenata koji su podvrgnuti potkoljenoj ili natkoljenoj amputaciji. Rezultati: 65 (39,4%) pacijenata su bili ženskog, a 100 (60,6%) pacijenata muškog spola. Prosječna starost je bila 70,92 (±10,95) godina. Starosni raspon je bio 29-90 godina. Reamputacija je izvršena kod ukupno 54 (32,7%) ispitanika, i to kod 36 (32,4%) ispitanika koji su podvrgnuti potkoljenoj amputaciji i 18 (33,3%) pacijenata koji su podvrgnuti natkoljenoj amputaciji. Zaključak: kao prediktori koji ubjedljivo nose značajan rizik od reamputacije su evidencija dijabetesa (p=0,012), hiperlipidemije (p=0,001), zavisnosti od pušenja (p=0,001) i traume bataljka (p=0,045).

Ključne riječi: amputacija donjih ekstremiteta, reamputacija, PAD

INTRODUCTION

Lower limb amputation is an unwanted outcome in the treatment of peripheral arterial disease. The total annual number of non-traumatic amputations in the USA is maintained at a level of about 150,000 per year (1). Despite numerous scientifically based approaches to peripheral vascular disease, it seems that the problem still exists, and along with it, the level of complications is

maintained. The most common local complications are ischemia, infection, and dehiscence, each of which correlates with re-amputation and significantly affects morbidity and mortality. Advances in the diagnosis and treatment of peripheral vascular disease and soft tissue infections have greatly influenced the fact that a significant number of patients are treated with ,,minor'' amputations that do not significantly disable them or affect statics and mobility. Unfortunately, the number of disabling - "major" amputations, which means below-the-knee and above-the-knee amputations, is still high (2).

Patients with limb loss are going to face this fact for the rest of their lives. Unfortunately, this is not the only problem, because in the postoperative period there is a danger of the cumulative effect of the combination of all co-morbid conditions, which can directly threaten life. It is estimated that postoperative complications following a below knee amputation are the cause of in-hospital death in 9% of those operated on, while this percentage is twice as high (18%) in patients who underwent an above knee amputation. Also, it is believed that more than two-thirds of patients with maior amputation will not survive the next five years (3,4).

Inadequate assessment in determining the level of amputation has long been indicated as the sole reason for re-amputation. Today, there is more and m ore evidence that there are other factors that can be predictors of re-amputation. Determining the level of amputation is based on objective parameters such as assessment of tissue vitality and quality at the planned level, degree of development of collateral blood vessels, co-morbid conditions such as diabetes, type of infection, pre-existing diseases of the vascular and cardiopulmonary apparatus, etc. Nevertheless, even after a good assessment, it sometimes happens that, under the influence of certain risk factors, the local status of the amputation stump indicates re-amputation (5).

AIM

The aim of this paper was to determine risk factors that had a direct or indirect influence on the occurrence of local complications, which would ultimately result in re-amputation, and to point out to amputation as a major medical and social problem.

MATERIALS AND METHODS

The plan of the research procedure was designed through the prospective collection and selection of variables, and subsequently, according to the model of a cohort study, a retrospective analysis of the data of a total of 216 patients hospitalized in the Clinical Center of the University of Sarajevo between January 2021 and December 2022 was performed. After the exclusion factors were taken into account, a final sample of 165 patients was obtained. The sample consisted of patients who, after exhausting vascular-surgical and angiology options in the treatment of peripheral arterial disease, underwent below knee or above knee amputation. Out of that number, 65 (39.4%) patients were female and 100 (60.6%) were male patients. The average age was 70.92 (±10.95) years. The age range was 29-90 years. The following elements were selected as basic variables: age, sex, type of anesthesia, presence of hypertension, hyperlipidemia, diabetes, active smoking addiction, chronic renal insufficiency, chronic obstructive pulmonary disease, and condition after stroke. As a final outcome - the focus is on the absolute and relative representation of the number of patients who underwent re-amputation. Statistical analyzes determined the influence of variables on the incidence of re-amputations in the group of patients with primary below knee amputation and in the group of patients with primary above knee amputation.

Basic characteristics were collected and presented as number of cases and percentage representation. Categorical values were analyzed with the $\chi 2$ test and Fisher's test. Student's T-test and Mann-Whitney U test were used to analyze quantitative values. A multivariate logistic regression was performed to assess the association between individual factors and postoperative complications. Statistical hypotheses were tested at the level of $\alpha=0.05$, i.e. the difference between the samples was considered significant if $p<0.05$. Statistical analyzes were performed using IBM SPSS Statistics ver. 21.0.

RESULTS

The gender distribution shows that the majority of the sample is filled by male patients with participation slightly less than 2/3. This result is justified by the fact that all risk factors for the occurrence of peripheral blood vessel disease are more common in the male population. The choice of anesthesia was adapted to the local findings and the general condition of the patient, and it is evident that above knee amputations and re-amputations were performed

Table 1 **Demographic data and comorbidity of patients.**

Variables (n=165)	Total (n=111; 63.3%)	BKA group (n=54; 32.7%)	AKA group	P
Age, years (SD)	70.92±10.95	69.82±10.93	73.19±10.74	0.051
Gender				0.672
Male	100 (60.6%)	42 (37.8%)	31 (57.4%)	
Female	65 (39.4%)	69 (62.7%)	23 (42.6%)	
Anesthesia				**0.031***
Spinal	15 (9.1%)	15 (13.5%)	0	
GEA	150 (90.9%)	96 (86.5%)	54 (100%)	
HTA	107 (64.8%)	65 (58.6%)	42 (77.8%)	**0.024***
Diabetes	131 (79.4%)	90 (81.1%)	41 (75.9%)	0.573
HLP	88 (53.3%)	58 (52.3%)	30 (55.6%)	0.816
Smoking	59 (35.8%)	39 (35.1%)	20 (37%)	0.947
Hemodialysis	8 (4.8%)	7 (6.3%)	1 (1.9%)	0.275
HOPD	31 (18.8%)	16 (14.4%)	15 (27.8%)	0.064
St.post ICV	8 (4.8%)	5 (4.5%)	3 (5.6%)	0.717
Tumor	10 (6.1%)	5 (4.5%)	5 (9.3%)	0.298
Re-amputation	54 (32.7%)	36 (32.4%)	18 (33.3%)	0.978
Trauma	4 (2.4%)	3 (2.7%)	1 (1.9%)	0.967

GEA- General anesthesia, HTA-Hypertension, HLP- hiperlipidemia, HOPB-chronic obstructive pulm. disease

As shown in Table 1, even 79% of patients suffered from diabetes. Almost 2/3 of patients (64.8%) were registered hypertensive, and more than 1/3 (35.8%) of them were active in smoking adiction with chronic obstructive pulmonary disease (18.8%). A statistically significant difference was recorded in the representation of hypertensive patients in the group of subjects undergoing below knee amputation (77.8%) p=0.024. In addition to extremity and coronary artery disease, blood vessel diseases were also registered in other organ systems. In the total sample, 8 (4.8%) patients had renal-vascular disease with chronic renal insufficiency, and an additional 8 (4.8%) patients had cerebral-vascular disease with various forms of consequent neurological outcomes. In 4 (2.4%) patients, the trauma of the amputated stump was recorded in the immediate postoperative period, and the injury itself required re-amputation. Re-amputation was performed in a total of 54 (32.7%) subjects; in 36 (32.4%) subjects who underwent below-the-knee amputations, and 18 (33.3%) patients who underwent above-the-knee amputations. In 152 subjects (92.12%), a combination of several associated co-morbid conditions was recorded.

Table 2 **Predictors of local complications after maior amputations.**

	OR	(95% CI)	P
Diabetes	0.112	(0.020 – 0.615)	**0.012**
HLP	0.024	(0.005 – 0.106)	**0.001**
Smoking	0.083	(0.026 – 0.265)	**0.001**
Trauma	0.045	(0.002 – 0.095)	**0.045**

After analyzing the data, it was determined that diabetes, hyperlipidemia, smoking addiction, and stump trauma were the greatest risk for re-amputation (Table 2). All examined variables showed statistical significance, and could be considered as strong predictors for re-amputation. Further analysis revealed that the combination of the four listed conditions could be considered as an undoubted predictor for re-amputation.

DISCUSSION

Inadequate assessment in determining the level of amputation has long been indicated as the sole reason for re-amputation. Today, there is more and more evidence that there are other factors that can be predictors of re-amputation. The indication and determination of the level of amputation is now based on the observation of objective parameters such as assessment of vitality and tissue quality at the planned level, degree of development of collateral blood vessels, co-morbid conditions such as diabetes, type

of infection, pre-existing diseases of the vascular and cardiopulmonary apparatus, etc. Nevertheless, even after a good assessment, it often happens that, under the influence of certain risk factors, the local status of the amputation stump indicates re-amputation (6).

Czerniecky JM, et al., from the War Veterans Hospital in Seattle (USA) published a report from a ten-year study devoted to the risks of ipsilateral reamputation after primary "major" amputation of the lower extremity. The main result of that study indicated that one quarter of patients (24.4%) underwent re-amputation within 12 months of the primary amputation. For this purpose, a model is offered that highlights 11 predictors/risk factors for re-amputation. Among the leading predictors is the level of primary amputation, which may suggest an unjustified assessment of the functional capacity of collateral blood vessels that participate in the perfusion of the amputated stump, or an individual design in the performance of the procedure (7).

A similar study was published in Sweden and, in addition to the aforementioned predictors, highlighted non-healing ulcer and ischemic pain as the main cause for re-amputation. The same refers to the correct assessment of other risk factors (8).

Information that are coming from the recent literature directed our research towards looking at the problem of re-amputation from several angles. Taking into account the extended list of possible variables, we expected that diabetes and smoking might take the leading place in the list of risk factors for re-amputation. A group of researchers from the Center for the Mobility of Amputees in Seattle, USA, showed an extended interest in identifying risk factors. In their research, a wide list of independent variables was taken into account, and among others, alcohol abuse, vascular reoperations, leukocytosis and pedal-brachial index were included in the analysis. The research identified the same risk factors that were highlighted in our research as dominant predictors of re-amputation (9).

In the conclusion of the report published as an review of several separate studies that addressed the risks for amputation and re-amputation, it was pointed out that long-term diabetes, neuropathy, positive smoking history are strong predictors of re-amputation procedures (10).

According to reports from research conducted in the Asian population, the risk factors of re-amputation are dialysis, obesity and excessive use of alcoholic beverages. That means that investigated predictors were the same as in our sample. The main reason for the primary amputation was certainly peripheral arterial disease, but in more than half of the patients with risk-factors that are mentioned, dehiscence of the operative wound occurred and re-amputation followed (11). A multicentre study conducted on over 5,000 subjects by a group of authors from the USA, Israel and the Netherlands considered the problem of readmission of patients, their local and systemic complications. Advanced age, hyperlipidemia, septic condition of the wound, cardio-pulmonary co-morbidities, and surgical technique are the main predictors of re-amputation in the first 30 postoperative days after lower leg amputations. In conclusion, this report states that in 1/5 of patients undergoing lower leg amputation, re-amputation can be expected under the influence of the investigated predictors (12).

An international study conducted under the supervision of an expert team from Baltimore, USA, also confirms the presence of identical risk factors (renal insufficiency, peripheral arterial disease and smoking addiction) that can be called predictors of re-amputation in patients undergoing amputation of the lower limb in a period shorter than 60 days after the primary amputation (13).

A positive history of lower limb amputation and re-amputation was associated with advanced diabetic nephropathy, generalized atherosclerosis and in a study conducted at the University Hospital of Paris (14).

In our research, the conclusion of the aforementioned study was confirmed and a significant influence of diabetes, hyperlipidemia, and a positive history of smoking on the incidence of re-amputation was determined.

CONCLUSION

Predictors that carry the significantly highest risk of re-amputation are records of diabetes, hyperlipidemia, smoking addiction, and stump trauma.

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Difference of P100 latency parameters in patients with schizophrenia and migraine headache using visual evoked potentials (VEPs)

Razlike u parametrima P100 latencija kod oboljelih od shizofrenije i migrenozne glavobolje primjenom vizuelno evociranih potencijala (VEP)

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ABSTRACT

Introduction: schizophrenia is today accepted as a neurobiological disorder with strong neurocognitive components, and neuropsychological research is based on determining the specificity of neurocognitive patterns, which contributes to clarifying the neuroanatomical and neuropsychological systems underlying the disease, making a clinical contribution to the development of more effective rehabilitation measures. While cognitive dysfunction, including memory and attentional deficits, are well known in schizophrenia, basic sensory processing deficits are evident too. A primary approach to analyzing integrity of visual processing is the use of visual evoked potentials (VEPs). The VEPs have the advantage that they are nonbehavioral and so provide an objective measure of brain function. Visual evoked potentials (VEPs) abnormalities have been a fairly consistent finding in patients with schizophrenia, and these highlight the importance of sensory processing deficits, in addition to higher cognitive dysfunction, for understanding the pathophysiology of schizophrenia. Aim: to determine the difference of P100 latency parameters in patients with schizophrenia and migraine headache using visual evoked potentials (VEPs). Materials and methods: this was a prospective, comparative study conducted at the Clinic of Psychiatry and Clinic of Neurology of the Clinical Center University of Sarajevo (CCUS) and it included 80 patients of both sexes, from 21 to 67 years of age, classified into two groups. Results: multivariate analysis of variance was used to examine whether there is a statistically significant difference in the latency parameters of the P100 wave between the observed and control groups. The results indicate that there is a statistically significant difference in the latency parameters of the P100 wave-prolongation, the entire visual field of both eyes, the entire visual field-left eye, the right visual field-left eye, the left visual field-left eye in the group of patients with schizophrenia compared to the control group of respondents. Conclusion: little is known about the association of schizophrenia with the occipital lobe or whether the visual symptoms exacerbate if the occipital lobe is severely damaged is not yet known. Our study is useful to initiate new questions and recommendations for further studies, specifically on changes in the occipital lobe in the schizophrenic patient's brain.

Keywords: visual pathway, schizophrenia, migraine headache, VEPs

SAŽETAK

Uvod: shizofrenija se smatra neurobiološkim poremećajem sa jakim neurokognitivnim komponentama, a neuropsihološka istraživanja se zasnivaju na utvrđivanju specifičnosti neurokognitivnih obrazaca, odnosno neuroanatomskoj osnovi bolesti i kreiranju efikasnijih mjera rehabilitacije. Dok je kognitivna disfunkcija, uključujući deficit pamćenja i pažnje, dobro poznata kod shizofrenije, evidentano je oštećenje bazičnog senzornog procesuiranja. Analiza integriteta vizuelne obrade je omogućena primjenom vizuelno evociranih potencijala (VEP), koji prikazuju objektivnu procjenu moždane funkcije. Promjene u nalazu vizuelno evociranih potencijala kod oboljelih od shizofrenije (VEP) su predstavljale prilično konzistentan nalaz naglašavaju važnost senzornih deficita u procesuiranju što je od značaja razumijevanje patofiziologije shizofrenije. Cilj: utvrditi razlike u parametrima P100 letencija kod oboljelih od shizofrenije i migrenozne glavobolje primjenom vizuelno evociranih potencijala (VEP). Materijali i metode: ova prospektivno, komparativna studija provedena je na Klinici za psihijatriju i Klinici za neurologiju Kliničkog centra Univerziteta u Sarajevu (CCUS). Istraživanjem je obuhvaćeno 80 pacijenata oba spola, od 21 do 67 godina starosti, podijeljenih u dvije grupe. Rezultati: multivarijantnom analizom je ispitano je da li postoji statistički značajna razlika u parametrima latencije P100 valova između posmatrane i kontrolne grupe. Rezultati pokazuju da postoji statistički značajna razlika u parametrima latencije u smislu

njene prolongacije u području cijelog vidnog polja oba oka, cijelog vidnog polja-lijevog oka, desnog vidnog polja-lijevog oka, lijevog vidnog polja- lijevog oka u grupi oboljelih od shizofrenije u odnosu na kontrolnu grupu. Zaključak: malo se zna o uzročno posljedičnoj vezi shizofrenije i okcipitalne moždane regije, odnosno da li se vizuelno procesuiranje pogoršava ako je prisutan deficit okcipitalne regije mozga. Naša studija otvara niz pitanja što stvara potrebu za daljnja istraživanja, posebno u vezi promjenama u području okcipitalne moždane regije oboljelih od shizofrenije.

Ključne riječi: vidni put, shizofrenija, migrenozna glavobolja, VEP

INTRODUCTION

The name schizophrenia comes from Eugen Bleuler, who was the first to use this term in 1911 for a disease that was known until then as dementia praecox. However, Emil Kraepelin is credited with the nosological definition of this disease in 1896, because he was the first to notice what was common in a series of diverse psychopathological manifestations and clinical pictures of catatonia, hebephrenia and paranoid dementiae praecox. The term dementia praecox itself dates back to 1851, when Morel in his "Clinical Studies" used it to denote a disorder that begins very early, in adolescence, and leads to intellectual decline. Schizophrenia is today accepted as a neurobiological disorder with strong neurocognitive components, and neuropsychological research is based on determining the specificity of neurocognitive patterns, which contributes to clarifying the neuroanatomical and neuropsychological systems underlying the disease, making a clinical contribution to the development of more effective rehabilitation measures (1,2).

The debate about the "functional" versus the "organic" nature of schizophrenia, based on the neurobiological conceptualization of this disorder since the time of Emil Krepelin, is still relevant today (3). While cognitive dysfunction, including memory and attentional deficits, are well known in schizophrenia, recent work has also shown basic sensory processing deficits. Deficits are particularly prominent in the visual system and may be related to cognitive deficits and outcome (4). A primary approach to analyzing integrity of visual processing is the use of visual evoked potentials (VEPs). The VEPs have the advantage that they are nonbehavioral and so provide an objective measure of brain function. Visual evoked potentials (VEPs) abnormalities have been a fairly consistent finding in patients with schizophrenia, and these highlight the importance of sensory processing deficits, in addition to higher cognitive dysfunction, for understanding the pathophysiology of schizophrenia (5).

Understanding the nature of sensory processing deficits may provide insight into mechanisms of pathology in schizophrenia, impaired signal amplification, and could lead to treatment strategies including sensory processing rehabilitation that may improve outcome (6). The VEPs provide an objective measure of brain function, analyzing integrity of visual processing. Results from behavioral and electrophysiological studies support early visual processing dysfunction in schizophrenia, with preferential deficits being found in the magnocellular pathway, though parvocellular deficits have been found as well. Preferential magnocellular dysfunction may provide a substrate for dorsal stream dysfunction as well as higher level cognition deficits and outcome (7).

AIM

The aim of the study was to determine the difference of P100 latency parameters in patients with schizophrenia and migraine headache using visual evoked potentials (VEPs).

MATERIALS AND METHODS

Patients and study design

This prospective, comparative study was conducted at the Clinic of Psychiatry and Clinic of Neurology of the Clinical Center University of Sarajevo (CCUS). The study included 80 patients of both sexes, from 21 to 67 years of age, classified into two groups: S group included 40 patients with schizophrenia (21 males and 19 females) and M (control) group with 40 patients with migraine headache (10 males and 30 females).

Neurophysiological method - Visual evoked potentials (VEPs)

Visual Evoked Potentials (VEPs), as a measurement of the electrical signal, recorded at the scalp over the occipital cortex of 80 human brains in response to light stimulus, were examined at the Clinic of Neurology of the CCUS. The VEPs were used primarily to measure the functional integrity of the visual pathways from retina via optic nerves to the visual cortex of the brain. Visually evoked potentials elicited by flash stimuli can be recorded from many scalp locations in humans. Visual stimuli stimulate both primary visual cortices and secondary areas. Clinical VEPs are usually recorded from occipital scalp overlying the calcarine fissure. This is the closest location to primary visual cortex (Brodmann's area 17). The Ethics Committee of the Clinical Center University of Sarajevo gave an ethical consent to perform the study. All subjects signed a written informed consent for the use of the results obtained for publication before the enrolment.

Patients (S group) included in the study were 18 to 67 years old, hospitalized and under antipsychotic drugs at the Clinic of Psychiatry, diagnosed with schizophrenia according to the ICD-10 criteria (8). Patients were included into the research on the basis of consecutive admissions, taking into account that all of them were with a long psychiatric history (at least 5 years of hospital treatment) with signed information consent within clinical research. The criteria for the exclusion referred to the appearance of psychotic phenomenology within neurological disease, organic psychosyndrome, somatic disease, neurological disorder (head trauma, brain insult, epilepsy), information on drug or alcohol abuse, or those who did not sign informed consents for voluntary participation.

For the group of patients with schizophrenia, the average age was 41.50 (SD±10.44; range 22-67 years). The control group (H group) represented patients 18 to 55 years old, based on admissions at the Department of Neurology, diagnosed with migraine headache criteria, and were tested with the test scales of assessment with the signed informed consent for voluntary participation (9). This group included subjects who had never suffered from psychotic or severe neurological disorders (head injuries, epilepsy) or diseases, and in whose medical history there was no information on drug or alcohol abuse, with no metal content in the body and who signed informed consent for voluntary participation. The average age of the control group was

38.50 (SD±6.59; range 30–53) years. The groups were equal according to age (p=0.691).

Methods

Neurophysiological method -Visual evoked potentials (VEPs) Patients were subjected to examination by Visual evoked potentials (VEPs) and patterns for psychophysical and electrophysiological experiments were generated using a Medelec Synergy, Version 10.1 (Oxford Instruments Medical, United Kingdom), applying a unipolar montage technique where reference electrode (surface gold electrode) was placed 5–9 cm above the nasion point on the sagittal line between the nasion and Cz point, the active electrode was placed 2–4 cm above the posterior external protuberance on the line between the latter and Cz, while the ground surface electrode was placed on the chin to reduce artifacts. The pattern used was alternate pattern, each evoked potential recorded right and left eyes was recorded and processed, then the evoked potential was recorded from both eyes, and processed to calculate P100 latency. Recording was repeated 3 times for each patient and the mean was taken for recordings measured for each patient to minimize recording artifacts.

For all experimental runs, the stimulus consisted of a checkerboard pattern with equal numbers of light and dark checks (16 black and 16 white, size 2x2 cm). Luminance was 50 cd/m2, Michelson contrast = 80%. Each check subtended a visual angle of 0.65° both horizontally and vertically, while the checkerboard as a whole subtended visual angles of 5.25° vertically and horizontally. In all experimental runs the checkerboard was presented in the center of a monitor with a gray background. Visual-evoked potentials were recorded from the occipital site relative to the vertex site reference by means of gold-cup electrodes placed on the midline of the scalp. The ground was placed at the parietal site. Visually evoked potentials elicited by flash stimuli can be recorded from many scalp locations in humans. Visual stimuli stimulate both primary visual cortices and secondary areas. Clinical VEPs is usually recorded from occipital scalp overlying the calcarine fissure. This is the closest location to primary visual cortex (Brodmann's area 17).

A common system for placing electrodes is the "10-20 International System" which is based on measurements of head size (10). The mid-occipital electrode location (OZ) was on the midline. The distance above the inion calculated as 10% of the distance between the inion and nasion, which is 3-4 cm in most adults (the inion is the most prominent projection of the occipital bone at the posteroinferior part of the skull) (lower rear). Lateral occipital electrodes are at similar distance off the midline. Another set of locations was the "Queen Square system" in which the mid-occipital electrode is placed 5 cm above the inion on the midline and 5 cm lateral from that location for lateral occipital electrodes (11). There is a prominent negative component at peak time of about 75 msec (N75), a larger amplitude positive component at about 100 msec (P100) and a more variable negative component at about 145 msec (N145). The major component of the VEPs is the large positive wave peaking at about 100 milliseconds. The VEsP waveform, amplitudes and peak times depend upon the parameters of the stimulus. Steady state VEPs are those recorded using stimulation rates of 3 or more per second. Transient VEPs were recorded using rates of less than 3 per second. For all experimental runs, the stimulus consisted of a checkerboard pattern with equal numbers of light and dark checks. Each check subtended a visual angle of 0.65° both horizontally and vertically, while the checkerboard as a whole subtended visual angles of 5.25° vertically and horizontally. In all experimental runs the checkerboard was presented in the center of a monitor with a gray background. The stimulation of the entire field of view with both eyes, then the whole field of view individually for left and right and for the halves of the visual fields of both eyes. Eye that was not watching was covered.

Average values of latency (the entire eye field both eyes) of the healthy population for the comparison were as follows- P100 latency (ms): entire field of view (both eyes) 89.06, (left eye) 92.28, (right eye) 97.91, right field of view (left eye) 89.10, (right eye) 101.05, left field of view (left eye) 91.91, (right eye) 100.78.

Statistical analysis

The research task was to define the differences between patients with schizophrenia and patients with migraine headache according to difference of P100 latency parameters using visual evoked potentials (VEPs). For the purposes of correlation and associative analysis multivariate analysis of variance was applied using T-test of paired samples and Levene`s test for equality of variances. Differences in which the p value was less than 0.05 (p 0.05) were considered statistically significant.

RESULTS

Demographic data of subjects

The sample consisted (schizophrenic patients) of 21 (52.5%) male and 19 (47.5%) female, control group of 10 (25.0%) male and 30 (75.0%) female. Analysis regarding gender demonstrated statistically significant difference in control group (χ2=6.173; df=1; p=0.012). More subjects in that group were women with higher prevalence of migraine headache in female population (15%-17% female instead male of 6%; 2:1-3:1) (Table 1).

Table 1 **Distribution according to gender.**

		Gender		
		Female	Male	Total
Group	Schizophrenia	19	21	40
		47.5%	52.5%	100.0%
		38.8%	67.7%	50.0%
	Control	30	10	40
		75.0%	25.0%	100.0%
		61.2%	32.3%	50.0%
Total		49	31	80
		61.3%	38.8%	100.0%
		100.0%	100.0%	100.0%

Analysis of subjects according to age

Comparative analysis regarding age in both groups demonstrated that there wasn`t a statistically significant difference in the investigated sample (t=1.346; p=0.1821).Average age of patients in the time of study was 41.50±10.43 years, and of controls 38.50±9.48 years. The youngest subject in schizophrenia

group was 22, and the oldest one was 67, in the control group the youngest was 20, and the oldest 55 (Table 2.).

Comparative analysis regarding age in both groups demonstrated that there was not a statistically significant difference in the investigated sample (t=1.346; p=0.1821).

Table 2 **Age distribution of patients.**

	No (%) of patients			
	Schizophrenia group		Control group	
Age (years)	Male	Female	Male	Female
20-30	5 (23.8)	1 (5.3)	4 (0.4)	6 (0.2)
30-40	8 (38.1)	5 (26.3)	1 (0.1)	12 (0.4)
40-50	5 (23.8)	8 (42.1)	3 (0.3)	9 (0.3)
50-60	2 (9.5)	4 (21.1)	2 (0.2)	3 (0.1)
60-70	1 (4.8)	1 (5.3)	/	/
Total	21	19	10	30

Comparative analysis of P100 latency in patients and controls using visual evoked potentials (VEPs)

The correlation of P100 latency of the human brain was examined in 80 patients (patients with schizophrenia and controls) using visual evoked potentials (Table 3).

Group		Arithmetic mean	Standard deviation	N
P100 latency (ms) entire visual field-both eyes	Schizophrenia	**97.103**	9.9815	40
	Control	89.058	6.9455	40
	Total	97.080	8.5440	80
P100 latency (ms) entire visual field – left eye	**Schizophrenia**	**97.155**	10.0635	40
	Control	92.283	7.6071	40
	Total	97.219	8.8638	80
P100 latency (ms) entire visual field – right eye	Schizophrenia	97.590	9.8037	40
	Control	97.905	6.8983	40
	Total	97.748	8.4241	80
P100 latency (ms) right visual field-left eye	**Schizophrenia**	**102.900**	10.8297	40
	Control	89.103	8.5570	40
	Total	102.001	9.7398	80
P100 latency (ms) right visual field – right eye	Schizophrenia	102.858	10.4677	40
	Control	101.048	8.4945	40
	Total	101.953	9.5154	80
P100 latency (ms) left visual field – left eye	**Schizophrenia**	**99.180**	10.3872	40
	Control	91.908	7.5120	40
	Total	99.544	9.0142	80
P100 latency (ms) left visual field – right eye	Schizophrenia	99.955	9.8875	40
	Control	100.778	7.1432	40
	Total	100.366	8.5804	80

Table 3 **Statistical descriptive parameters of P100 latency (ms) in both groups.**

Multivariate analysis of variance was used to examine whether there is a statistically significant difference in the latency parameters of the P100 wave between the observed and control groups. The difference in both eyes was analyzed, taking into account the entire visual field of both eyes, the right visual field of both eyes and the left visual field of both eyes. The results indicate that there is a statistically significant difference in the latency parameters of the P100 wave-prolongation, the entire visual field of both eyes, the entire visual field-left eye, the right visual field-left eye, the left visual field-left eye in the group of patients with schizophrenia compared to the control group of respondents (Table 4).

Table 4 **Parameters of P100 latency (ms) between the schizophrenia and control groups.**

		SS	df	MS	F	p
Schizophrenia	P100 latency (ms) entire visual field - both eyes	.040	1	.040	.001	.0381
	P100 latency (ms) entire visual field- left eye	.325	1	.325	.004	.0449
	P100 latency (ms) entire visual field – right eye	1.984	1	1.984	.028	.868
	P100 latency (ms) right visual field- left eye	64.620	1	64.620	.678	.0413
	P100 latency (ms) right visual field – right eye	65.522	1	65.522	.721	.398
	P100 latency (ms) left visual field-left eye	10.585	1	10.585	.129	.0321
P100 latency eye	(ms) left visual eye – right	13.538	1	13.538	.182	.671
Control	P100 latency (ms) entire visual field-both eyes	5766.908	78	73.935		
	P100 latency (ms) whole visual field- left eye	6206.497	78	79.570		
	P100 latency (ms) cijelo vidno polje - desno oko	5604.255	78	71.849		
	P100 latencija (ms) right visual field- left eye	7429.630	78	95.252		
	P100 latency (ms) right visual field- right eye	7087.398	78	90.864		
	P100 latency (ms) left visual field- left eye	6408.592	78	82.161		
	P100 latency (ms) left visual field- right eye	5802.726	78	74.394		
Total	P100 latency (ms) entire visual field-both eyes	5766.948	79			
	P100 latency (ms) entire visual field- left eye	6206.822	79			
	P100 latency (ms) entire visual field- right eye	5606.240	79			
	P100 latency (ms) right visual field- left eye	7494.250	79			
	P100 latency (ms) right visual field- right eye	7152.920	79			
	P100 latency (ms) left visual field – left eye	6419.177	79			
	P100 latency (ms) left visual field- right eye	5816.264	79			

The correlations between P100 latencies are all statistically significant and very high. All correlations are positive, which means that respondents who have e.g. the P100 latency of the entire field of vision of both eyes is usually higher and the P100 latency of the entire or partial field of vision in an individual eye is higher.

Correlations within the P100 latencies of the entire visual field are slightly higher than the other correlations and range from 0.038 to 0.045, while in the examined group, there are very high correlations between the P100 latencies of the right eye with the left and right visual fields P100 latencies of the partial visual field are from 0.041 to 0.032 The correlations are significantly higher than the correlations of the left eye with the right and left visual field. Multivariate analysis of variance was used to examine whether there is a statistically significant difference in the latency parameters of the P100 wave between the observed and control groups. The difference in both eyes was analyzed, taking into account the entire visual field of both eyes, the right visual field of both eyes and the left visual field of both eyes. The results indicate that there is a statistically significant difference in the latency parameters of the P100 wave-prolongation, the entire visual field of both eyes, the entire visual field-left eye, the right visual field-left eye, the left visual field-left eye in the group of patients with schizophrenia compared to the control group. group of respondents (Table 4.)

DISCUSSION

Patients with schizophrenia show severe neurophysiological deficits in brain information processing not only at cognitive levels (11-14), but also at perceptual levels (15,16). Perceptual deficits have been particularly well-documented in the visual system and have been shown to predict community outcome (17-21). In our study, in regard to the age of patients, the minimum age in both groups was around 20 years, while the maximum age in the group of patients with schizophrenia was 67, and in the control group 55. Members of the group diagnosed with schizophrenia were on average 3.5 years older than those in the control group. Neuronal connections, lateralization of brain functions and axonal myelination are established earlier in female brains than in those of males. This slower level of development could make the male brain more vulnerable to earlier damages, resulting in structural brain abnormalities associated with the early onset of the illness and its negative symptoms.

Schizophrenia is associated with deficits in higher order processing of visual information and steady state visual evoked potential responses recorded over the occipital cortex suggest a dysfunction of lower level visual pathways, which was more prominent for magnocellular than parvocellular biased stimuli. Our research conducted using VEPs revealed changes in the occipital lobe on left eye in schizophrenic patients (P100 latency prolongation) and difference degree of P100 medium latency was consistent with data of Bodis-Wollner and associates (23,24).

The finding of P100 deficits in patients, particularly overdorsal scalp, supports the view that schizophrenia is associated with impairment of early dorsal visual stream processing. The correlation is significantly higher in female subjects (37% of shared variance) than in male subjects (12% of shared variance). The correlations between the P100 latency are all statistically significant and very high, and all correlations are positive, which means that respondents who have the P100 latency of the entire visual field of both eyes is usually higher and the P100 latency of the entire or partial visual field in an individual eye is higher. The results are consistent with earlier findings where EP correlates with clinical symptomatology, especially EP latency correlates with disease severity. The findings are discussed in relation to concepts relevant to schizophrenia, including the dopamine hypothesis (25). The cognitive impairment seen in schizophrenia is not just due to deficits in higher order aspects of cognition but also encompasses significant deficits in early sensory processing. Changes in the volume in the occipital lobe are quite evident and further studies are required to better understand how the progressive brain changes affect the structural, functional, and metabolic activities of the occipital lobe in schizophrenia (26).

CONCLUSION

Little is known about the association of schizophrenia with the occipital lobe or whether the visual symptoms exacerbate if the occipital lobe is severely damaged is not yet known. Also, if the whole occipital lobe is involved in schizophrenia or just some part of it is involved also remains an unsolved mystery. Our study is useful to initiate new questions and recommendations for further studies, specifically on changes in the occipital lobe in the schizophrenic patient's brain.

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The comparative effectiveness of fingolimod and ocrelizumab in relapsing-remitting multiple sclerosis

Komparacija efikasnosti fingolimoda i okrelizumaba u liječenju relaps-remitirajuće multiple skleroze

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ABSTRACT

Introduction: multiple sclerosis (MS) is a chronic autoimmune disorder that attacks the myelin sheath in the central nervous system, leading to a wide range of symptoms and disability. Disease-modifying therapies (DMTs) are designed to reduce disease activity and slow the progression of disability. Aim: to compare the effectiveness of two DMTs, ocrelizumab and fingolimod, in reducing disease activity and disability progression in MS patients. Materials and methods: the study included 30 MS patients treated with either ocrelizumab or fingolimod and followed up for one year. Disease activity was measured using EDSS scores and magnetic resonance imaging (MRI) scans, which were taken before and after treatment. Results: the study found a significantly lower EDSS score after one year of treatment ($p<0.001$). The group of patients treated with fingolimod had significantly lower EDSS scores compared to those treated with ocrelizumab ($p=0.024$). There was no significant difference in the number of lesions on MRI scans after one year between the two treatment groups ($p>0.05$). Conclusion: our results suggests that early intervention with DMTs can slow the progression of disability in MS patients. Fingolimod may be a more effective treatment option for reducing disease activity and disability progression compared to ocrelizumab. However, further studies with larger sample sizes are needed to confirm these findings.

Keywords: comparative effectiveness, disease-modifying treatment, multiple sclerosis

SAŽETAK

Uvod: multipla skleroza (MS) je hronični autoimuni poremećaj koji napada mijelinsku ovojnicu u centralnom nervnom sistemu (CNS), što dovodi do širokog spektra simptoma i posljedičnog invaliditeta. Terapije koje modificiraju bolest (DMT) osmišljene su za smanjenje aktivnosti bolesti i usporavanje progresije invaliditeta. Cilj: usporediti učinkovitost dva lijeka koji modificiraju bolest, ocrelizumaba i fingolimoda, u smanjenju aktivnosti bolesti i progresije invaliditeta u bolesnika s MS-om. Materijali i metode: studija je uključila 30 bolesnika s multiplom sklerozom liječenih ocrelizumabom ili fingolimodom i praćenih godinu dana. Aktivnost bolesti mjerena je pomoću EDSS skale i nalaza magnetne rezonancije (MRI), koji su snimljeni prije i nakon tretmana. Rezultati: studija je pokazala značajno niži EDSS rezultat nakon godinu dana liječenja ($p<0,001$). Skupina pacijenata liječenih fingolimodom imala je značajno niže rezultate EDSS u usporedbi s onima liječenim okrelizumabom ($p=0,024$). Nije bilo značajne razlike u broju lezija na MRI snimkama nakon jedne godine između dvije liječene skupine pacijenata ($p>0,05$). Zaključak: naši rezltati sugeriraju da rana intervencija s DMT-om može usporiti napredovanje onesposobljenosti kod MS pacijenata. Fingolimod bi mogao biti učinkovitija opcija liječenja za smanjenje aktivnosti bolesti i progresije invaliditeta u usporedbi s okrelizumabom. Međutim, potrebna su daljnja istraživanja s većim uzorcima ispitanika kako bi se potvrdili ovi rezultati.

Ključne riječi: komparativna učinkovitost, liječenje koje mijenja bolest, multipla skleroza

comparative effectiveness, disease-modifying

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system, leading to disability and decreased quality of life. Relapsing-remitting multiple sclerosis (RRMS) is the most common subtype of MS, characterized by alternating periods of relapse and remission.

The goal of treatment for RRMS is to slow disease progression, reduce the frequency and severity of relapses, and improve patients' quality of life. Over the past few decades, several disease-modifying therapies (DMTs) have been developed and approved for the treatment of RRMS (1). These therapies work by modulating the immune system to reduce inflammation and damage to the nervous system.

There are currently several different classes of DMTs available for RRMS, including interferons, glatiramer acetate, oral medications such as fingolimod and teriflunomide, and monoclonal antibodies such as natalizumab and ocrelizumab. While each of

these medications has been shown to be effective in reducing relapse rates and slowing disease progression, the choice of therapy depends on several factors, including the patient's age, disease severity, comorbidities, and the presence of any medication side effects (1).

In recent years, there has been an increasing interest in personalized medicine approaches for the treatment of RRMS. This approach involves tailoring treatment to an individual patient's specific disease characteristics and response to therapy (2).

Despite the availability of multiple treatment options, some patients with RRMS may experience disease progression despite therapy. In these cases, switching to a different DMT or adding a second medication may be considered.

Fingolimod and ocrelizumab are two disease-modifying therapies approved for the treatment of RRMS by the United States Food and Drug Administration (FDA). However, the comparative effectiveness of these two drugs remains unclear. The choice of therapy depends on several factors, and personalized medicine approaches may offer additional benefits for patients. However, further research is needed to identify optimal treatment strategies for individual patients with RRMS.

AIM

The aim of this study was to compare the effectiveness of fingolimod and ocrelizumab in the treatment of relapsing-remitting multiple sclerosis (RRMS) by analyzing real-world data. The study also aimed to investigate the association between the use of these two disease-modifying therapies (DMTs) and the clinical outcomes in RRMS patients, including clinical activity of the disease evaluated with EDSS and radiological appearance of new contrast enhanced lesions.

MATERIALS AND METHODS

This retrospective cohort study which included 30 patiens was conducted at the Neurology Clinic of the Clinical Center University of Sarajevo (CCUS). The study identified patients who were diagnosed with RRMS and received treatment with either fingolimod or ocrelizumab at the CCUS in the period between 1 January and 31 December 2022. Patients were included in the study if they met the following criteria: 1) a confirmed diagnosis of RRMS based on the 2017 McDonald criteria, 2) treatment with either fingolimod or ocrelizumab for at least 12 months, and 3) availability of clinical and radiological data before and after treatment initiation. We reviewed the electronic medical records of eligible patients to collect demographic and clinical data, Expanded Disability Status Scale (EDSS) scores, and relapse history. We also collected MRI data, including T2 lesion volume and gadolinium-enhancing lesion appearance at baseline and at 12 months after treatment initiation. The outcome measure included appearance of the new gadolinium-enhancing lesion on MRI and EDSS scores from baseline to 12 months after treatment initiation.

Statistical analysis was performed using SPSS (version 20.0, SPSS Inc., Chicago, IL). Baseline characteristics of the two treatment groups were compared by Fisher's exact test and Mann-Whitney *U* test as appropriate. Odds ratios were calculated using logistic regression with the outcome variable EDSS after 1 year and the explanatory variables Treatment, Initial EDSS and No of lesions. We selected the candidate covariates from the set of collected variables in such a way that there were less than 20% of patients with missing data or variables with less than 5% missing values. The covariates Treatment, Initial EDSS and No of lesions were defined a priori based on data from the literature. The candidate covariates were included in a Least Absolute Shrinkage and Selection Operation (LASSO) penalized regression model. The penalty coefficient (lambda) was chosen so as to provide an estimation error lower than one standard deviation of the minimum error obtained by 10-fold cross-validation, while being as parsimonious as possible. No variable had a coefficient different from 0 with this lambda coefficient. The distribution of residuals not following a normal distribution, [Medistica., *pvalue.io, a graphic user interface to the R statistical analysis software for scientific medical publications*, 2020. Available on: https://www.pvalue.io] "we calculated confidence intervals and p-value by bootstrap (1000 iterations)." p values < 0.05 were considered significant.

The study was approved by the Ethical Comitee of the CCUS, and all patients provided written informed consent for the use of their medical records for the research purposes.

RESULTS

The study included 30 patients with initial EDSS 3.13± 1.27. We observed a significantly lower EDSS scores after one year (p <0.001) (Table 1).

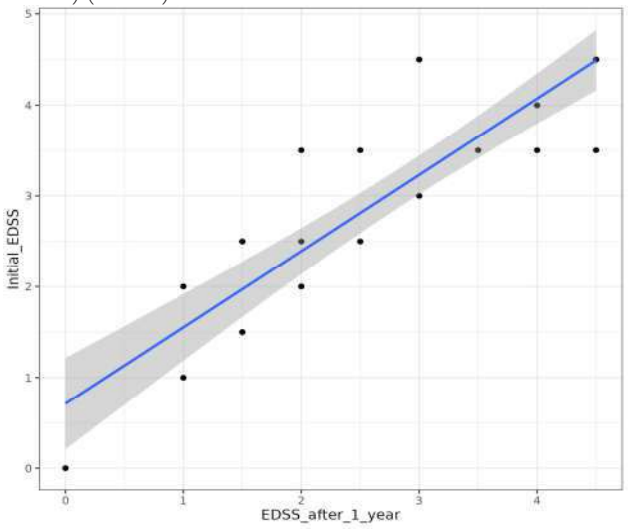

Figure 1 **Expanded Disability Status Scale (EDSS) scores at baseline and after 1 year.**

Comparing two groups of patients, EDSS scores after 1 year in group of the patients treated with fingolimod were significantly lower comparing to the patients treated with ocrelizumab (p = 0.024) (Table 2).

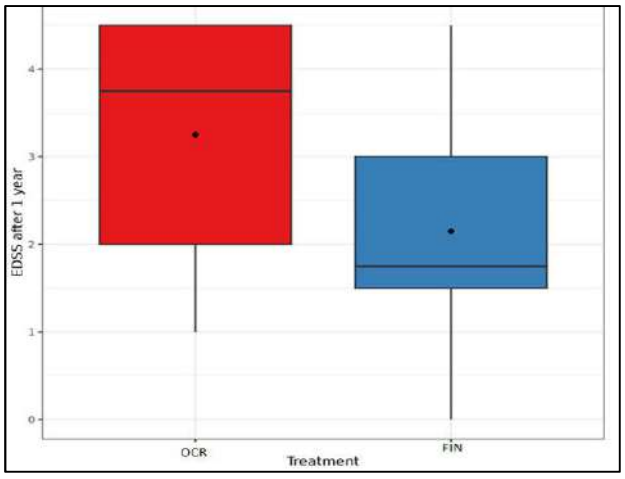

Figure 2 **Expanded Disability Status Scale (EDSS) scores after 1 year in patients treated with ocrelizumab and fingolimod.**

We observed that the average rank of MRI lesions was significantly different between the two time points ($p < 0.001$) (before and after intervention/treatment). However, we did not observed any significant difference in number of lesions after one year in patients treated with ocrelisumab compared to patients treated with fingolimod (Figure 3).

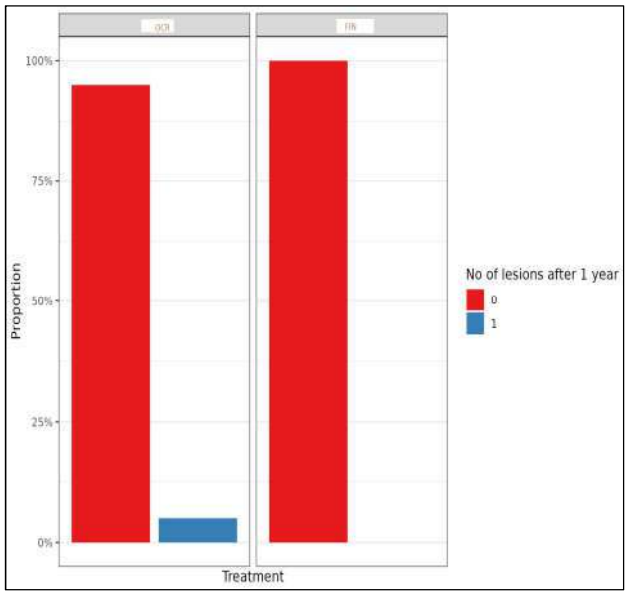

Figure 3 **Analysis of the treatment influence of gadolinium-enhancing lesion appearance.**

DISCUSSION

Disease activity in multiple sclerosis (MS) refers to the occurrence of relapses or new MRI lesions that are indicative of ongoing inflammation and damage in the central nervous system (CNS) (3). MS is a chronic autoimmune disorder that attacks the myelin sheath that covers nerve fibers in the brain and spinal cord. This damage disrupts the normal transmission of nerve impulses and can lead to a wide range of symptoms, including muscle weakness, numbness or tingling, difficulty with coordination and balance, vision problems, and cognitive impairment.

Disease activity can be measured using a variety of clinical and imaging-based tools. Relapses are typically defined as the appearance of new or worsening symptoms that last for more than 24 hours, and are often accompanied by evidence of new lesions on MRI scans (4). MRI scans can also be used to measure the number and volume of lesions, as well as the amount of brain tissue loss, which is an indicator of neurodegeneration (5).

Other measures of disease activity in MS include disability progression, which is typically assessed using the Expanded Disability Status Scale (EDSS) and cognitive impairment, which can be assessed using a battery of neuropsychological tests (6,7).

The presence of disease activity is an important consideration when choosing a treatment strategy for MS. Disease-modifying therapies (DMTs) are designed to reduce disease activity and slow the progression of disability.

The EDSS score is a useful tool for assessing disability in MS patients, and several studies have demonstrated a relationship between disease duration and EDSS scores. Chruzander C, et al., followed 118 patients with MS for 10 years and observed that median EDSS scores had changed from 5.0 at baseline to 6.5 at the 10-year follow-up (8).

Another study, published 13 years ago, followed 339 patients with relapsing-remitting MS for a median of 10 years (9). The study found that EDSS scores increased with disease duration, with a median EDSS score of 1.5 at diagnosis and 3.0 after 10 years of disease duration. The study also found that the rate of EDSS score increase varied depending on the age at onset and the initial EDSS score (9).

Rio J, et al., found that EDSS scores increased with disease duration, with a median EDSS score of 1.5 at diagnosis and 3.5 after 20 years of following 94 MS patients (10).

In our study we observed a significantly lower EDSS scores after one year proving that early intervention and treatment may slow the progression of disability in MS patients.

The choice of DMT depends on a number of factors, including the patient's disease activity, level of disability, age, and other health considerations. The current treatment landscape for MS includes disease-modifying therapies (DMTs) that aim to slow or halt disease progression. These treatments range from injectable therapies such as interferon beta-1a and glatiramer acetate to oral therapies such as fingolimod and teriflunomide, and infusion therapies such as ocrelizumab and natalizumab.

Clinical guidelines recommend more aggressive treatment strategies for patients with high disease activity, as these patients are at greater risk of disability progression and require more effective therapies to prevent further disease activity. For example, a study comparing the efficacy of fingolimod and interferon beta-1a in patients with high disease activity found that fingolimod reduced the annual relapse rate by 54% compared to interferon beta-1a (11). In contrast, less aggressive treatment strategies may be appropriate for patients with less active disease, as these patients may be at lower risk of disability progression and may benefit from less intensive therapies with fewer side effects (11).

In our study, we compared patients treated with ocrelizumab and fingolimod. Ocrelizumab is a monoclonal antibody that targets CD20-positive B cells, a type of immune cell that plays a role in the

development and progression of MS. In clinical trials, ocrelizumab has shown to reduce the frequency of relapses and slow the progression of disability in patients with relapsing-remitting MS. In one study, ocrelizumab reduced the annual relapse rate by 46% compared to a placebo (12). In another study, ocrelizumab reduced the risk of disability progression by 24% compared to interferon beta-1a (13).

Fingolimod is a sphingosine-1-phosphate receptor modulator that sequesters lymphocytes in the lymph nodes, preventing them from entering the central nervous system and causing inflammation. In clinical trials, fingolimod has been shown to reduce the frequency of relapses and slow the progression of disability in patients with relapsing-remitting MS. In one study, fingolimod reduced the annual relapse rate by 54% compared to interferon beta-1a (11). In another study, fingolimod reduced the risk of disability progression by 30% compared to a placebo (14).

A head-to-head comparison of ocrelizumab and fingolimod in a clinical trial has not been conducted. However, a network meta-analysis of randomized controlled trials comparing the efficacy and safety of various DMTs for relapsing-remitting MS found that ocrelizumab and fingolimod were similarly effective in reducing the frequency of relapses (15). This analysis including 14,096 participants from 23 trials concluded that all immunomodulatory drugs were more effective than placebo, and ocrelizumab was in a group of the most effective drugs (RRs ranging between 0.65 and 0.73) (15).

According to our research, EDSS scores after 1 year in group of the patients treated with fingolimod were significantly lower comparing to the patients treated with ocrelizumab.

On the other hand, multicenter, retrospective observational study carried in 16 centers came to conclusion that ocrelizumab was superior to fingolimod in providing better relapse control (16).

In our study, we observed that the average rank MRI lesions was significantly different (before and after the treatment). However, we did not observed any significant difference in number of lesions after one year in patients treated ocrelisumab compared to patients treated fingolimod.

In two identical phase 3 trials, the efficacy of ocrelizumab to subcutaneous interferon beta-1a in patients with relapsing-remitting multiple scleroses was compared (13). The trials enrolled a total of 1,832 patients and found that ocrelizumab reduced the number of new or enlarging lesions on MRI by 82-85% compared to placebo (13).

The phase III COMPARISON study compared the efficacy of fingolimod and interferon beta-1a in reducing disease activity in patients with relapsing-remitting multiple sclerosis (11). The study enrolled 1,327 patients and found that fingolimod reduced the number of new or enlarging lesions on MRI by 58% compared to interferon beta-1a (11).

It must be noted that these studies evaluated different aspects of fingolimod and ocrelizumab and cannot be directly compared to one another. However, both fingolimod and ocrelizumab have shown to be effective in reducing disease activity in patients with relapsing-remitting multiple sclerosis.

Overall, the efficacy of ocrelizumab and fingolimod are broadly proven, with both drugs having well-established positive influence on MS disease activity, measured clinically and radiologically.

This study has several limitations, including its retrospective design, the small sample size, and the potential for selection bias. In addition, the study was conducted at a single center, which may limit the generalizability of the results. Finally, the short follow-up period of 12 months may not capture long-term treatment outcomes.

CONCLUSION

Ocrelizumab and fingolimod are both effective DMTs for the treatment of relapsing-remitting MS. While a head-to-head comparison has not been conducted, our study suggests fingolimod may be a more effective treatment option for reducing disease activity compared to ocrelizumab. However, further studies with larger sample sizes are needed to confirm these findings.

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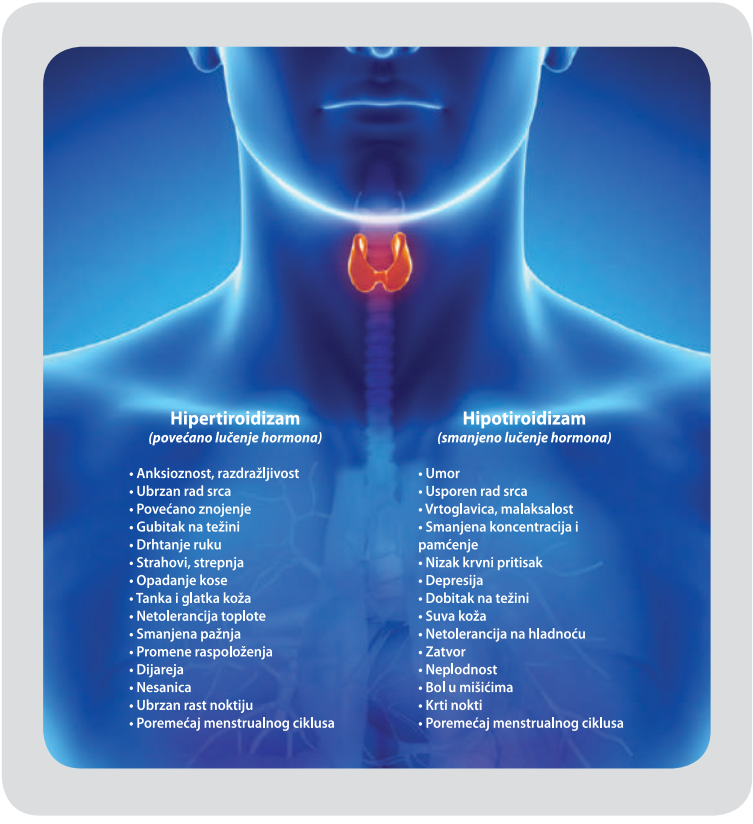

Impact of diabetes mellitus on early outcomes after lower leg amputations in patients with peripheral arterial occlusive disease

Utjecaj dijabetes melitusa na rane ishode nakon podkoljenih amputacija kod pacijenata sa perifernom arterijskom okluzivnom bolešću

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ABSTRACT

Introduction: peripheral arterial disease (PAD) is more common and more severe in patients with diabetes mellitus (DM) compared to those without DM. Patients with PAD and diabetes mellitus have a high risk of serious complications, such as amputation, which in these patients represent an unwanted outcome of treatment. Aim: to compare early perioperative outcomes after below knee amputation due to PAD in diabetic and non-diabetic patients. Materials and methods: the research was conducted in the form of data analysis of 111 below knee amputations in patients with PAD, who were hospitalized at the Clinical Center University of Sarajevo in the period between January 2020 and December 2022. Patients were divided into two groups; with diabetes (n=90; 81.1%) and non-DM (n=21; 18.9%). Study analysis included early perioperative outcomes: debridement for wound infection, re-amputation, blood transfusion, intensive care unit (ICU) admission, myocardial infarction (MI), and mortality. Results: no significant differences in demographic facts were recorded. In the group of patients with DM, a significantly higher number of patients with hypertension was found, (47 (52.2%) vs. 18 (85.7%), p=0.001), as well as the number of re-amputations 34 (37.8%) p=0.026 and blood transfusions 23 (25.6%) p=0.041, in insulin-dependent patients a statistically significantly higher number of ICU admissions was recorded 17 (30.9%) vs. 3 (8.6%) p=0.026. Conclusion: simultaneous existence of PAD and DM significantly complicates the treatment of these conditions and increases the total number of amputations, as well as re-amputations, blood transfusions and ICU admissions. For such patients, adequate follow-up and prevention of DM complications is crucial to avoid disease progression and eventual amputation.

Keywords: perioperative results, peripheral arterial disease, diabetes mellitus, amputation

SAŽETAK

Uvod: periferna arterijska bolest (PAB) je češća i teža kod pacijenata sa dijabetes melitusom (DM) u poređenju sa onima bez DM. Bolesnici sa PAB i dijabetes melitusom imaju visok rizik od ozbiljnih komplikacija, poput amputacije, koja kod tih pacijenata predstavljaju neželjeni ishod liječenja. Cilj: uporediti rane perioperativne rezultate nakon podkoljene amputacije zbog PAB kod pacijenata sa dijabetesom i nedijabetičara. Materijali i metode: Istraživanje je analiziralo podatke 111 podkoljenih amputacija kod pacijenata sa PAB, koji su hospitalno tretirani između januara 2020. i decembra 2022. godine u Kliničkom centru Univerziteta u Sarajevu. Pacijenti su podijeljeni u skupinu sa dijabetesom (DM) (n=90;81.1%%) i ne-DM skupinu (n=21;18.9%). Rezultati studije uključivali su rane periopeartivne rezultate: debridman zbog infekcije rane, reamputacije, transfuziju krvi, prijem u jedinicu intenzivne terapije (JIT), infarkt miokarda (IM) i smrtnost. Rezultati: nisu zabilježene statistički značajne razlike u demografskim faktorima. U skupini pacijenata sa DM je utvrđen je značajno veći broj pacijenata sa hipertenzijom (47 (52.2%) vs 18 (85.7%), p=0.001, kao i broj reamputacija 34 (37.8%), p=0.026 i transfuzie krvi 23 (25.6%), p=0.041, kod je insulin ovisnih pacijenata evidentiran statistički značajno veći broj prijema u JIT 17 (30.9%) vs 3 (8.6%) p=0.026. Zaključak: istovremeno postojanje PAB i DM značajno otežava liječenju ovih stanja, te povećava ukupan broj amputacije, kao i reamputacije, transfuzija krvi i prijema u JIT. Za takve pacijente je adekvatno praćenje i prevencija komplikacija DM ključno za izbjegavanje progresije bolesti i eventualne amputaciju.

Ključne riječi: perioperativni rezltati, periferna arterijska bolest, diabetes mellitus, amputacija.

INTRODUCTION

Peripheral arterial disease (PAD) is one of the most common vascular diseases (1), in which limb amputation represents an undesirable treatment outcome. PAD leads to complete or partial occlusion of one or more peripheral arteries of the upper and lower limbs, usually due to atherosclerosis of blood vessels, which can lead to reduced blood flow or tissue loss. In diabetes mellitus (DM), the arteries of the lower limbs are mostly affected, and the distal arteries are the most commonly involved (2).

Current literature indicates that risk factors for PAD include conditions such as hypertension, hyperlipidemia, smoking, and DM (3). PAD is more prevalent and severe among DM patients compared to non-DM patients. Patients with DM, complicated by PAD, have a worse quality of life, functional capacity and an overall worse prognosis compared to patients with PAD alone (4).

DM is one of the main risk factors for the development of PAD and it is an independent predictor of increased limb amputation and mortality in patients with PAD (5,6). Patients with PAD and DM often have infra-inguinal and crural lesions (7), which are often complex and highly calcified with unsatisfactory acute and poor long-term outcomes (8).

The risk of developing PAD is four times higher in patients with DM, and it has been evaluated as the strongest risk factor for developing PAD (9,10). Considering this, patients with DM and PAD are at high risk of ischemic events and subsequent amputations (11). It has been reported that one of four people with diabetes develop peripheral arterial disease, which, if severe, may require amputation.

Complications of DM are not only common, but devastating, and include lower extremity amputations, with DM being the most common cause of non-trauma-related lower extremity amputations. There is a wide range in the proportion of lower limb amputations caused by DM, and studies show that up to 90% of lower limb amputations worldwide are related to DM, and that up to 70% of patients who undergo lower limb amputation die within 5 years of surgery (12).

Compared to amputations in people without diabetes, amputations due to diabetes more often involve younger people and a lower level of amputation (13). For patients with PAD and DM, amputation is a life-changing outcome.

DM is an independent predictor of increased limb amputation and mortality in patients with PAD (5,6). The stated effect of DM is one of the reasons why we decided to to this research., a swell as the fact that patients with diabetes may be exposed to a higher risk of adverse events when undergoing surgery. Stress due to trauma, operative blood loss, and intraoperative anesthesia will further increase the blood glucose levels in patients with diabetes (14). Stress response can also induce diabetic comorbidities including ketoacidosis and hyperglycemic hyperosmolar syndrom (15).

AIM

The aim of this study was to compare early perioperative results after lower leg amputation due to peripheral arterial disease in diabetics and non-diabetics, with an additional focus on perioperative results in these patients depending on the type of DM treatment (insulin-dependent and insulin-independent patients).

MATERIALS AND METHODS

The data were collected prospectively, and according to the cohort study model, a retrospective data analysis was performed. The study analyzed 164 patients treated at the Clinical Center University of Sarajevo in the period from January 2021 to December 2022. All patients underwent below-the-knee amputation after all vascular, surgical and angiology treatment modalities had been used. By applying the exclusion factor, a sample of 111 patients was formed. The sample was divided into two groups; group with DM (90; 81.1%) and group of patients without DM (21; 18.9%). Patients with DM were also compared in relation to insulin dependence in the treatment of DM.

The following variables were collected for each patient: age, gender, history of hypertension (HTA), hyper-lipidemia (HLP), smoking addiction, history of chronic obstructive pulmonary disease (COPD), history of end-stage renal disease, data on previous stroke, tumor, type of anesthesia (local, general). Perioperative (<30 days) results were analyzed: debridement due to wound infection, re-amputation, blood transfusion, admission to intensive care unit (ICU), myocardial infarction (MI) and mortality.

Statistical analysis

Baseline characteristics were collected and presented as number of cases and percentage representation. Categorical values were analyzed with the $\chi 2$ test and Fisher's test. Student's T-test and Mann-Whitney U test were used to analyze quantitative values. Statistical hypotheses were tested at the level of $\alpha=0.05$, i.e. the difference between the samples was considered significant if $p<0.05$. Statistical analyzes were performed using IBM SPSS Statistics ver. 21.0.

RESULTS

The average age of the subjects in the study was 69.82 years (standard deviation, ±10.93), ranging from 29 to 88 years of age, the average age of the subjects in the group with DM was 69.47 years (standard deviation, ± 10.51), ranging from 41 to 88 years, while the average age in patients without DM was 71.33 years (standard deviation, ±12.77), ranging from 29 to 86 years (p=0.257). The representation of men was dominant in both groups (62.2% vs. 61.9%) without statistical significance, p=1.00. The choice of anesthesia was adapted to the patient's general condition and local findings, and most amputations were performed under general anesthesia, only 12.2% of amputations in the group of patients with DM and 19% of amputations in the group of patients without DM were performed under spinal anesthesia.

The representation of most preoperative risk factors and comorbidities in the studied groups did not show statistical significance: smoking addiction 32 (35.6%) vs 7 (33.3%), p= 1.00; hyperlipidemia 50 (55.6%) vs 8 (38.1%), p=0.230; COPD 13 (14.4%) vs 3 (13.3%); p=1.00; renovascular disease with chronic renal failure 6 (6.7%) vs 1 (4.8%); p=1.00, post-stroke condition 4 (4.4%) vs 1 (4.8%); p=1.00.

A statistically significant difference in the representation of hypertensive patients in the group of patients with DM was evident 47 (52.2%) vs. 18 (85.7%), p=0.001*, a statistically significant difference in the representation of patients with a tumor was recorded in the group without DM 2 (2.2%) vs 3 (14.3%), p=0.046* (Table 1).

Table 1 **Demographic, perioprocedural data, comorbidity and risk factors.**

Variable	Total (111)	DM (90; 81.1%)	non-DM (21; 18.9%)	P
Age	69.82 (±10.93)	69.47(±10.51)	71.33(±12.77)	0.257
Gender				1.00
M	69 (62.2%) 42	56 (62.2%) 34	13 (61.9%)	
F	(37.8%)	(37.8%)	8 (38.1%)	
COPD	16 (14.4%)	13 (14.4%)	3 (14.3%)	1.00
Renal failure	7 (6.3%)	6 (6.7%)	1 (4.8%)	1.00
stroke	5 (4.5%)	4 (4.4%)	1 (4.8%)	1.00
Tumor	5 (4.5%)	2 (2.2%)	3(14.3%)	**0.046***
HTA	65 (41.4%)	47 (52.2%)	18 (85.7%)	**0.001***
HLP	58 (52.3%)	50 (55.6%)	8 (38.1%)	0.230
Smoking addiction	39 (35.1%)	32 (35.6%)	7 (33.3%)	1.00
Anesthesia				0.478
Spinal	15(13.5%) 96	11(12.2%) 79	4(19%) 17	
OET	(86.5%)	(87.8%)	(81%)	

After analyzing data on perioperative results between patients with DM and patients without DM, there was no significant difference between the analyzed groups in the number of wound debridements after amputation 9 (10.9%) vs 1 (4.8%) p=0.684; admission of patients to the ICU 20 (22.2%) vs 1 (4.8%) p=0.117; number of deaths and myocardial infarction (MI) 6 (6.7%) vs 1 (4.8%) p=1.00. In the group of patients with DM, a significantly higher number of reamputations 34 (37.8%) p=0.026 and blood transfusions 23 (25.6%) p=0.041 was found (Table 2).

Table 2 **Perioperative (<30 days) results: DM / non-DM.**

Variable	Total (111)	DM (90; 81.1%)	non-DM (21; 18.9%)	P
Debridement	10(9%)	9 (10%)	1 (4.8%)	0.684
Transfusion	24 (21.6%)	23 (25.6%)	1(4.8%)	**0.041***
Re-amputation	36 (32.4%)	34 (37.8%)	2 (9.5%)	**0.026***
ICU admission	21 (18.9%)	20 (22.2%)	1 (4.8%)	0.117
MI	5 (4.5%)	4 (4.4%)	1 (4.8%)	1.00
death	7 (6.3%)	6 (6.7%)	1 (4.8%)	1.00

After the analysis of perioperative data, and depending on the method of DM treatment (insulin-dependent and non-insulin-dependent patients), a significantly higher number of admissions to the ICU was recorded in the group of patients with insulin dependence 17 (30.9%) vs. 3 (8.6%) p=0.026 (Table 3).

Table 3 **Perioperative (<30 days) results - insulin dependent and insulin non-dependent.**

Variable	Total (90)	Insulin depend (55; 61.1%%)	Insulin non-depend (35; 38.9%)	P
Debridement	9(10%)	6 (10.9%)	3 (8.6%)	1.00
Transfusion	23 (25.6%)	13 (23.6%)	10(28.6%)	0.627
Re-amputation	34 (37.8%)	24 (43.6%)	10 (28.6%)	0.225
ICU admission	20 (22.2%)	17 (30.9%)	3 (8.6%)	**0.026***
MI	4 (4.4%)	3 (5.5%)	1 (2.9%)	1.00
death	6 (6.7%)	3 (5.5%)	3 (8.6%)	0.674

DISCUSSION

Diabetes is one of the main risk factors for the development of PAD and it is an independent predictor of increased limb amputation and mortality in patients with PAD. In patients with diabetes, the arteries of the lower extremities are mostly affected, and the below knee arteries are the most commonly involved (2). The high prevalence of DM in patients with PAD in this study is consistent with several other studies showing DM as an important risk factor for PAD (16-18).

Our research indicates a higher frequency of hypertension in patients with PAD and DM, which is in accordance with some studies that highlighted this condition as one of the most common co-morbidities in such patients (19).

Similar to our investigation, other studies have shown a high percentage of amputations (from 25% to 90%) in patients with PAD and DM (20,21). A study conducted in Sweden, which included 31,354 patients, investigated the risk of non-traumatic lower limb amputations in patients with DM (22). Our investigation indicated a significantly higher percentage of amputations in patients with DM (81.1%) compared to the above. The reason for the higher number of amputations may be the higher average age of the subjects, which in our study was 69.47 (range 41 to 88 years) compared to 45.4 years (range 25.2-69.7 years) in the Swedish study. A higher average age indicates a longer duration of DM in our study, which can explain the higher number of amputations as a complication of DM. The reason for the higher number of amputations in our study can be explained by the fact that it included a specific population of patients with PAD and DM, unlike the previous study, which analyzed only patients with DM.

A possible reason for the higher number of amputations in patients with PAD and DM could be the absence of typical symptoms such as claudication due to diabetic polyneuropathy. The lack of complaints can result in a lower rate of realization of diagnostic procedures, and thus insufficient and inadequate therapy.

Research conducted by Norvell DC, et al., indicates that DM is one of the important predictors of re-amputations (23). This statement is consistent with the results of our study, which indicates a higher number of re-amputations in patients with DM. In these patients, a more frequent indication for blood transfusion was recorded, which is expected, because patients with re-amputation underwent additional surgical treatment, which results in greater blood loss compared to a single amputation treatment.

The reason for the higher number of admissions to the ICU in insulin-dependent patients lies in the fact that a significantly higher number of re-amputations were performed in the group of patients with DM. This data is consistent with the data of other studies (24), which also indicate an increased perioperative cardiovascular risk in insulin-dependent patients. We are not aware of the similar research in Bosnia and Herzegovina, which gives this study additional significance.

The results of the research by Mohammedi K, et al., highlight the importance of lower limb amputation as a key predictor for premature death in patients with diabetes (25).

Research conducted by Most and his colleagues indicates that amputation rates caused by diabetes increase with age and are higher in men. The relative risk of lower extremity amputation for diabetics compared to the non-diabetic population is highest in the under-45 age group, although the attributable risk is highest in older population. Given the above, people with diabetes have 15 times higher risk of amputation than people without diabetes (26).

CONCLUSION

Treatment of patients suffering from PAD and DM at the same time is significantly more difficult. Such patients are faced with a significantly higher risk of amputation than patients with individual diseases. Our research shows the effect of DM on patients who suffer from PAD at the same time. Our results indicate that, even after applying all available vascular-surgical and angiological options, the combination of diabetes and PAD leads to a significantly higher number of amputations, re-amputations, needs for blood transfusion and the number of ICU admissions. Adequate glycemic control and prevention of DM complications is crucial in avoiding disease progression and eventual amputation.

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Our contribution to the reduction of cardiovascular diseases in Bosnia and Herzegovina!
Naš prilog redukciji kardiovaskularnih bolesti u Bosni i Hercegovini!

The impact of feeding type (mother's milk vs. milk formula) on extra uterine growth restriction in preterm infants under 32 gestational weeks

Uticaj načina ishrane majčinim mlijekom u odnosu na adaptiranu mliječnu formulu na ekstrauterinu restrikciju rasta kod nedonoščadi ispod 32 sedmice gestacije

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ABSTRACT

Introduction: extrauterine growth restriction is an identifiable marker for insufficient growth during hospitalization, common among preterm infants. Due to the different feeding types, and other possible factors there is a concern that some babies could have short and long term complications. Aim: to determine the influence of nutritional type and other risk factors for insufficient postnatal weight gain in preterm infants at the Pediatric Clinic of the Clinical Center University of Sarajevo (CCUS). Materials and methods: this was a cross-sectional study that included 123 preterm infants admitted at the Pediatrics Clinic of the CCUS. The population included preterm infants born under 32 gestational weeks. Patients were categorized into two groups based on the type of nutrition. Results: out of 123 preterm infants included in this study, 59 infants were fed with mother's milk while 64 were fed with adapted milk formula. Descriptive statistic showed that there was no significant difference in two compared groups. 61 patient met the criteria for EUGR according to a cross-sectional model. Conclusion: from descriptive statistics aspect we found no significant difference in weight gain model among the researched groups. Out of 123 preterm infants 61 were considered to have EUGR but there was no significant difference between nutritional type and insufficient postnatal weight gain. One of the main conclusions was that since percentage of patients considered to have EUGR was high, the focus should be put on improvement of nutritional approach.

Keywords: preterm infant, postnatal weight gain, extrauterine growth restriction

SAŽETAK

Uvod: restrikcija rasta ekstrauterinog porijekla prepoznatljiv je marker za nedovoljan rast tokom hospitalizacije, uobičajen među nedonoščadi. Zbog različitih vrsta hranjenja i drugih mogućih faktora, postoji zabrinutost da bi neke bebe mogle imati kratkoročne i dugoročne komplikacije. Cilj: utvrditi ut icaj prehrane i drugih faktora rizika za nedovoljno postnatalno dobivanje na težini kod nedonoščadi na Pedijatrijskoj klinici Kliničkog centra Univerziteta u Sarajevu (KCUS). Materijali i metode: ovo je presječna studija koja je uključivala 123 nedonoščadi primnjenih na Pedijatrijsku kliniku KCUS-a. Populacija je uključivala nedonoščad rođenu ispod 32 gestacijske sedmice. Pacijenti su kategorizirani u dvije skupine na temelju vrste prehrane. Rezultati: od 123 nedonoščadi uključene u ovu studiju, 59 ih je hranjeno majčinim mlijekom, dok su 64 nedonoščeta hranjena prilagođenom mliječnom formulom. Deskriptivna statistika pokazala je da nije bilo značajne razlike između dvije uspoređene skupine. 61 pacijent ispunio je kriterije za EUGR prema presječnom modelu. Zaključak: iz deskriptivnog statističkog aspekta nismo pronašli značajnu razliku u modelu dobivanja na težini među istraženim skupinama. Od 123 nedonoščadi za 61 se smatralo da imaju EUGR, ali nije bilo značajne razlike između prehrambenog tipa i nedovoljnog postnatalnog dobivanja ne težini. Jedan od glavnih zaključaka je da bi, s obzirom na to da je postotak pacijenata koji spadaju u skupinu sa EUGR-om bio visok, naglasak trebalo staviti na poboljšanje pristupa načinu i vrsti prehrane.

Ključne riječi: nedonoščad, postnatalno dobivanje na težini, ekstrauterina restrikcija rasta

INTRODUCTION

Preterm infants are proven to have higher risk of adverse health outcomes, such as the development of metabolic syndrome and cognitive impairment. The most recent evidence highlights that nutrition, body composition development, and early postnatal growth may play a role in the programming of these processes. Human milk feeding has been recommended as the natural feeding for preterm infants and as a cost-effective strategy for reducing disease and economic burden. Human milk feeding in preterm infants, although related to a slower weight gain than formula feeding, is associated with a better recovery of body composition through the promotion of fat-free mass deposition, which may ultimately lead to better metabolic and neurodevelopmental outcomes. Promotion and support of human milk feeding should be considered a priority in preterm infants' care (1). Beyond somatic growth, breast milk as a biologic fluid has a variety of other benefits, including modulation of postnatal intestinal function, immune ontogeny, a lower incidence of infectious diseases and better brain development. Although breastfeeding is highly recommended, breastfeeding may not always be possible, suitable or solely adequate so it needs to be enriched by fortifier. Infant formula is an industrially produced substitute for infant consumption. Infant formula attempts to mimic the nutritional composition of breast milk as closely as possible, and is based on cow's milk or soymilk. A number of alternatives to cow's milk-based formula also exist (2). In preterm and low birth weight infants, feeding with formula milk, compared with unfortified term human milk, leads to a greater rate of growth in the short term. The limited data available do not allow definite conclusions on whether adverse outcomes, including necrotising enterocolitis, are increased in infants who receive formula milk compared with term human milk. There are no data from randomized trials on the comparison of feeding with formula milk versus nutrient-fortified breast milk. This limits the implications for practice of this review as nutrient fortification of breast milk is now a common practice in neonatal care (3).

Extra uterine growth restriction (EUGR) is an identifiable marker for insufficient growth during hospitalization, common among preterm infants. Current definitions for EUGR are varied and can be classified as cross-sectional (weight at a given t-time <10th centile) or longitudinal (weight loss between birth and a given t-time >1SD) (4). Due to the different feeding types, and other possible risk factors there is a concern that some babies could have short and long term complications. Several studies have shown the association between poor postnatal growth and an increased morbidity and mortality both in the neonatal period and in later life. EUGR also influences neurodevelopmental outcomes of extremely low birth weight infants (ELBW), and may have significant effects on cardio-metabolic health (insulin resistance, diabetes mellitus, and hypertension) in later childhood and even adulthood (5). EUGR/PGF (postnatal growth failure) is diagnosed when weight is <10th percentile at either discharge or 36-40 weeks postmenstrual age. Although in common use, the phrases EUGR/PGF have limitations since they: (i) are not predictive of adverse outcome; (ii) are based only on weight without any consideration of head or length growth, proportionality, body composition, or genetic potential; (iii) ignore normal postnatal weight loss; (iv) are usually assessed prior to growth slowing of the reference fetus, around 36-40 weeks, and (v) are usually based on an arbitrary statistical growth percentile cut-off. Focus on EUGR/PGF prevalence may benefit with better attention to nutrition but may also harm with nutrition delivery above infants' actual needs (6).

AIM

The aim of this study was to determine the influence of nutritional type and other risk factors for insufficient postnatal weight gain in preterm infants at the Pediatric Clinic of the Clinical Center University of Sarajevo.

MATERIALS AND METHODS

This was a cross-sectional study which included 123 preterm infants admitted at the Pediatrics Clinic of the CCUS in the period from 1 January to 30 December 2018. The population included, preterm infants, born under 32 weeks of gestation. Patients were categorized into two groups based on the type of nutrition (mother's milk and adapted milk formula).

Parameters as gender, gestational week, birth weight, head circumference at birth and discharge, day of first feeding and day of full intake, gaining BW and days of hospitalization, collected from patient's charts, were compared between these two groups in order to establish the correlation between the two types of nutrition and EUGR at discharge. Mother's risk factors, presence of NEC (Necrotizing enterocolitis defined according to Bell's criteria, stage 2 or higher) and application of inotropes and caffeine were also taken in consideration. Gestational age was calculated based on the last menstrual period. Body weight and head circumference were measured by birth as well as before discharge. Percentile and *z* scores of weight at birth were calculated using the Fenton growth charts as well as the size at discharge. The definition of EUGR was taken as a weight under 10th percentile at given time for affiliating gestational week.

Statistical analysis was performed with IBM Statistics SPSS v 25.0 considering that the distributions didn't allowed normal distribution, non-parametric tests as the Chi-Square, Mann-Whitney U were used. Linear regression model was created for examination of influence of other risk factors (for which it was possible to be narrowed down as acceptable for inclu sion in the analysis). Cross tabulation was used in gender distribution comparison between the two main groups. All possible regressions were conducted with covariates based on the *p* value ($p < 0.10$) in the univariate analysis.

RESULTS

The study included 123 (58 female and 65 male) infants born under 32 weeks of gestation who were divided according to type of feeding into mother's milk (MM) and adapted milk formula (AMF) groups. In the MM group there were no children fed with mother's milk with additional fortifier. The results were shown in the table below:

Table 1 **Perinatal characteristic and body size of study population fed with mother's milk (MM group) and adapted milk formula (AMF group).**

	MM group (n = 59)	AMF group (n = 64)	p
Gestational age (weeks)	30.02 ± 1,76	30.22 ± 1,79	0.39
Birth weight (grams)	1583.30 ± 413.88	1476.87 ± 433.96	0.15
Head circumference at birth (cm)	29.01 ±1.97	28.90 ± 2.12	0.70
Head circumference at discharge (cm)	31.90 ± 1.01	31.81 ± 1.01	0.64
Day of first feeding	2.79 ±1.60	2.72 ±1.96	0.72
Full intake (day of life)	13.98 ±7.47	15.44 ±9.37	0.60
Gaining BW (day of life)	18.32 ±8.29	17.62 ±6.16	0.84
Days of hospitalization	38.07 ±18.60	42.08 ±22.33	0.48

Table 2 **Fraction of male and female patients and type of nutrition in EUGR and non-EUGR population.**

	EUGR	Non EUGR	Total
Adapted milk formula	56.3%	43.7%	100%
Mother's milk	42.37%	57.63%	100%
Male patients	33	32	65
Female patients	28	30	58
Percentage	49.59%	50.41%	100%
Total (male/female)	61	62	123
Mean Z-score	0.57±0.90 (range -1.50-2.89)	-0.58±0.74 (range -2.20 -1.51)	
(H=43.452; p<0.0001) (Chi-square=2.365; p=0.087)			

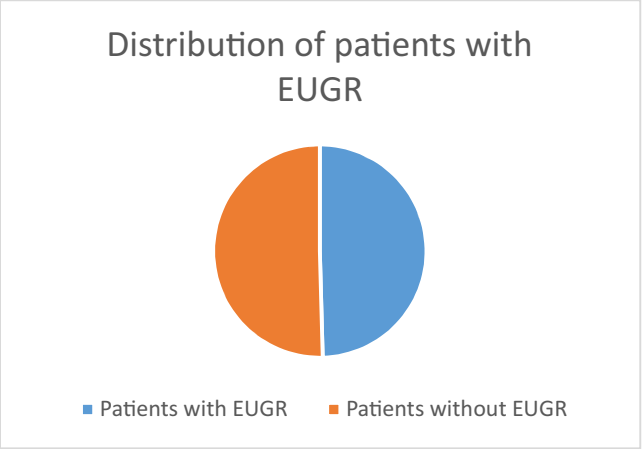

Figure 1 **Distribution of patients with EUGR.**

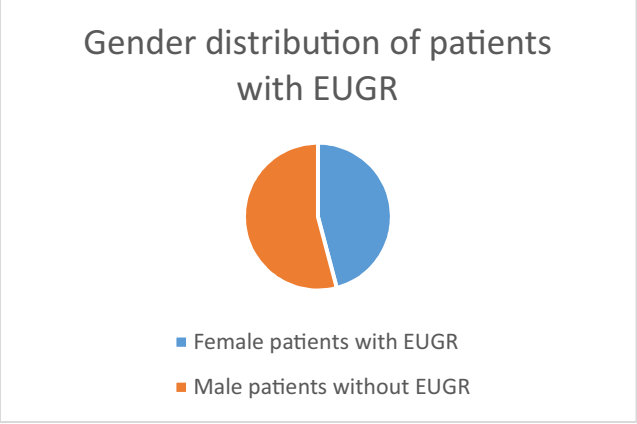

Figure 2 **Gender distribution of patients with EUGR.**

After defining groups of EUGR and non EUGR patients we analyzed the influence of different factors on EUGR at discharge. We found two variables that were significantly different between EUGR and non EUGR patients such as: gestational weeks (p=0.006), meaning that children born after shorter gestation were more prone to be EUGR, and days of hospitalization (p=0.001), meaning that EUGR children, as expected, spent more time in hospital as compared to non EUGR group.

Other analyzed variables which showed no difference between EUGR and non EUGR patients were: gender (p=0.58), Apgar score in the 1st minute (p=0.43), Apgar in the 5th minute (p=0.29), respiratory distress syndrome (RDS) (p=0.2), mechanical ventilation (p=0.56), surfactant (p=0.72), inotrope support (p=0.99), use of caffeine citrate (p=0.51), day of first feeding (p=0.52), day of full intake (p=0.59), necrotizing enterocolitis (NEC) (p=0.99), persistent ductus arteriosus (PDA) (P=0.96), bronchopulmonary dysplasia (BPD) (p=0.83), Intraventricular hemorrhage (IVH) (p=0.93), hypoglycemia (p=0.92).

DISCUSSION

Thanks to many prenatal and postnatal strategies based on well-designed studies, the survival of premature infants is constantly increasing, but the intact survival of these infants remains a significant challenge for the neonatologists. Current neonatal nutrition practice shows a significant calorie and protein deficit during early postnatal life. Consequently, many preterm infants are growth-restricted by the time they are ready for hospital discharge (7). As many studies have demonstrated that inadequate early nutrition has an adverse influence on long-term developmental outcome extra uterine growth restriction (EUGR) became a major clinical problem in very-low-birth-weight (VLBW) infants. (8) EUGR is defined as having a measured growth parameter (weight, length, or head circumference) that is <10th percentile of intrauterine growth expectation based on estimated postmenstrual age (PMA) in premature (23-34 weeks estimated gestational age) neonates at the time of hospital discharge (8). The incidence of postnatal growth failure in VLBW infants ranges between 43% and 97% in various centers (9-14). EUHGR is another important parameter, defined as decreased head circumference -for age-Z scores to <2 SD, and has been associated with suboptimal neurodevelopmental outcomes (15).

As far as we know, no study has been done in our country to determine the incidence of EUGR among preterm infants in neonatal intensive care units. With this study we wanted to determine the frequency of children with EUGR in our department. In our study, out of total number of 123 patients, we found 61 with EUGR (49.59%), which was comparable with other authors like Kavurt S, et al. (2018) (15) who had screened 140 preterm infants and postnatal growth retardation (PNGR) was detected in 46 babies (37%). Sakurai M, et al described a population of 416 infants of GA ≤32 weeks from 22 centers in Japan born in 2002, among whom the incidence of EUGR was 57%, 48%, and 6% for weight, length, and head circumference, respectively (16). Being aware of the importance of postnatal weight gain on overall long-term health the American Academy of Pediatrics Committee on Nutrition recommends the nutritional goals of preterm infants to provide nutrient that permits the postnatal growth rate and the composition of weight gain to approximate that of a normal fetus of the same PMA and to maintain normal concentrations of blood and tissue nutrients (17).

There are three stages of nutrition support in preterm infants: (1) early aggressive nutrition during the first several weeks after birth (acute stage); (2) fortified human milk or preterm formula for the intermediate period when infants are commonly slowly advanced to full enteral nutrition (growing care stage); and (3) the post discharge stage (7,12,16,18,19).

The aim of our study was also to explore the impact of two different nutritional types (mother's milk vs. adapted milk formula) on weight gain and EUGR at discharge. There are well known significant benefits from mothers' own milk for preterm infants, but mother's own milk is nutritionally inadequate to meet the needs of infants weighing <1500 g at birth, unless it contains multinutrient human milk fortifiers (HMFs) (20). Out of all patients fed with adapted milk formula 56.3% were considered having EUGR while 42.37% patients fed with mother's milk formula were considered having EUGR at discharge (Chi-square=2.365; p=0.087) so statistical significant difference couldn't be found. One of the limitations of our study was that we added no fortifier to mother's milk. In our study gestational age was proven to be non-independent variable related to longer time period for gaining birth weight. Other studies confirmed this observation (7, 15). As expected, EUGR newborns needed more days of hospitalization before reaching birth weight. As EUGR is recognized as a pathological pattern of physical progression in preterm infants with long-term consequences, it is necessary to find ways to reduce it. This was done at the New York State Regional Perinatal Center where neonatologists using quality improvement principles sought to improve neonatal growth by adopting better nutritional practices identified through literature review and collaborative learning. They achieved a 19% reduction in postnatal growth restriction. The project participants achieved the desired changes in: initiation of feedings, earlier breast milk fortification, and evaluation of feeding tolerance (21). This study, which determined the frequency, represents the first step in our intention to reduce EUGR.

CONCLUSION

Out of 123 preterm infants 61 patients (49.59%) were considered to have EUGR at discharge, which was worrisome percentage and should be further investigated. Nutritional type (MM vs. AMF) showed no effect on gaining weight in preterm infants and occurrence of EUGR. Lower gestational age was proven to be a risk factor for EUGR. Children with restricted postnatal growth needed longer hospitalization. Focus should be put on improving nutritional approach and feeding methods in order to prevent EUGR. In future, new studies should be conducted so that advancements of new improvements and changes in practice could be measured accordingly.

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Retroperitoneal liposarcoma radiologically and biochemically mimicking pheochromocytoma - case report

Retroperitonealni liposarkom sa radiološkim i biohemijskim oponašanjem feohromocitoma - prikaz slučaja

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ABSTRACT

Introduction: retroperitoneal liposarcoma is an extremely rare malignant tumor with an incidence of around 2-3/1 million. Liposarcoma can develop in any part of the body that contains fat. Only 15% of liposarcomas develop retroperitoneally. Case presentation: we present a case of a 68-year-old female patient with non specific symptoms that were present for the last six months, and which intensified in the last month due to the mass effect of the retroperitoneal tumor. The patient underwent a radical nephrectomy and she was under the constant control of oncologist. Conclusion: for diagnosis and treatment there is a crucial importance a multidisciplinary and multimodal approach that includes specialists from different branches of medicine - specialist in family medicine, radiologist, surgeon, gastroenterologist, anesthesiologist, pathologist, oncologist. The method of choice for treatment is total tumor resection given that local recurrences are common and occur in 2 /3 of patients.

Keywords: liposarcoma, retroperitoneum, multidisciplinary, multi-modality approach

SAŽETAK

Uvod: retroperitonealni liposarkom predstavlja izuzetno rijedak maligni tumor sa incidencom 2-3 na million stanovnika. Može se razviti u bilo kojem dijelu tijela koji sadrži mast. Samo 15% liposarkoma lokalizirano je retroperitonealno. Prikaz slučaja: prezentujemo slučaj pacijentice u dobi od 68 godina sa nespecifičnim simptomima koji su bili prisutni u posljednjih šest mjeseci, a koji su se intenzivirali u posljednih mjesec dana usljed efekta mase retroperitonealnog tumora. Pacijentici je urađena radikalna nefrektomija te je pod stalnom kontrolom onkologa. Zaključak: za dijagnosticiranje i tretman od presudnog značaja jeste multidisciplni-rani kao i multimodalitetni pristup koji uključuje specijaliste različitih grana medicine - spec. porodične medicine, radiolog, hirug, hastroenterolog, anesteziolog, patolog, onkolog. Metoda izbora za liječenje je totalna resekcija tumora jer su lokalni recidivi česti i javljaju se kod dvije trećine pacijenata.

Ključne riječi: liposarkom, retroperitoneum, multidisciplinarni, mul- timodalitetni pristup

INTRODUCTION

Retroperitoneal liposarcoma is one of the most frequent primary retroperitoneal neoplasms. It is a tumor of mesenchymal origin that most often occurs in the age group of 40 - 60 years, without gender predilection (1). The most common histological subtype is well-differentiated liposarcoma (about 55% of cases). One of the most significant differential diagnoses of retroperitoneal liposarcoma is pheochromocytoma, due to the rare tendency of retroperitoneal liposarcomas to biochemically resemble pheochromocytoma (probably due to mass effect on the adrenal gland) (2). Also, the radiological differentiation of two lesions can be extremely difficult due to similar localization, as well as similar radiological characteristics. The only clue that it is liposarcoma can be the presence of macroscopic fat in the tumor, which is extremely rare in pheochromocytoma (2). Suspicion of pheochromocytoma is extremely important due to the necessary preoperative preparation of the patient, as well as intensive monitoring during the surgical procedure (3). We present a case of retroperitoneal liposarcoma that resembles pheochromocytoma biochemically and radiologically.

CASE REPORT

A 68-year-old woman, whose complaints started six months ago and which reflected in pain under the right rib cage extending into the back, accompanied by nausea reported to the emergency department. The complaints had become more intense during the last month; she felt weakness, malaise, loss of appetite and, for the past few days, fever up to 37.5. She visited the Clinic of Emergency Medicine, where physical examination revealed palpation sensitivity and pain under the right rib cage and pain in the right lower back spreading to the abdomen. For the past six years, her blood pressure had been oscillating occasionally and during the last month she was experiencing hypertension, despite the prescribed therapy. Cholecystectomized in 2018, with pathological diagnosis of chronic cholecystitis. In 2020, excision of a pathologically verified hemangioma on the lower lip was performed. On admission, a sonographic examination of the abdomen was performed, which recorded an enlarged right kidney with longitudinal diameter of 12 cm, bizarre appearance and heteroechoic parenchyma. Laboratory findings on admission showed leukocytosis, elevated CRP, pathological hepatogram, pathological urine, elevated metanephrine values, vanillinmandelic acid (VMA) (Table 1).

Table 1 **The laboratory values on admission**.

Analysis	Value	Reference value
Leukocytes	12,68	4 - 10
Erythrocytes	4.80	3.8 - 5
Hemoglobin	132	120 – 160
Hematocrit	43	37 – 47
Thrombocytes	268	150 – 400
Glucose	6.6	3.3 – 6.1
Urea	3.1	2.0 – 7.8
Creatinine	66	63 - 109
AST	56	0 - 31
ALT	88	0 - 36
LDH	275	123 - 243
GGT	143	9 - 35
CRP	71.3	0 - 5
Metanefrine	69.9	<65
VMA	40.3	8.1 – 37.8

An MRI examination of the abdomen was performed, on which the right adrenal gland was not visualized, and in its space a large expansive formation of most likely adrenal origin was localised, which was clearly limited, with inhomogeneous structure, partly cystic, partly solid in character, paravertebrally not clearly separated from parietal peritoneum (Figure 1).

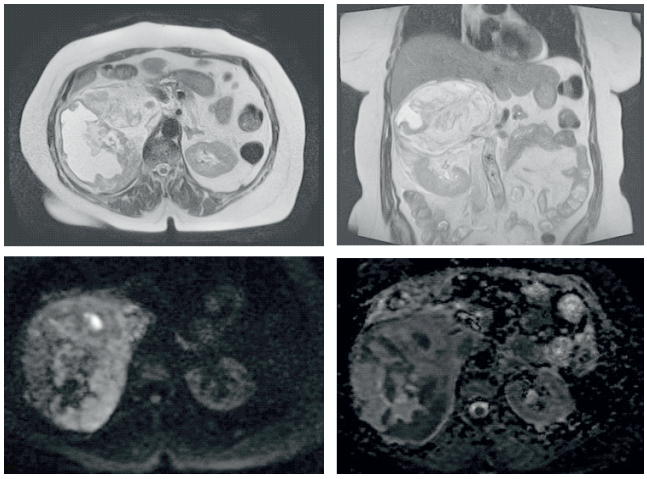

Figure 1 **Tumor image on MRI, (top left-axial T2-TSE, top right coronal T2-TSE, bottom left DWI axial, bottom right ADC).**

On the in/out of phase sequences, the tumor was hypointense, without a drop in signal intensity on the out of phase sequence, which indicated the absence of microscopic fat (Figure 2).

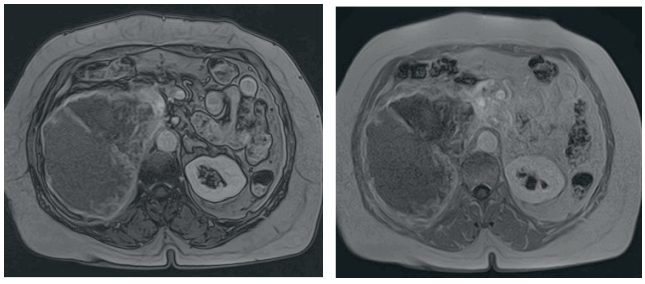

Figure 2 **Tumor image on MRI, T1 axial (in/out of phase).**

The patient was hospitalized at the Clinic for Endocrinology and a pheochro- mocytoma was suspected, given the radiological findings and elevated values of VMA and metanephrine (catecholamine hyperactivity of the tumor). Surgery was indicated with prior in-hospital preparation with alpha and beta blockers according to vital parameters.

After adequate preoperative preparation, the patient was hospitalized at the Urology Clinic, where radical surgery was performed, right-sided radical nephrectomy and adrenalectomy, the right kidney and right adrenal gland were removed along with the surrounding fat tissue. Final pathohistological diagnosis: Liposarcoma (dedifferentiated type), grade 3 - retroperitoneum. The tumor did not infiltrate the right adrenal gland or the right kidney. The patient was presented at the oncology board, which recommended a systemic chemotherapy. After the therapy, a re - staging CT scan of the whole body was performed, which was normal with no signs of metastatic disease or local recurrence (Figure 3).

Figure 3 **CT abdomen, axial. Postoperatively, surgical clip material, no residual tumor or recurrence.**

DISCUSSION

We presented the case of a 68-year-old female patient with non-specific symptoms that had been present for the past six months, which intensified over the past month due to the effect of a tumor mass localized in the right hemiabdomen. After the radiological examination of the patient, i.e. MRI examination of the abdomen, the radiologist suspected that it was a tumor mass of adrenal gland origin. After the examination by the endocrinologist, taking into account the elevated values of metanephrine and VMA, as well as the MRI examination of the abdomen, the patient's symptomatology in terms of the impossibility of controlling hypertension despite therapy, it was suspected that it was a pheochromocytoma. The radiological findings were in favour of pheochromocytoma due to the absence of intracellular fat on in phase/out of phase sequences. In addition, CT is also an important link in the diagnostic treatment of such patients. Although the suspicion of pheochromocytoma was a contraindication for the use of iodine contrast medium in the past, clinical studies have proven that this is not the case (4). In the case of the presented patient, the CT scan was performed in a private office outside our institution.

The general rule is that tumors of adrenal origin tend to grow large, usually over 3 cm, with an average size of approximately 5 cm (5). However, the same applies to liposarcomas, therefore the size of the tumor itself cannot be an important factor in the differentiation of these lesions, as our case shows. Differentiation of such lesions is especially difficult in cases of dedifferentiated liposacroma, such as ours.

The method of choice for treatment is total tumor resection if possible (6). Recurrences at the site of a previously verified tumor are common, occurring in two thirds of patients, precisely because of incomplete resection and extirpation of the tumor (7). A pathohistological finding is necessary for the final diagnosis. Of crucial importance for diagnosis and treatment is a multidisciplinary and multimodal approach that includes specialists from different disciplines - family medicine specialist, radiologist, surgeon, gastroenterologist, cardiologist, pathologist, oncologist, anesthesiologist.

The specific cause of retroperitoneal liposarcoma is still unknown (8). It is considered that there is a connection with mechanical damage to tissues or internal organs, as well as that it occurs in the background of benign formations. It is mostly detected in the later stage of the disease, when the tumor reaches a certain size, or incidentally due to the absence of symptoms and slow growth of the tumor. Most often, it gives hematogenous metastases in the liver and lungs. The prognosis depends on the histological subtype of the tumor. The five-year survival rate is about 50 % (9).

CONCLUSION

Radiological preoperative differentiation of tumors is sometimes impossible, due to similar behavior on radiological modalities, similar localization and infiltrative behavior, but also biochemical mimicry. Therefore, in case of doubt as to whether it is a liposarcoma or a pheochromocytoma, we suggest preoperative preparation and an operative approach as if it was a pheochromocytoma.

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