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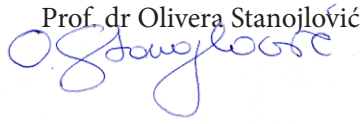

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ORIGINAL ARTICLE

Stress in pregnant women during the COVID-19 pandemic

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Summary

Introduction: Pregnancy is a vulnerable period in a woman's life when psychological distress can have negative consequences on both the mother and the fetus. Pregnant women and women in labor are at an increased risk of developing a more severe clinical picture of COVID-19 infection compared to non-pregnant women.

Aim: Examination of stress in pregnant women in Serbia during the COVID-19 pandemic.

Material and methods: Pregnant women were given an anonymous questionnaire during outpatient prenatal care. Socio-demographic characteristics, obstetric factors, COVID-19 history, DASS-21 questionnaire, and PREPS questionnaire were examined.

Results: Within the PREPS questionnaire, the average score for the domain "preparedness for childbirth" is 2.4±0.9, for the domain "infection" 2.9±1.0, and for the domain "positive appraisal" 3.7±0.8. A positive, weak, statistically significant correlation was registered between the domains "childbirth preparedness" and the domains "depression" and "anxiety" in the DASS-21 questionnaire. A positive, moderate, statistically significant correlation was found between the domain "childbirth preparedness" and the domain "stress" on the DASS-21 questionnaire. A positive, weak, statistically significant correlation was registered between the domain "infection" and "stress" on the DASS-21 questionnaire.

Conclusion: Two years after the pandemic was officially declared, pregnant women had either had a previous COVID-19 infection or had been vaccinated against it, so the scores of the domains "preparation for childbirth" and "infection" were lower than expected, while the score for the domain "positive appraisal" was higher compared to the studies conducted at the beginning of the pandemic. The obtained results strengthen future research on the association of depression, stress, and anxiety with stress in pregnancy caused by the COVID-19 pandemic.

Keywords: pregnancy, stress, COVID-19, DASS-21, PREPS

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INTRODUCTION

Pregnant women may be especially vulnerable to the negative impacts of events related to the COVID-19 pandemic and the stress they entail (1). Pregnancy is a sensitive period and can have negative consequences for the mother and the fetus. Throughout the period of COVID-19 pandemic depression and anxiety symptoms were heightened in pregnant women. These symptoms may have lasting effects on their children and relate to a raised risk of preterm birth, postpartum depression, and behavioral difficulties (2).

Throughout COVID-19, pregnant women perceived uplifted problems with mental health and stress, which can be dangerous to the fetus and the parent-child relationship (3). On the other hand, the study showed that the COVID-19 pandemic did not alter levels of observed stress and life pleasure in the tardy stage of pregnancy (4). Moreover, in comparison with pregnant women before the pandemic, pregnant women during the COVID-19 pandemic noticed a significant growth in symptoms of anxiety and depression (5).

The aim of this research was to examine stress among pregnant women in Serbia during the COVID-19 pandemic.

MATERIAL AND METHODS

A cross-sectional study was conducted in a Community Health Center in Belgrade, Serbia, from January to February 2022. The Ethical Committee approved this study under the license number 28711. An anonymous questionnaire was given to pregnant women to fill out during an outpatient examination. The questionnaire consisted of 5 parts: (1) socio-demographic characteristics (age, level of education, financial and marital status, (2) obstetric factors (gestational age, pregnancy planning, nulliparity, high-risk pregnancy, chronic diseases, infertility treatment), (3) COVID-19 history (whether they had had COVID-19 before and after pregnancy, vaccination status against COVID-19, loss of job due to pandemic, death of loved ones due to COVID-19), 4) DASS-21 questionnaire (21 questions to assess depression, anxiety and stress) and (5) PREPS questionnaire (15 questions to assess stress in pregnant women due to the COVID-19 pandemic in three domains: preparedness for childbirth, infection, positive evaluation).

Descriptive and analytical statistics were used in the statistical processing of data. From the methods of descriptive statistics, measures of central tendency (arithmetic mean, median), measures of variability (standard deviation and range), and absolute and relative numbers were used. The T-test (numerical data) and Chi-square test (nominal data) were used to compare statistically significant differences between groups. Pearson's or Spearman's correlation coefficient was used to examine the relationship, depending on the distribution of the data. Data processing was done using SPSS software, and a p-value <0.05 was considered statistically significant.

RESULTS

Sociodemographic characteristics

This research included 65 pregnant women with an average age of 32±4.9 years (23-45 years). **Table 1.** shows the socio-demographic characteristics of pregnant women.

Table 1. Sociodemographic characteristics of the examined pregnant women

		n (%)
Marital status:	married	41 (63.1)
	cohabitation	17 (26.2)
	single	6 (9.2)
	divorced	1 (1.5)
Employment:	employed	59 (90.8)
	unemployed	4 (6.2)
	student	2 (3.1)
Educational background:	college	11 (16.9)
	secondary school	14 (21.5)
	faculty	40 (61.5)
I currently live in	the city	61 (93.8)
	the village	4 (6.2)
How do you assess your financial status?	above average	5 (7.7)
	below average	2 (3.1)
	average	55 (84.6)
	the answer is missing	3 (4.6)

Two-thirds of pregnant women were married, and one third lived in cohabitation. Over 90% of pregnant women were employed, and two-thirds were highly educated. The majority, 85% of pregnant women, assessed their financial status as average, 7.7% above average, 3.1% below average, and 4.6% of pregnant women did not answer this question.

Obstetric factors

The average gestational age of pregnancy was 23.1±9.6 weeks. A total of 62 (95.4%) pregnant women declared that the current pregnancy had been planned. Previous birth was noted in 34 (52.3%), while 31 (47.7%) participants were primiparous. Of the women who had previous pregnancies, 25 (73.5%) had one birth, while 9 (26.5%) had two births. A total of 6 (9.2%) pregnant women were previously treated for infertility. For up to a year, 53 (81.5%) participants tried to get pregnant, 8 (12.3%) for more than a year, and 4 pregnant women did not answer this question. Eleven (16.9%) pregnant women reported having chronic diseases, while 2 (3.1%) reported having emotional or psychiatric problems.

COVID-19 history

Out of 65 pregnant women, 19 (29.2%) stated that they had had COVID-19 before the current pregnancy, 36 (55.4%) had never had COVID-19, and 10 (15.4%) pregnant women did not know with certainty whether they had suffered from COVID-19 before the current pregnancy or not. A total of 8 (12.3%) pregnant women had had an infection during the current pregnancy, and two pregnant women (3.1%) did not know for sure. Sixteen (24.6%) participants stated that they had been in contact with a COVID-19-positive person during their pregnancy. A total of 33 (50.8%) pregnant women were vaccinated against COVID-19, of which 27 received two doses and 6 received three doses of the vaccine.

Table 2. Results of the DASS-21 questionnaire by domains

Domain		n (%)
Anxiety	normal	17 (24.6)
	mild	34 (49.3)
	moderate	14 (20.3)
	difficult	4 (5.8)
Stress	normal	64 (92.8)
	mild	3 (4.3)
	moderate	2 (2.9)
	difficult	0 (0)
Depression	normal	59 (86.8)
	mild	8 (11.8)
	moderate	1 (1.5)
	difficult	0 (0)

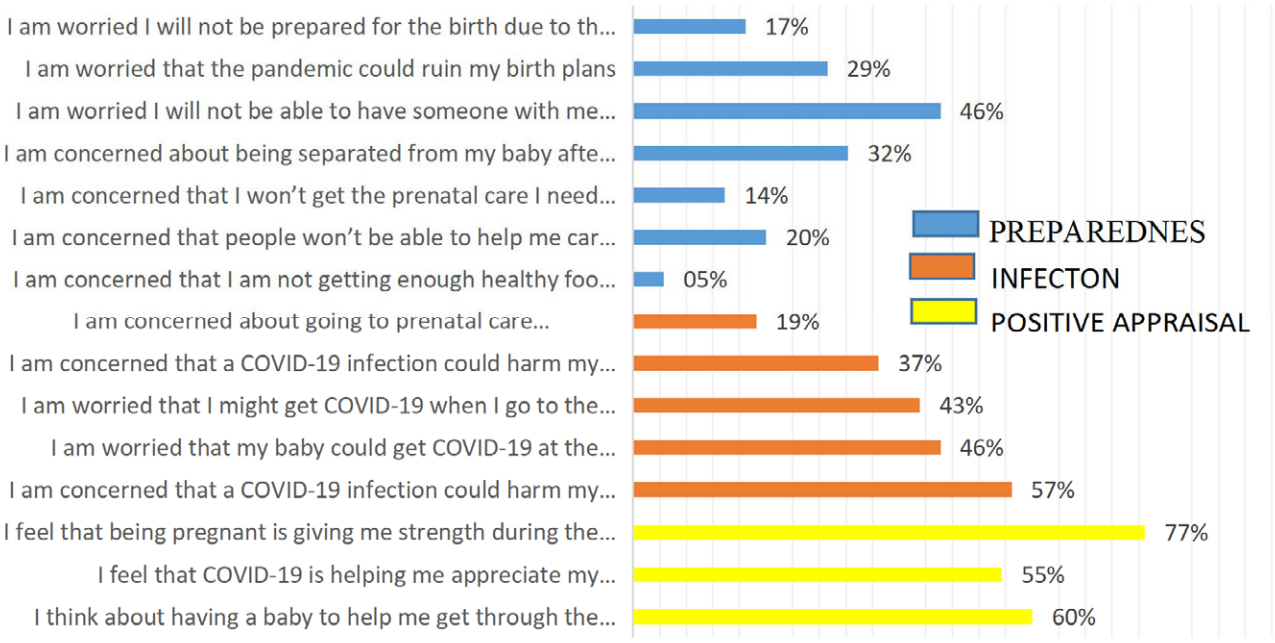
DASS-21 questionnaire

The results of the DASS-21 questionnaire according to domains are shown in **Table 2.**

Moderate anxiety was present in one fifth of pregnant women, while 5.8% had a more severe form of anxiety. Moderate stress and depression were present in less than 5% of pregnant women. No pregnant women were recorded in the category of "severe depression" and "severe stress."

PREPS questionnaire

Within the PREPS questionnaire, the average score for the domain "preparedness for childbirth" is 2.4±0.9, for the domain "infection" 2.9±1.0, and for the domain "positive evaluation of pregnancy" 3.7 ±0.8. **Graph 1** shows the percentage of responses ≥4 on a Likert scale ("agree", "strongly agree"). In the domain of "preparedness", 46.2% of women stated that they were afraid that, due to the pandemic, they would not be able to have their partner present during childbirth. One third of pregnant women said they were worried about being separated from their babies after giving birth due to the COVID-19 pandemic. One-fifth stated that they feared they would not be provided with adequate care after giving birth due to the COVID-19 pandemic. In the domain of "infection," about half of the surveyed pregnant women stated that they feared COVID-19 could endanger the health of their babies (56.9%), that they were worried that their babies could get COVID-19 in the maternity hospital (46.2%), and that they themselves could get COVID-19 in the maternity hospital (43.1%). Every third participant was afraid that COVID-19 could endanger her pregnancy, and about one fifth of them were worried that they could get sick by going to regular gynecological-obstetrical examinations.



Graph 1. Percentage of responses ≥4 on the Likert scale ("agree", "strongly agree")

Table 3. Correlation of PREPS questionnaire domains and vaccination status/previous COVID-19 infection

	No previous infection and no vaccine		Previous infection or vaccination		
	Arithmetic mean	SD	Arithmetic mean	SD	p
Infection	2.91	0.90	2.94	1.05	0.919
Preparedness for childbirth	2.30	0.76	2.44	0.97	0.565
Positive valuation	3.95	0.69	3.65	0.90	0.194

The relationship between the PREPS questionnaire and vaccination status/previous COVID-19 infection was examined **(Table 3)**. No statistical significance was observed.

The correlation of the domains of the PREPS questionnaire with the domains of the DASS-21 questionnaire was examined **(Table 4)**. A positive, weak statistically significant correlation was registered between the domain of readiness for childbirth and the domains of depression and anxiety in the DASS-21 questionnaire. A positive, moderately statistically significant correlation was registered between the domain of preparedness for childbirth and the domain of stress in the DASS-21 questionnaire. A positive, weak statistically significant association was registered between the domains of infection and stress in the DASS-21 questionnaire. No statistically significant association of the domain of infections with the domain of depression and anxiety in the DASS-21 questionnaire was found. There was no statistically significant correlation between the positive valuation domain and the DASS-21 questionnaire.

Table 4. Correlation of PREPS questionnaire domains with DASS-21 questionnaire domains

		Depression	Stress	Anxiety
Preparedness for childbirth	r	0.284*	0.337**	0.276*
	p	0.024	0.006	0.028
Infection	r	0.142	0.249*	0.223
	p	0.266	0.046	0.079
Positive valuation	r	-0.068	0.157	-0.001
	p	0.598	0.211	0.993

DISCUSSION

Like other studies (6, 7), this study's participants were surveyed by filling out questionnaires during outpatient examinations at gynecological-obstetrical clinics. In a study conducted in the USA by Preis et al. (8), as well as in studies conducted in Germany and Poland, pregnant women completed an anonymous survey online (9, 10).

The average age of pregnant women examined in Serbia coincides with the age of pregnant women examined in previous studies – 30 to 32 years of age (6-10). In this study, 89.3% of the surveyed women were married or cohabiting, which is relatively lower compared to previous studies. In Italy 99.2% and in Spain 92,7% of pregnant women stated they were in a stable relationship. (6,7,9,10).

The largest number of participants in Serbia (90.8%) were employed, which is about 15% more than the results obtained in other studies. Studies conducted in Spain and Poland showed that the number of employed participants was lower, around 75% (7,10).

The percentage of highly educated participants in Serbia was relatively high. The Polish study showed a similar level of education, while the Spanish study showed a 20% lower frequency of highly educated pregnant women (7, 10).

The frequency of primiparous women in our study was similar to studies from Italy, Spain, Germany and Poland. About half of the pregnant women were primiparous (7-10). The frequency of chronic diseases is similar to the results of a study conducted in Italy, less than a fifth of pregnant women had associated diseases (6). A 1.2-1.6% higher percentage of couples treated for infertility was observed in Serbia compared to similar studies in other countries (9,10). The frequency of emotional and psychiatric diseases among pregnant women was about 3%, as in the study conducted by Colli et al. (6). There is notable variation in PREPS questionnaire scores among currently existing studies. By comparing the average score of the "preparedness for childbirth" domain obtained by this study, a lower value is determined compared to all previous studies - in Spain (value 3.51), the USA (value 3-4), Poland (value 2.99±1 .14) and Germany (2.93±0.94). By comparing the average score of the domain "infections" obtained by this study, a lower value is determined compared to most previous studies - in Poland (value 3.46±0.95), Spain (value 3.10) and the USA (value 3-4), while only in the German study (2.60±1.03) was this value lower. By comparing the average score of the domain "positive evaluation of pregnancy" obtained by this study, the highest value is determined in relation to all previous studies - in Poland (value 1.85±0.87), Germany (2.05±0.91), the USA (value 2-3) and Spain (value 3.10). One of the main reasons for such results could be the fact that all the compared studies (7-10) were conducted in 2020, i.e., the same year when the COVID-19 pandemic was declared and when there was not enough knowledge about SARS-CoV-2 as a new virus. Also, two years had passed since the beginning of the pandemic, and a large number of pregnant women had been hospitalized for COVID-19 or had been vaccinated.

Due to the fact that a significant number of pregnant women were afraid that COVID-19 could threaten the existing pregnancy, childbirth, and the health of the newborn, health institutions at all levels of healthcare should be empowered to design or improve programs to reduce the fear of pregnant women caused by the COVID-19 pandemic.

In the second part of this study, the DASS-21 questionnaire was used to examine depression, stress and anxiety. Compared to studies conducted in Canada, Iran, and Malaysia, anxiety among pregnant women in Serbia during the COVID-19 pandemic is 1.3-5.4 times higher, but depression is 2.5-2.8 times less common. The exception are the results obtained in Malaysia, which are three times lower than the results of this study. The frequency of stress among pregnant women is 4.5 times higher compared to the study in Iran and 1.2 times lower than the study in Malaysia. In this study, there was no recorded case of severe depression or severe anxiety, while in other studies, they are present with a frequency of 0.5% to 9.3% for severe depression, i.e. 9.3% for severe stress (2, 11, 12).

CONCLUSION

Two years upon the start of the pandemic, pregnant women had already suffered from COVID-19 infection or had been vaccinated, so the scores obtained for the domains "preparation for childbirth" and "infection" were expectedly lower, while the score for the domain "positive evaluation of pregnancy" was higher compared to studies that were carried out at the beginning of the pandemic. The obtained results strengthen future research on the association of depression, stress and anxiety with stress in pregnancy caused by the COVID-19 pandemic.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Conception and design: KK, JML, AK
Data collection: AK, KK
Statistical analysis: JML
Writing the article: KK, NB, JML
Critical revision of the article: JML, AK
Final approval of the article: KK, AK, NB, JML

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STRES KOD TRUDNICA TOKOM COVID-19 PANDEMIJE

Konstantin Kostić[1,2], Aleksandra Kostić[3], Nikolina Banjanin[2,4], Jelena Milin-Lazović[2,5]

Sažetak

Uvod: Trudnoća je osetljiv period u životu žene kada psihološki distres može imati negativne posledice po majku i plod. Trudnice i porodilje su pod povećanim rizikom za oboljevanje težom kliničkom slikom od infekcije izazvane kovidom 19 u poređenju sa ženama koje nisu trudne.

Cilj rada: Ispitivanje stresa kod trudnica u Srbiji tokom pandemije kovida 19.

Materijal i metode: Anonimni upitnik dat je na popunjavanje trudnicama prilikom ambulantnog pregleda. Ispitivane su socijalno-demografske karakteristike, akušerski faktori, istorija oboljevanja od kovida 19, DASS-21 upitnik i PREPS upitnik.

Rezultati: U okviru PREPS upitnika, prosečna ocena za domen „pripremljenosti za porođaj" je 2,4±0,9, za domen „infekcija" 2,9±1,0, a za domen „pozitivno vrednovanje trudnoće" 3,7±0,8. Pozitivna, slaba statistički značajna povezanost registrovana je između domena pripremljenost za porođaj sa domenima depresija i anksioznost na DASS-21 upitniku. Pozitivna, umerena statistički značajna povezanost registrovana je između domena pripremeljenost za porođaj sa domenom stres na DASS-21 upitniku. Pozitivna, slaba statistički značajna povezanost je registrovana između domena infekcija i stres na DASS-21 upitniku.

Zaključak: Dve godine od početka pandemije trudnice su preležale infekciju izazvanu kovidom 19 ili su vakcinisane, pa su dobijeni skorovi domena „pripremljenosti za porođaj" i „infekcija" očekivano niži, dok je skor za domen „pozitivno vrednovanje trudnoće" viši u poređenju sa studijama koje su sprvedene na početku pandemije. Dobijeni rezultati osnažuju buduća istraživanja o povezanosti depresije, stresa i anksioznosti sa stresom u trudnoći prouzrokovanim pandemijom kovida 19.

Ključne reči: trudnoća, stres, COVID-19, DASS-21, PREPS

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ORIGINAL ARTICLE

Acute radiation toxicity in glioblastoma patients undergoing hypofractionated radiotherapy

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Summary

Introduction. Hypofractionated radiotherapy is the preferred regimen for older patients with glioblastoma and those with poor prognostic factors. Acute radiation toxicity remains a concern in these cases.

Aim. We conducted a retrospective analysis aiming to show the acute toxicity profile in patients with glioblastoma treated with hypofractionated radiotherapy, with or without temozolomide.

Material and Methods. This study included 25 patients with diagnosed glioblastoma who underwent a hypofractionated regimen of radiotherapy, with a dose of 40 Gy in 15 fractions or 34 Gy in 10 fractions. Acute radiation toxicity was observed during the treatment and graded according to Common Terminology Criteria for Adverse Events, version 5.0.

Results. Radiation toxicity was found in 60% of the patients. The majority of the patients with toxicity (80%) had toxicity grade 1. Fatigue was the most common grade 1 toxicity that was observed. One patient (6.7%) exhibited grade 3 radiation toxicity (somnolence and worsening of existing neurological condition). No patients had grade 4 radiation toxicity. A statistically significantly higher number of patients who experienced radiotoxicity were predominantly distributed in the group with tumors located in more than one lobe, multifocal or multicentric tumor compared to patients who had a tumor in one lobe ($p < 0.01$).

Conclusions. A hypofractionated regimen of radiotherapy represents a favorable option for the treatment of older patients with glioblastoma or those with poor prognosis, with an acceptable acute radiation toxicity profile.

Keywords: glioblastoma, hypofractionated radiotherapy, acute toxicity

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INTRODUCTION

Since 2005, the standard postoperative treatment for patients with glioblastoma has included concomitant radiotherapy (RT) with temozolomide (TMZ) and adjuvant TMZ, up to 6 cycles (1). Conventional fractionation implies prescribing a radiotherapy dose of 60 Gy in 30 fractions (1). For patients aged ≥ 65-70 years with poor performance status (Eastern Cooperative Oncology Group, ECOG, Performance Status 3 and 4) and with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter, hypofractionated radiotherapy is the preferred regimen (2–4). According to the European Society for Radiotherapy and Oncology and Advisory Committee on Radiation Oncology Practice guideline (ESTRO-ACROP) from 2016 and, guideline ESTRO and European Association of Neuro-Oncology (EANO) (ESTRO-EANO) from 2023, the most recommended radiotherapy dose in the hypofractionated regimen for glioblastoma patients is 40.05 Gy in 15 fractions (3,4). Nevertheless, 34 Gy in 10 fractions and 25 Gy in 5 fractions could be alternative hypofractionated schemes in some cases (3,4). Hypofractionated radiotherapy regimens are recommended for different groups of patients. A recent study investigated a moderately hypofractionated radiation therapy regimen in younger patients with good performance status, with a dose of 50 Gy in 20 fractions (5).

Delineation of the target volumes for hypofractionated radiotherapy should not be different from target volume delineation in those patients with conventional fractionation (3). Radiotherapy can be planned using 3D-conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT), or volumetric-modulated arc therapy (VMAT) (3).

Acute toxicity of the radiation treatment with or without chemotherapy with temozolomide could have a deleterious effect on the quality of life of some patients, and even pause or stop the treatment (6). However, in patients with glioblastoma and other high-grade gliomas, there is not much data about the toxicity profile of the hypofractionated regimen of radiotherapy. Even when there are data, they are poorly described (5). Although the brain is considered late-responding tissue with regard to radiotherapy effects, brain edema is one of the acute radiation toxicities (7) causing different symptoms, especially during hypofractionated radiotherapy (7,8).

This study aims to show the radiation toxicity profile in patients with glioblastoma who underwent hypofractionated radiotherapy with or without temozolomide.

MATERIAL AND METHODS

This retrospective study included 25 patients with histopathology-confirmed glioblastoma, (*isocitrate dehydrogenase*) IDH-*wild type* CNS WHO grade 4, treated with radiotherapy at the Institute for Oncology and Radiology of Serbia and/or with chemotherapy with TMZ at the Institute for Oncology and Radiology of Serbia and Clinic for Neurosurgery, University Clinical Center of Serbia, in the period 2023-2024. All data were obtained from medical records at the Institute for Oncology and Radiology of Serbia. The study was approved by the Ethical Research Committee of the Institute for Oncology and Radiology of Serbia, No 01-1/2024/1188.

All patients in the study underwent hypofractionated radiotherapy, with a total dose of 40.05 Gy in 15 fractions or 34 Gy in 10 fractions. Radiotherapy was planned with intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) **(Figure 1)**.

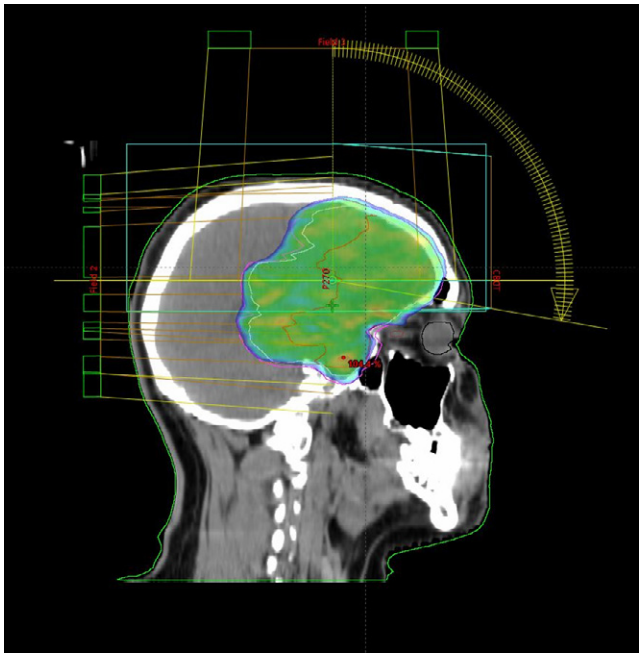

Figure 1. Volumetric modulated arc therapy (VMAT) in patients with glioblastoma treated with a hypofractionated regimen of radiotherapy. The green color in the brain represents 95% of the isodose distribution. The red color inside the green color represents gross tumor volume (GTV), the yellow color represents a margin of the clinical target volume (CTV), and the pink color represents a margin of planning target volume (PTV); a line with divisions and a triangle at the end (arc) of the line VMAT technique and radiation fields (Material from the Institute for Oncology and Radiology of Serbia).

Delineation of the target volumes was contoured according to ESTRO-ACROP guidelines for target delineation of glioblastomas. Patients who were eligible for chemotherapy (patients aged 18-75, ECOG PS < 3, with normal hematological, hepatic, and renal function) were prescribed temozolomide according to the protocol.

Patients were followed minimum once a week during the treatment. Acute radiation toxicity that was observed in patients during the treatment included fatigue, headache, worsening of existing neurological conditions, seizures, somnolence, and confusion. Radiation toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (9). Patients with

hematological toxicity and nausea were not included in this retrospective study. As the assessment of acute radiation toxicity of hypofractionated radiotherapy was our primary goal, we did not assess the overall survival of our patients.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 29.0 (IBM Corporation, Armonk, NY, USA) statistical software. Regarding descriptive statistics, measures of central tendency were used. Categorical data were analyzed using the Chi-square test, and Student's t-test was used for numerical data. P value < 0.05 was considered statistically significant.

RESULTS

Out of 25 patients included in the study, 60% were male. The mean age was 68.1 ± 8.8 years. Fifteen patients (60%) had multifocal, multicentric tumors, or tumor foci in more than one brain lobe. The majority of the patients (92%) included in the study underwent surgical resection (supramaximal resection, total resection, near-total resection, subtotal resection, or partial resection), while 8% of the patients underwent only tumor biopsy. More than half of the patients (56%) had tumor recurrence and/or remaining tumor before radiotherapy. 56% of the patients had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score 1, while 44% of the patients had ECOG PS scores 2 and 3. More than two-thirds of the patients (64%) had multiple comorbidities. Radiation toxicity was experienced in 15 patients (60%), while 80%

Table 1. Patient's clinical characteristics and demographic data

	Frequency (percent) of patients/mean ± standard deviation
Sex	
Male	15 (60%)
Female	10 (40%)
Age	68.1 ± 8.8*
Histopathology	
Glioblastoma, IDH-wild type CNS WHO grade 4	25 (100%)
Tumor site	
1 lobe	10 (40%)
> 1 lobe, multifocal or multicentric	15 (60%)
Surgical treatment	23 (92%)
Biopsy	2 (8%)
Tumor recurrence and/or tumor remaining	14 (56%)
ECOG PS**	
1	14 (56%)
2	8 (32%)
3	3 (12%)
Comorbidity	
1	9 (36%)
≥ 2	16 (64%)
Radiotherapy dose	
40.05 Gy/15 fractions	24 (96%)
34 Gy/10 fractions	1 (4%)
Concurrent TMZ***	15 (60%)
Radiation toxicity	15 (60%)
Grade of radiation toxicity	
1	12 (80%)
2	2 (13.3%)
3	1 (6.7%)

*Age at diagnosis was presented as means ± standard deviation
** ECOG PS - Eastern Cooperative Oncology Group Performance Status
***TMZ - Temozolomide

Table 2. Clinical characteristics of patients with glioblastoma treated with hypofractionated radiotherapy in relation to radiation toxicity

	Radiation toxicity	*p* value
Age		
< 70	7 (46.7%)	0.742
≥ 70	8 (53.3%)	
Tumor remaining/recurrence of the tumor		
No	6 (40%)	0.622
Yes	9 (60%)	
ECOG PS*		
1	7 (46.7%)	0.250
≥ 2	8 (53.3%)	
Tumor site		
1 lobe	3 (20%)	**0.01**
≥ 2 lobes, multifocal/ multicentric tumor	12 (80%)	
Comorbidities		
0, 1	5 (33.3%)	0.734
≥ 2	10 (66.7%)	
	15 (100%)	

* ECOG PS - Eastern Cooperative Oncology Group Performance Status

of the patients with toxicity had toxicity grade 1. The most common grade 1 toxicity observed was fatigue, followed by headache. One patient (6.7%) exhibited grade 3 radiation toxicity in the group with toxicity. This patient experienced grade 3 somnolence, as well as worsening of existing neurological condition. No patients had grade 4 radiation toxicity. Complete patients' clinical characteristics and demographic data are presented in **Table 1.**

We also analyzed whether sex, age (< 70 and ≥ 70), tumor recurrence and the tumor remaining, ECOG PS (1 and ≥ 2), tumor site (1 lobe and more than 1 lobe, multifocal/multicentric tumor) and comorbidities (without comorbidity or 1 comorbidity and ≥ 2 comorbidities) are associated with radiation toxicity. We did not find statistical significance for observed data, except for the tumor site. A statistically significantly higher number of patients who experienced radiotoxicity were predominantly distributed in the group with tumors located in more than 1 lobe, multifocal or multicentric tumor (80%) compared to patients who had a tumor in one lobe (20%) (**p < 0.01**) **(Table 2)**.

DISCUSSION

A hypofractionated regimen of radiation therapy is usually the recommended treatment for patients with glioblastoma and those with bad ECOG or Karnofsky performance status, poor prognosis, and/or for older patients. Given that older patients with glioblastoma tolerate the treatment less effectively compared to younger patients (6), many hypofractionated regimens have been recommended as a standard treatment for these patients. One of the concerns during hypofractionated regimens is acute and late toxicity. In a meta-analysis published in 2017, Liao et al. reported that patients older than 70 years treated with hypofractionated radiotherapy had better overall survival (OS) rates than patients treated with standard (conventional) fractionation, and the toxicity profile was similar between the groups (10). In our study, 15 patients (60%) experienced toxicity. Most of our patients experiencing toxicity (80%) had grade 1 toxicity, while toxicity grade 2 was observed in 13.3% of the patients and grade 3 in 6.7%. All of our patients received uninterrupted treatment. Brandes et al. reported that 25% of the patients treated with standard radiotherapy and concurrent and adjuvant temozolomide experienced mental deterioration. However, mental deterioration was observed immediately after completing concomitant treatment and six months after the treatment. No strictly acute radiation toxicity was observed and reported in these patients (6). Out of 15 patients with glioblastoma with poor prognostic factors included in the study, Jablonska et al. stated that grade 2 acute toxicities were observed in 3 patients during the treatment with hypofractionated radiotherapy and concomitant TMZ (11). The authors reported perilesional brain edema, hematological toxicity, anorexia, and asthenia as observed toxicities (11). These toxicities could be a consequence of concurrent treatment, as all patients in their study had concurrent treatment, while in our study 40% of the patients did not have concurrent treatment. In general, during concurrent treatment, there

can be no clear indication of whether a certain symptom is a result of a single treatment. Nevertheless, hematological toxicity can be related mostly to temozolomide and antiepileptic drugs (12,13).

Primarily, a hypofractionated regimen of radiation therapy may cause toxicity in the late-responding neural tissue (14). However, possible acute radiation toxicity should not be neglected. Radiation brain injury could be explained by processes such as blood-brain barrier breakage, neural progenitor cell death, and astrocyte senescence, leading to a neuroinflammation cascade and causing multiple symptoms and clinical signs (15).

Chang et al. investigated the outcomes of patients with glioblastoma treated with hypofractionated radiotherapy (16). The authors did not report significant acute toxicity in the observed group of patients (16). They assessed acute toxicity according to the daily dosage of corticosteroid therapy, and a median dose of dexamethasone was 16 mg per day. In our study, acute toxicity was not assessed according to the usage of the steroids. Rather, acute toxicity was assessed during the treatment and graded according to CTCAE, version 5.0. Nevertheless, in their study, the hypofractionated regimen involved a radiotherapy dose of 50 Gy in 20 fractions (2,5 Gy per day), and the radiotherapy was carried out in two phases, which differs from our study. In our study, radiotherapy was carried out in a single phase, and the daily radiation dose per fraction was slightly higher (2.67 Gy/day in twenty-four patients, and 3.4 Gy/day in one patient). A higher daily dose could potentially increase acute radiation toxicity. Steroids are often prescribed in patients receiving whole-brain radiotherapy (WBRT) or partial brain radiotherapy for primary brain tumors. The important question arises whether all patients undergoing hypofractionated radiotherapy should receive steroids in advance, even before starting radiation. The above-mentioned study reported no significant acute toxicity during radiotherapy (16), but in our study, most of the patients had grade 1 toxicity (80%) and steroids were prescribed individually. Marantidou et al. concluded that in patients with malignant glioma, bad performance status at the beginning of radiation therapy, and unresected tumors are the predictive factors of steroid use (17).

Older age (18) and poor performance status are recognized as factors for increased toxicity in patients who underwent chemoradiotherapy (19). Concerns for increased toxicity in older patients with glioblastoma are multiple comorbidities and different geriatric conditions, such as malnutrition (20). Furthermore, we analyzed whether clinical and demographic characteristics had an impact on acute radiation toxicity. Comparing the two groups, with and without tumor recurrence and the remaining tumor, there was no significant difference in occurrence of toxicity. Similarly, we did not find any statistically significant differences when comparing age, ECOG performance status, and comorbidities between the groups regarding occurrence of toxicity. However, patients with tumors extended in more than one lobe, and those with multifocal and multicentric tumors, experienced toxicity significantly more than patients with tumors located in one brain lobe. Treatment volumes and irradiated volumes could have a significant influence on the toxicity profile. Larger treatment volumes carry a higher risk of toxicity and radiotherapy-induced edema (7), and poor tolerance to the treatment. Brain tolerance to ionizing radiation is directly related to the radiation volume and the radiation dose (21). The blood-brain barrier disruption could cause acute leukoencephalopathy which is manifested by symptoms such as fatigue and headache (17). In addition to tumor cells, in tumors, there are numerous components such as immune cells, blood vessels, and metabolites (22). After radiation, the microenvironment can change, and proinflammatory cytokines are released, even from dying tumor cells (22). Proinflammatory mediators such as Interleukin-1, Interleukin-6, Tumor Necrosis Factor-α, and Transforming Growth Factor-β are observed after exposure to ionizing radiation in several organs, including the brain (21). It should be noted that patients with glioblastoma who receive temozolomide, may experience increased acute radiation toxicity. One reason is that temozolomide, in addition to its other mechanisms of action, acts as a radiosensitizing agent on glioma cells and fibroblasts (23). Additionally, worsening of neurological conditions of the patients, seizures and other symptoms may happen independently of radiation therapy. Tumor progression and neurological damage can also cause a patient's bad condition during the treatment, which can be difficult to assess.

Several ongoing research initiatives aim to investigate further hypofractionation schemes in glioblastoma driven by the belief in the positive radiobiological effect of hypofractionation in glioblastoma, such as overcoming the radioresistance of glioblastoma cells and reduced toxicity. FLASH radiotherapy, with an ultra-high dose rate (more than 40 Gy per second), is one of the possible future treatments (24). FLASH radiotherapy was investigated on animal models (mice) with glioblastoma, and the authors reported that FLASH radiotherapy with hypofractionated regimens can reduce neurotoxicity (25).

Limitations

Our study has a few limitations. First of all, it is a retrospective study. We believe that by conducting a prospective study more precise data could be obtained. Also, we observed 25 patients treated with hypofractionated therapy with or without temozolomide. With a larger number of patients, the study results would be stronger. Considering acute toxicity, we tried to focus on and observe symptoms and signs that were more related to radiotherapy. We did not include patients who had any hematological toxicity. However, temozolomide is a radiosensitizing

agent, so we cannot claim that all observed toxicity is associated with radiotherapy only.

CONCLUSIONS

A hypofractionated regimen of radiotherapy represents a favorable option for the treatment of older patients with glioblastoma or those with poor prognostic features. Acute toxicity of the hypofractionated regimen in our study was acceptable and did not require pausing or stopping the treatment. Since there are no clear recommendations for steroid use during hypofractionated radiotherapy, this study opens new questions about steroid use and steroid dosage in these patients. We encourage other researchers to further investigate hypofractionated radiotherapy and proper supportive therapy in patients with glioblastoma.

Conflicts of interest: None to declare.

Author contribution: Aleksandar Stepanović, Marina Nikitović, and Tatjana Arsenijević contributed to the conception and design of the work; Aleksandar Stepanović, Aleksandar Tomašević and Katarina Kopčalić contributed to the acquisition, analysis and interpretation of data; Aleksandar Stepanović, Ivan Bogdanović, and Bojana Poparić-Banđur contributed to the conception and design of the manuscript and preparation of the draft of the manuscript.

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AKUTNA RADIJACIONA TOKSIČNOST KOD PACIJENATA SA GLIOBLASTOMOM KOJI SU LEČENI HIPOFRAKCIONISANOM RADIOTERAPIJOM

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Sažetak

Uvod. Hipofrakcionisana radioterapija je preporučeni režim radioterapije za starije pacijente sa glioblastomom, kao i za pacijente sa nepovoljnim prognostičkim faktorima. Pojava akutne radijacione toksičnosti je jedna od dilema kod primene hipofrakcionisanog režima radioterapije.

Cilj. Sproveli smo ovu retrospektivnu studiju sa ciljem da prikažemo profil akutne toksičnosti kod pacijenata sa glioblastomom lečenih hipofrakcionisanim režimom radioterapije, sa ili bez primene temozolomida.

Materijal i metode. Ova studija je obuhvatila 25 pacijenata sa dijagnostikovanim glioblastomom koji su bili lečeni hipofrakcionisanom radioterapijom, sa ukupnom dozom od 40 Gy u 15 frakcija ili 34 Gy u 10 frakcija. Akutna radijaciona toksičnost koja je zabeležena tokom tretmana, gradirana je prema *Common Terminology Criteria for Adverse Events, version 5.0*.

Rezultati. Akutna radijaciona toksičnost je zabeležena kod 60% pacijenata. Većina pacijenata sa toksičnošću (80%) imala je gradus 1 toksičnosti. Najčešća toksičnost gradusa 1 koju su pacijenti imali bio je zamor. Jedan pacijent (6,7%) je imao radijacionu toksičnost gradusa 3 (somnolenciju i pogoršanje postojećeg neurološkog deficita). Nije zabeležena radijaciona toksičnost gradusa 4. Statistički značajno veći broj pacijenata koji su imali radiotoksičnost bili su raspoređeni u grupi pacijenata koji su imali tumor u više od jednog moždanog režnja, multifokalni ili multicentrični tumor, u poređenju sa pacijentima koji su imali tumor u jednom moždanom režnju ($p < 0.01$).

Zaključci. Hipofrakcionisani režim radioterapije predstavlja povoljnu opciju za lečenje starijih pacijenata sa glioblastomom ili onih pacijenata sa lošom prognozom, sa prihvatljivim profilom akutne radijacione toksičnosti.

Ključne reči: glioblastom, hipofrakcionisana radioterapija, akutna toksičnost

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Car index as a predictor of mortality in hospitalized patients with COVID-19-associated pneumonia

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Summary

Introduction/Aim: COVID-19-associated pneumonia is a serious form of the disease that can result in severe life-threatening complications. This study aims to evaluate the prognostic value of the CAR index in hospitalized patients with COVID-19-associated pneumonia.

Material and Methods: This was a single-centre prospective study conducted at the University Clinical Centre Zvezdara during April 2020 which included hospitalized patients diagnosed with moderate to severe COVID-19-associated pneumonia. The COVID-19 infection was verified by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test on a sample obtained from a swab of the nasopharynx. The CAR was calculated as CRP and albumin ratio.

Results: Two hundred and eight hospitalized patients with COVID-19-associated pneumonia were enrolled. Average age was 54.5±14.6 years, and participants were predominantly male (64.4%). Comorbidities were present in 67.3% of patients. The overall in-hospital mortality was 14.4%. CAR index level of 2.0 was identified as the cut-off point for predicting mortality, with sensitivity of 86% and specificity of 72% (AUC=0.844). In univariate regression analysis age, comorbidities, breathing difficulties and CAR index were identified as significant predictors of mortality ($p<0.050$ for all). In the multivariate analysis, age (RR=1.06; 95% CI: 1.02-1.09; p=0.001) and CAR index (RR=1.12; 95% CI: 1.02-1.23; p=0.019), were independent predictors of mortality in COVID-19-associated pneumonia patients.

Conclusion: This study demonstrated that routine blood testing can be beneficial in identifying COVID-19 patients with associated pneumonia who are at an increased mortality risk. The CAR index is a widely accessible, simple inflammatory marker that can be a valuable indicator for early differentiating levels of severity in patients hospitalized due to COVID-19-associated pneumonia.

Keywords: CAR index, COVID-19, pneumonia, mortality

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INTRODUCTION

The SARS-CoV-2 pandemic has caused a severe public health crisis and placed considerable pressure on healthcare systems worldwide. It has emerged as a significant threat to global well-being, resulting in over seven million documented fatalities, according to the WHO (1–4). COVID-19 commonly manifests with a range of symptoms, fever, persistent cough, breathing difficulties, extreme fatigue, and muscle aches being the most frequent ones. In addition to the usual symptoms, in some cases, COVID-19 patients have been shown to develop severe pneumonia, which can progress to acute respiratory distress syndrome (ARDS) (5–9)China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV. This progression can also result in the failure of organs other than the lungs and, in the most severe cases, death (5–7, 10)China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV.

COVID-19-associated pneumonia is a serious form of the disease that can result in severe life-threatening complications (6). Better patient care and more effective treatment plans require early and accurate predictions of patient outcomes. Although age, comorbidities, and clinical symptoms are helpful indicators of the disease prognosis, identifying more reliable prognostic markers has become a crucial aspect of clinical management for COVID-19-associated pneumonia patients (6, 10–12)especially in patients admitted to ICU as it can provide more useful consumption of health resources, as well as prioritize critical care services in situations of overwhelming number of patients. Materials and Methods. A multivariable predictive model for mortality was developed using data solely from a derivation cohort of 160 COVID-19 patients with moderate to severe ARDS admitted to ICU. The regression coefficients from the final multivariate model of the derivation study were used to assign points for the risk model, consisted of all significant variables from the multivariate analysis and age as a known risk factor for COVID-19 patient mortality. The newly developed AIDA score was arrived at by assigning 5 points for serum albumin and 1 point for IL-6, D dimer, and age. The score was further validated on a cohort of 304 patients admitted to ICU due to the severe form of COVID-19. Results. The study population included 160 COVID-19 patients admitted to ICU in the derivation and 304 in the validation cohort. The mean patient age was 66.7 years (range, 20-93 years.

Since its discovery as an acute-phase protein, CRP has served as a systemic marker for tissue damage, infection, and inflammation (13,14). During acute inflammatory responses, CRP expression quickly rises from its referent level (13,14), which makes it a valuable indicator in tracking the progression of COVID-19, enabling early identification of severe cases and helping to reduce mortality rates (6,15–17) making it important to understand the peculiarities of different populations. The aim of this study was to identify the main predictors associated with in-hospital mortality due to COVID-19 in Vilnius, Lithuania. Materials and methods This was a retrospective observational cohort study conducted at Vilnius University Hospital Santaros Clinics, Lithuania. The study included SARS-CoV-2 positive patients aged over 18 years and hospitalized between March 2020 and May 2021. Depersonalized data were retrieved from electronic medical records. The predictive values of laboratory parameters were evaluated using ROC analysis. Multivariable binary logistic regression was performed to reveal predictors of in-hospital mortality due to COVID-19. Results Among 2794 patients, 54.4% were male, the age median was 59 years (IQR 48-70. Albumin is another marker commonly measured in COVID-19 patients. Inflammation greatly influences this hepatically synthesized protein, hindering its formation and accelerating its degradation, leading to reduced quantities in the bloodstream. Hospitalized patients with low admission levels of serum albumin exhibit an increased risk of death, both in the short and long term (18). Observations in COVID-19 patients further support this association between low albumin and poor prognosis, linking low albumin levels to a less favorable outcome (19).

Combining CRP and albumin into a single index offers a valuable approach to assessing inflammation. This method efficiently merges CRP and albumin information by calculating their ratio, resulting in an index that directly correlates with infection severity. An increased ratio indicates a more severe state of inflammation (20). Increased levels of C-reactive protein (CRP) indicate the presence of acute inflammation, while low levels of albumin in the blood signal a state of inadequate nutrition and chronic inflammation. Combining these characteristics into a unified index may provide a more comprehensive understanding of the patient's condition in contrast to analyzing individual indicators separately. The C-reactive protein-to-albumin ratio (CAR) has garnered attention as a reliable prognostic factor in many diseases (21–23) using Cox proportional hazard model and Kaplan-Meier survival analysis. The 28-day mortality was 28.0%. In the univariate analysis, the Acute Physiology and Chronic Health Evaluation II (APACHE II, prompting further investigation about its potential in predicting mortality in patients with COVID-19 and its common complications (24,25). Therefore, this study aims to evaluate the prognostic value of the CAR index in hospitalized patients with COVID-19-associated pneumonia.

MATERIALS AND METHODS

This single-center prospective study was conducted at the University Clinical Centre Zvezdara in April 2020, involving hospitalized patients diagnosed with moderate to severe COVID-19-associated pneumonia. For conducting this research, the approval from the Ethics Committee of the University Clinical Centre Zvezdara was obtained.

COVID-19 infection was confirmed through a real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test on a nasopharyngeal swab sample. Patients were excluded if they had a history of hematological and/or autoimmune cancers. The patients' data were extracted from the electronic hospital information system, while anamnestic data were collected during the first day of hospitalization. Each patient underwent a chest X-ray to verify the diagnosis and location of pneumonia. Hematological and biochemical laboratory values were gathered within the first 24 hours of admission as part of the routine assessment. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the proportion of neutrophils by the percentage of lymphocytes. The CAR was calculated by dividing the value of CRP by the value of albumin. Pulse oximetry was monitored at regular intervals of two hours or continuously in individuals with severe COVID-19-associated pneumonia. Patients whose oxygen saturation levels were equal to or below 92% received oxygen treatment. The discharge criteria for patients were a negative nasopharyngeal swab and a radiographically confirmed reduction of pneumonia symptoms.

Statistical analysis

The descriptive statistics, including means, medians, standard deviations, and percentiles for numerical variables and absolute numbers and percentages for categorical variables, were used to characterize the study sample. Associations between categorical data were evaluated using the Pearson chi-square test or Fisher's exact test. Student's t-test or Mann-Whitney U test were used for numerical data to evaluate differences between patients with lethal outcomes and discharged patients. Univariate and multivariate logistic regression analyses were used to establish factors related to overall mortality. Significant variables from univariate analysis were included in multivariate regression, with mortality as the outcome. The results were expressed as relative risk and the corresponding 95% confidence interval (CI). Model discrimination performance was tested by means of sensitivity and specificity. The C statistic, representing the area under the receiver operating characteristic (ROC) curve, was used for the overall assessment of the predictive model. In all analyses, the level of statistical significance was set at $p \leq 0.05$. SPSS version 25 statistical software (Chicago, IL, USA) was used to perform the statistical analysis.

RESULTS

Two hundred and eight hospitalized patients with COVID-19-associated pneumonia took part in the study. The average age was 54.5±14.6 years, and the patients were predominantly male.

Table 1 presents the characteristics of the study population based on the occurrence of the lethal outcome. The overall in-hospital mortality of patients with COVID-19-associated pneumonia was 14.4%. The mean age was significantly higher in the lethal outcome group (67.8±13.0 years) compared to the non-lethal group (52.3±13.6 years) ($p<0.001$). Obesity was significantly more prevalent in patients with lethal outcome (30.0%) compared to discharged patients (14.6%) ($p=0.037$). Similarly, hyperlipoproteinemia (53.3% vs. 20.8%, $p<0.001$), diabetes mellitus (50.0% vs. 17.4%, $p<0.001$), chronic renal failure (16.7% vs. 6.2%, $p=0.046$), cardiovascular disease (73.3% vs. 52.8%, $p=0.036$), hypertension (70.0% vs. 46.1%, $p=0.015$), and the presence of comorbidities (90.0% vs. 63.5%, $p=0.004$) were all significantly more prevalent in the lethal outcome group. Coronary heart disease, autoimmune disease, pulmonary disease, and cancer did not show significant differences between the groups **(Table 1)**.

Table 1. Characteristics of study population according to lethal outcome

Variables	Total n=208	Exitus letalis: No n=178	Exitus letalis: Yes n=30	p
Gender-Male	134 (64.6)	112 (62.9)	22 (73.3)	0.270
Age*	54.6±13.5	52.3±13.6	67.8±13.0	**<0.001**
Smoking	34 (16.3)	32 (18.0)	2 (6.7)	0.121
Obesity	35 (16.8)	26 (14.6)	9 (30.0)	**0.037**
Hyperlipoproteinemia	53 (25.5)	37 (20.8)	16 (53.3)	**<0.001**
Diabetes mellitus	46 (22.1)	31 (17.4)	15 (50.0)	**<0.001**
Chronic renal failure	16 (7.7)	11 (6.2)	5 (16.7)	**0.046**
Cardiovascular disease	116 (55.8)	94 (52.8)	22 (73.3)	**0.036**
Hypertension	103 (49.5)	82 (46.1)	21 (70.0)	**0.015**
Coronary heart disease	25 (12.0)	18 (50.0)	7 (70.0)	0.261
Autoimmune disease	23 (11.1)	19 (10.7)	4 (13.3)	0.667
Pulmonary disease	8 (3.8)	7 (3.9)	1 (3.3)	1.000
Cancer	4 (1.9)	3 (1.7)	1 (3.3)	0.466
Comorbidities	140 (67.3)	113 (63.5)	27 (90.0)	**0.004**

Data are presented as n (%) and Pearson chi-square test or Fisher's exact test were used; *Data are presented as mean±sd and Student's t-test was used;

Table 2. Patients' symptoms at admission according to lethal outcome

Variables	Exitus letalis		p
	No n=178	Yes n=30	
Asymptomatic form of the disease	6 (3.4)	0 (0)	0.308
Prolonged contact with an infected person	27 (15.3)	3 (10)	0.582
Number of days from the onset of symptoms until admission to the hospital*	6 (1 - 22)	6.5 (2 - 15)	0.431
Breathing difficulties	34 (19.2)	16 (53.3)	**<0.001**
Cough	131 (73.6)	24 (80.0)	0.456
Fever	160 (89.9)	27 (90.0)	1.000
Fatigue	111 (62.4)	30 (100)	**<0.001**
Sore throat	18 (10.1)	1 (3.3)	0.321
Runny nose	10 (5.6)	0 (0)	0.363
Myalgia	28 (15.7)	4 (13.3)	1.000
Smell blindness	11 (6.2)	1 (3.3)	1.000
Taste blindness	12 (6.7)	0 (0)	0.222
Conjunctivitis-No	178 (100)	30 (100)	NA
Headache	17 (9.6)	0 (0)	0.141
Diarrhea	15 (8.4)	4 (13.3)	0.489
Loss of appetite	19 (10.7)	4 (13.3)	0.752
Chest pain	20 (11.2)	4 (13.3)	0.758

Data are presented as n (%) and Pearson chi-square test or Fisher's exact test were used; *Data are presented as median (range) and Mann-Whitney U test was used;

Symptoms experienced by patients with COVID-19-associated pneumonia based on their lethal outcome status are presented in **Table 2**. None of the patients with lethal outcome were asymptomatic. The median number of days from symptom onset to hospital admission was similar between the groups, with 6 days for the non-lethal group and 6.5 days for the lethal group (p=0.431). Breathing difficulties were significantly more prevalent in the lethal outcome group (53.3%) compared to the non-lethal group (19.2%) (p<0.001). Fatigue was present in all patients with lethal outcome (100%). All patients in both groups were free of conjunctivitis **(Table 2)**.

The use of mechanical ventilation was significantly more common among patients with lethal outcome (73.3%) compared to those who survived (5.1%) (p<0.001). Similarly, oxygen (O2) therapy was required for nearly all patients in the lethal outcome group (96.7%). The median number of days on O2 therapy was significantly longer for patients with lethal outcome compared to those who survived (8 days and 4 days, respectively; p=0.003). The median number of days of hospitalization differed significantly between the groups (p=0.001). Patients with lethal outcome had a shorter median hospital stay (8.5 days, range 1-22) compared to those who survived (14 days, range 3-44) **(Table 3)**.

Patients with lethal outcome had significantly higher median leukocyte counts (p<0.001) and neutrophil counts (p<0.001), while lymphocyte counts (p<0.001), eosinophil counts (p<0.001) and total protein levels were significantly lower in the lethal outcome group compared to those who survived. The neutrophil-to-lymphocyte ratio (NLR) was higher in the lethal outcome group than in the non-lethal group (p<0.001). Monocyte counts did not differ significantly between the groups (p=0.306). Patients with lethal outcome had significantly higher median uric acid levels (375.5, range 110-760) compared to

Table 3. Oxygen support in COVID-19-associated pneumonia patients according to lethal outcome

Variables		Exitus letalis		p
		No n=178	Yes n=30	
Mechanical ventilation		9 (5.1)	22 (73.3)	**<0.001**
O2 therapy		87 (48.9)	29 (96.7)	**<0.001**
Number of days on O2 therapy*		4 (0 - 32)	8 (1 - 30)	**0.003**
Oxygen therapy	Up to 5l	33 (40.7)	0 (0)	**<0.001**
	Over 5l to 10l	26 (32.1)	2 (7.7)	
	Over 10l	22 (27.2)	24 (92.3)	
Number of days of hospitalization*		14 (3 - 44)	8.5 (1 - 22)	**0.001**

Data are presented as n (%) and Pearson chi-square test or Fisher's exact test were used; *Data are presented as median (range) and Mann-Whitney U test was used;

Table 4. Patients' hematological and biochemical parameters at admission according to lethal outcome

Variables	Exitus letalis		p
	No n=178	Yes n=30	
Leukocytes	5.4 (1.8 – 19.3)	8.3 (2.6 – 22.5)	**<0.001**
Neutrophils	3.6 (0.9 – 17.6)	7.1 (2.0 – 20.6)	**<0.001**
Lymphocytes	1.1 (0.3 – 32.4)	0.7 (0.1 – 2.3)	**<0.001**
NLR	3.2 (0.7 – 27.6)	7.9 (0.3 – 95.3)	**<0.001**
Eosinophils	0 (0 – 1.9)	0 (0 – 0.1)	**<0.001**
Monocytes	0.4 (0.1 – 0.7)	0.3 (0.1 - 1)	0.306
Uric acid	270 (90 - 645)	375.5 (110 - 760)	**0.038**
D dimer	1.1 (0.1 – 31.1)	2.1 (0.5 – 13.2)	**0.027**
CRP	26.2 (0.2 – 371.8)	98.4 (28.5 – 420.9)	**<0.001**
Albumin	36 (22 - 48)	31 (18 - 38)	**<0.001**
CAR	2.2 (0 – 14.3)	3.2 (0.7 - 15)	**<0.001**
Total protein	71 (54 - 82)	64 (51 - 80)	**<0.001**

Data are presented as median (range) and Mann-Whitney U test was used;

those who survived (270, range 90-645) (p=0.038). D-dimer levels were also significantly elevated in the lethal outcome group compared to the non-lethal group (2.1 vs. 1.1, respectively; p=0.027). CRP levels were significantly higher in the lethal outcome group (p<0.001), while albumin levels were significantly lower in the lethal outcome group (p<0.001) compared to those who survived. In the lethal outcome group, the median CAR index was 3.2 (range 0.7-15), whereas in the non-lethal outcome group, the median CAR index was 2.2 (range 0-14.3). This difference was statistically significant (p < 0.001) **(Table 4)**.

The optimal cut-off value for the CAR index was determined based on ROC curve analysis. The area under the curve (AUC) value for the CAR index was 0.844. This analysis identified a CAR index level of 2.0 as the cutoff point for predicting mortality in COVID-19-associated pneumonia patients, with a sensitivity (Sn) of 86% and a specificity (Sp) of 72% **(Figure 1)**.

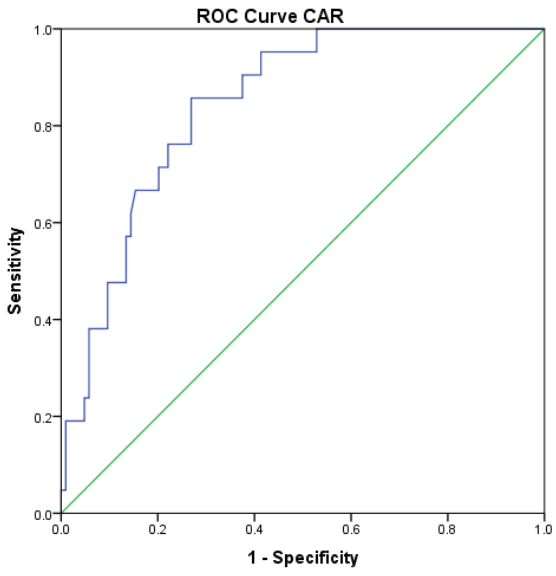

Figure 1. ROC curve for CAR index

The results of univariate and multivariate logistic regression analyses with lethal outcomes are presented in Table 5. In univariate regression analysis, age (p<0.001), comorbidities (p=0.019) and breathing difficulties (p=0.001) were identified as significant predictors of mortality in COVID-19-associated pneumonia patients. The CAR index was another significant factor, with an RR of 1.16 (95% CI: 1.06-1.28, p=0.001) **(Table 5)**.

In the multivariate regression analysis, age, with an RR of 1.06 (95% CI: 1.02-1.09, p=0.001) and CAR index, with an RR of 1.12 (95% CI: 1.02-1.23, p=0.019), were independent predictors of mortality in COVID-19-associated pneumonia patients **(Table 5)**.

DISCUSSION

The results of our study emphasize the significance of the CAR index in predicting mortality risk in hospitalized patients with COVID-19-associated pneumonia. The CAR index of ≥2.0 has been shown to be a reliable prognostic indicator for mortality in patients with COVID-19-associated pneumonia. It demonstrates high sensitivity in identifying those at risk of death and moderate specificity in accurately identifying those not at risk.

Our study has demonstrated that COVID-19 has a significant mortality rate, with the overall mortality of hospitalized patients being 14.4%. This finding aligns with a study conducted in Lithuania, which reported an in-hospital mortality rate of 12.7% (15) and closely matches the 13% mortality rate found by Fakih et al. in the US (26) and 13.9% case fatality rates reported in a systematic review by Rodriguez-Morales et al. (27). In contrast, Gujski et al. in Poland reported a higher in-hospital mortality rate of 18.4% (28). Moreover, research carried out in the UK revealed a death rate of 32.4% among patients who were hospitalized (19). This finding aligns with anoth-

Table 5. Univariate and multivariate regression analysis with mortality as dependent variable

Variables	Univariate analysis				Multivariate analysis			
	RR	95% CI	p		RR	95% CI	p	
Age	1.06	1.03	1.09	**<0.001**	1.06	1.02	1.09	**0.001**
Comorbidities	4.15	1.26	13.69	**0.019**				
Breathing difficulties	3.26	1.58	6.71	**0.001**				
CAR	1.16	1.06	1.28	**0.001**	1.12	1.02	1.23	**0.019**

RR-relative risk; CI-Confidence Interval;

er study that included 16.749 hospitalized patients with COVID-19 in the UK, which indicated a mortality rate of 33% (29). However, it is important to note that mortality rates within hospitals varied between several waves of the COVID-19 pandemic and across different populations (30–32).

From the first COVID-19 cases, it was observed that symptomatic patients had flu-like symptoms: fever, cough, fatigue, slight dyspnea, sore throat, headache, conjunctivitis, and gastrointestinal issues (33)a novel coronavirus from the same family as SARS-CoV and Middle East respiratory syndrome coronavirus, has spread worldwide leading the World Health Organization to declare a pandemic. The disease caused by SARS-CoV-2, coronavirus disease 2019 (COVID-19. In our study, breathing difficulties and fatigue were more frequently present at the beginning of the disease in deceased patients, which aligns with the findings of other authors (5)China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV.

Patients with COVID-19-associated pneumonia with a fatal outcome were more likely to have pre-existing conditions such as diabetes, obesity, hypolipoproteinemia, chronic renal failure, cardiovascular disease, and hypertension, compared to those who survived in our study. The role of comorbidities in COVID-19 mortality has been well-documented, with one recent meta-analysis specifically examining the prevalence of diabetes, hypertension, obesity, and asthma. This publication reports an overall incidence of hypertension, affecting 39% of patients, diabetes and obesity in 27% of patients. Additionally, the study found an 18% death rate among hospitalized patients with COVID-19 worldwide (34).

Diabetes is a prevalent comorbidity in COVID-19 patients, associated with severe complications (35)Setting, and Participants: Case series of patients with COVID-19 admitted to 12 hospitals in New York City, Long Island, and Westchester County, New York, within the Northwell Health system. The study included all sequentially hospitalized patients between March 1, 2020, and April 4, 2020, inclusive of these dates. Exposures: Confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2. In a study conducted on 5700 COVID-19 patients from 12 hospitals in the USA, diabetes was identified as the third most common comorbidity, present in approximately 34% of patients, following hypertension (56%), and obesity (42%) (35)Setting, and Participants: Case series of patients with COVID-19 admitted to 12 hospitals in New York City, Long Island, and Westchester County, New York, within the Northwell Health system. The study included all sequentially hospitalized patients between March 1, 2020, and April 4, 2020, inclusive of these dates. Exposures: Confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2. As in our study, publications consistently indicate that diabetes exacerbates the severity of COVID-19 outcomes (36). Patients with diabetes who had blood glucose level higher than 10 mmol/L had two to three times higher risk of severe COVID-19 and mortality compared to patients without diabetes (37)219 participants from IDF's Western Pacifi c Region who took part in the survey, there were almost equal numbers of men (2,124.

Obesity is a recognized risk factor for cardiovascular and respiratory complications, and its prevalence has raised concerns about its impact on COVID-19 outcomes (38,39). It increases the expression of ACE-2 receptors, contributes to organ damage, increases abdominal pressure, limits chest expansion and movement, and leads to insufficient respiratory compensatory function (40–43). Additionally, it impairs immune function and promotes inflammation, all of which may exacerbate the severity of COVID-19 (39). Studies indicate that higher body mass index (BMI) correlates with increased risks of hospitalization, ICU admission, and death in COVID-19 patients (44). The results of our study provide additional supporting evidence for the association between obesity and increased COVID-19 mortality rates.

Existing research has established a clear association between chronic cardiac disease and worse outcomes in COVID-19 patients. Studies have consistently shown that pre-existing chronic cardiac disease is a major risk factor for worse outcomes in COVID-19 patients who develop pneumonia (45). This increased risk is likely due to the significant strain severe pneumonia places on the heart's ventricles. This strain can lead to left ventricular dysfunction, potentially progressing to cardiogenic shock. Our findings align with existing research demonstrating a strong correlation between chronic cardiovascular disease (CVD) and increased mortality in patients with COVID-19 (46)epidemiology, clinical features, progression, and prognosis of the disease. Early identification of risk factors and clinical outcomes might help in identifying critically ill patients, providing appropriate treatment, and preventing mortality. We conducted

a prospective study in patients with flu-like symptoms referred to the imaging department of a tertiary hospital in Iran between March 3, 2020, and April 8, 2020. Patients with COVID-19 were followed up after two months to check their health condition. The categorical data between groups were analyzed by Fisher's exact test and continuous data by Wilcoxon rank-sum test. Three hundred and nineteen patients (mean age 45.48 ± 18.50 years, 177 women. A meta-analysis by Zhao et al. revealed that CVD elevated the mortality risk for COVID-19 patients by approximately fivefold (47).

Arterial hypertension is one of the most prevalent comorbidities found in COVID-19 patients. Despite its common occurrence, it remains unclear whether hypertension itself is a direct aggravating factor or if its impact is mainly due to its frequent association with older age and the resultant weakened immune system (48).

Recent meta-analysis reported an increase in mortality in overweight and obese COVID-19 patients in ten out of eleven analysed studies. Only one study did not find a difference in mortality between overweight and normal-weight patients. However, overweight patients demonstrated an increase in the severity of symptoms (12,34,49–52)and the clinical and laboratory characteristics associated with severity of illness. Design Prospective cohort study. Setting Single academic medical center in New York City and Long Island. Participants 5279 patients with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2.

The majority of routine laboratory parameters measured at admission were significantly different in deceased patients compared to patients who survived. These included the number of leukocytes, neutrophils, lymphocytes, and eosinophils, as well as D dimer, CRP, albumins, total protein, uric acid, and the NLR and CAR index. Our findings are in agreement with those of other authors (17,53–55) and highlight the potential prognostic value of these markers in COVID-19-related pneumonia. Considering that each of these parameters may be performed routinely, the significance of their predictive value lies in their wide availability.

Age and the CAR index were independent predictors of fatal outcomes in our study. Older patients were recognized to be at risk for mortality in almost all studies (24,56). CRP and albumin are often used to measure the level of inflammation (22). After the production of various cytokines in the infection (and some other conditions), the increase in C-reactive protein (CRP) is stimulated, and its high levels are associated with poor prognosis in critically ill patients (21,57)using Cox proportional hazard model and Kaplan-Meier survival analysis. The 28-day mortality was 28.0%. In the univariate analysis, the Acute Physiology and Chronic Health Evaluation II (APACHE II. Decreased serum albumin concentration was also shown to be a predictor of mortality in previous studies (18,21). CRP and albumin are known as positive and negative acute phase reactants, but their ratio (CRP/albumins) is considered a more precise indicator of inflammation (20,22).

The first study to report a significant and positive correlation between the CAR index and the severity of COVID-19 was published in 2020 by Wang et al. Consistent with our study's results, this study found that the level of CAR index was significantly higher among patients with severe COVID-19 in comparison with patients with non-severe symptoms. The results of the multivariate regression analyses that were reported in this research further demonstrated that CAR is an independent risk factor for the severity of COVID-19 (25). Another study, conducted in Turkey in 2021, evaluated the predictive value of the CAR index among COVID-19 patients. The authors of this study demonstrated the effectiveness of using the CAR for early differentiation of COVID-19 severity in hospitalized patients. The multivariate logistic regression analysis model in this study supports the claim that in severe cases of COVID-19, CAR can be considered a distinct risk factor. The ROC curve analysis performed in this study identified 0.9 as the relevant cut-off value of the CAR index for discrimination of severe COVID-19 patients, with 69.1% sensitivity and 70.8% specificity. In addition, the CAR index demonstrated a higher AUC in ROC analysis compared to CRP, indicating its superiority as a marker for early identification of severe COVID-19 (24).

This study has several limitations. Due to the small sample size, single-centre design, and inclusion of only hospitalized patients, it is not possible to generalize our results to the population of COVID-19 patients not requiring hospital admission. Larger multi-centre studies are necessary to confirm the use of CAR as a cost-effective prognostic index.

CONCLUSION

This study demonstrated that routine blood testing can be beneficial in identifying COVID-19 patients with associated pneumonia who are at a higher risk of mortality. The CAR index is a widely accessible, simple inflammatory parameter that can be a valuable indicator for early differentiating levels of severity in patients who have been admitted to hospital due to COVID-19-associated pneumonia. Using the CAR index ensures patient monitoring and management during pandemics such as COVID-19.

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CAR INDEKS U PREDIKCIJI MORTALITETA KOD PACIJENATA HOSPITALIZOVANIH USLED PNEUMONIJE IZAZVANE KOVIDOM 19

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Sažetak

Uvod/Cilj rada: Pneumonija izazvana kovidom 19 predstavlja ozbiljan oblik bolesti koji može dovesti do teških komplikacija koje ugrožavaju život. Ova studija ima za cilj da proceni prognostičku vrednost CAR indeksa kod hospitalizovanih pacijenata sa pneumonijom izazvanom kovidom 19.

Metod: Istraživanje je sprovedeno kao prospektivna kohortna studija u Univerzitetskom kliničkom centru Zvezdara tokom aprila 2020. Godine. U studiju su uključeni pacijenati koji su hospitalizovani zbog dijagnostikovane umerene do teške pneumonije uzrokovane kovidom 19. Infekcija usled kovida 19 potvrđena je reakcijom lančane polimeraze reverznom transkripcijom u realnom vremenu (RT-PCR) iz brisa nazofarinksa. CAR indeks je izračunat kao količnik CRP-a i albumina.

Rezultati: U studiju je uključeno 208 hospitalizovanih pacijenata sa pneumonijom izazvanom kovidom 19, prosečne starosti 54,5±14,6 godina, pretežno muškog pola (64,4%). Komorbiditeti su bili prisutni kod 67,3% pacijenata. Ukupan bolnički mortalitet iznosio je 14,4%. Vrednost CAR indeksa od 2,0 identifikovana je kao tačka preseka za predikciju mortaliteta, uz senzitivnost od 86% i specifičnost od 72% (AUC=0,844). U univarijantnoj regresionoj analizi, starost, komorbiditeti, otežano disanje i CAR indeks identifikovani su kao značajni prediktori mortaliteta (p<0,050, za sve analize). U multivarijantnoj analizi, starost (RR=1,06; 95% CI: 1,02-1,09; p=0,001) i CAR indeks (RR=1,12; 95% CI: 1,02-1,23; p=0,019) bili su nezavisni prediktori mortaliteta kod hospitalizovanih pacijenata sa pneumonijom izazvanom kovidom 19.

Zaključak: Rutinska analiza krvi može biti korisna u identifikaciji pacijenata sa pneumonijom izazvanom kovidom 19 koji su pod povećanim rizikom od letalnog ishoda. CAR indeks je široko dostupan, jednostavan inflamatorni marker koji može biti indikator za ranu diferencijaciju težine bolesti pacijenata sa pneumonijom uzrokovanom kovidom 19.

Ključne reči: CAR indeks, kovid 19, pneumonija, mortalitet

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ORIGINAL ARTICLE

Age, Glasgow Coma Scale and vasopressors as predictors of mortality in traumatized patients treated in the ICU

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Summary

Introduction: Trauma represents one of the most significant problems in public healthcare worldwide. It is one of the leading causes of mortality, particularly among children and young adults, but with a significant majority of non-fatal injuries that result in life-long disabilities and health consequences. Proper and timely identification of patients with a higher risk of mortality is crucial for better outcomes in patients who suffer from trauma. The aim of this study is to identify potential predictors of in-hospital mortality among patients who suffered trauma and are treated in the ICU (Intensive Care Unit).

Methods: The retrospective cohort study was conducted in a trauma, 12-bed ICU at the University Emergency Centre, University Clinical Centre of Serbia, Belgrade. All consecutive patients with blunt trauma were admitted to the ICU between August 2021 and August 2022. The primary outcomes of interest were all-cause in-hospital mortality. A value of $p < 0.05$ was considered statistically significant.

Results: GCS (Hazard ratio 0.924 95%CI 0.873 – 0.979), vasopressors (Hazard ratio 3.47 95%CI 1.373 – 8.787) and age (Hazard ratio 1.030 95%CI 1.014 – 1.047) can independently predict in-hospital mortality.

Conclusion:This study suggests risk factors for unfavorable clinical outcomes after severe

trauma. It may be essential to properly and promptly differentiate between individuals with lower

prognoses, which can lead to prompt and more aggressive treatment of these patients and might

decrease in-hospital mortality. Age, vasopressors and mechanical ventilation, in particular, may be helpful indicators of in-hospital mortality of traumatized patients treated in the ICU.

Keywords: GCS, age, vasopressors, ICU

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INTRODUCTION

Trauma represents one of the most significant problems in healthcare worldwide and, as such, is a great socioeconomic burden. It is one of the leading causes of mortality, particularly among children and young adults, but with a significant majority of non-fatal injuries that result in life-long disabilities and health consequences. Another noteworthy aspect of trauma are its long-term psychological health effects (1).

Several factors are identified as hallmarks of trauma lethality, so it could be predicted if death would occur within minutes, hours, or weeks after trauma. The leading cause of death following trauma is typically severe damage to the central nervous or cardiovascular systems. However, in ICU settings, death is more commonly attributed to sepsis or multiple organ failure (MOF) (2).

Studies have revealed a number of risk factors for the development of MOF, which can lead to death. The most common factors that stand out are age, gender, weight, head injury, traumatic coagulopathy and thrombocytopenia, and hemodynamic status of patients when admitted (3,4).

Considering all this, proper and timely identification of patients with a higher risk of mortality is crucial for better outcomes in patients who suffered from trauma. The aim of this study is to identify potential predictors of in-hospital mortality among patients who suffered from trauma and are treated in the ICU.

PATIENTS AND METHODS

Study design and population

The retrospective cohort study was conducted in a trauma, 12-bed ICU at the Emergency Centre, University Clinical Centre of Serbia, Belgrade. All consecutive patients with blunt trauma were admitted to the ICU between August 2021 and August 2022. The criteria for the inclusion were patients with blunt trauma who were older than 18 years admitted to ICU, a known mechanism of injury. Exclusion criteria were unknown patient identity, patients treated in another health institution for more than 24 hours, and patients who did not live more than 24 hours upon admission. All the necessary data were taken from the Emergency Center's information system (Heliant). The Institutional Review Board approved the study.

Evaluation upon admission

The patients were initially examined and cared for in the emergency room of the Emergency Center according to the trauma protocol. Vital parameters and prescribed therapy were recorded in the hospital's information system. After the diagnosis and the decision on further treatment, the patients were admitted to the ICU. Upon the admission to the ICU, data collected included sociodemographic characteristics of patients, the mechanism of injury, trauma distribution (head, thoracic, abdomen, etc.), the Abbreviated Injury Scale (AIS) score, the Injury Severity Score (ISS), and the patients underlying diseases. Also, factors such as the Glasgow Coma Scale (GSC), the need for blood products, the use of vasopressors, oxygen support, the need for mechanical ventilation (MV), the need for emergency surgery and clinical characteristics (body temperature, systolic and diastolic blood pressure, HR, SpO2) were recorded. According to the ICU treatment protocol, all patients had laboratory analyses (complete blood count, coagulation status, and biochemical analyses) and arterial gas analyses performed upon admission to the ICU. In addition to these values, all important clinical data about the patients were recorded in the electronic database.

Diagnosis and definition

The AIS is the anatomic scale used most widely for rating injury severity (17,18) and it has been used in conjunction with the ISS to identify the effects of multiple injuries on trauma victims (19). AIS and ISS were used to compare injuries. Severe trauma was defined as ISS above 15. The need for vasopressors was defined as mean blood pressure (MAP) lower than 65 mm Hg despite adequate fluid resuscitation. First line of vasopressors was Norepinephrine, infusion started with 0.05-0.1 mcg/kg/min and titrated upwards to achieve desired blood pressure. As other vasopressor support we used Vasopressin administered at a fixed rate of 0.03 units/min up to 0.04-0.06 units/min and Epinephrin with initial dose 0.01-0.1 mcg/kg/min. The need for oxygen support was defined as SpO2 below 89%. GCS below eight and SpO2 below 89% on O2 therapy were indications for mechanical ventilator support [20]. Indication for emergency surgery was provided by the treating emergency surgeons, neurosurgeons, or traumatologists. Coagulopathy refers to a disorder where the blood's ability to clot is impaired, leading to either excessive bleeding (due to inadequate clot formation) or thrombosis (due to excessive clot formation). In trauma patients, coagulopathy is often multifactorial and can result from tissue injury, shock, consumption of clotting factors, and the body's response to trauma. Coagulopathy in trauma patients is associated with poorer outcomes, including increased morbidity and mortality. Resuscitation protocols for post-traumatic coagulopathy focus on early recognition, targeted interventions, and aggressive management to stabilize and optimize the patient's coagulation status. Massive transfusion was defined as the need for more than ten units of packed red blood cells within 24 hours (21).

Outcomes

The primary outcomes of interest were all-cause in-hospital mortality.

Statistical analysis

Data are presented as the median (interquartile range [IQR]) for continuous variables and as the frequency (%) for categorical variables. The Man-Whitney U test was used for the two-group mean comparisons. Categorical data were compared using the Pearson test or Fisher exact test. Patient characteristics such as age, gender, comorbidity, injury characteristics and severity, and clinical characteristics were analyzed in a univariable Cox regression analysis. Parameters that were associated with higher mortality in the univariable analysis ($p < 0.20$), were entered in a multivariable model, and Cox regression was performed. Odds ratios with 95% confidence intervals were computed. A value of $p < 0.05$ was considered statistically significant. All analyses were performed using the SPSS (SPSS Inc. Chicago, USA), version 17.0 for Windows.

RESULTS

Of 193 patients admitted to the ICU during the study period, 148 (76.7%) were males, and the mean age of patients was 50.4±18.7. A total of 51 (26.4%) patients died. The sociodemographic characteristics of patients are shown in **Table 1**. One hundred and forty-two patients (73.6%) had polytrauma, whereas 45 (23.3%) had isolated traumatic brain injury (TBI). There is statistically significant difference comparing ISS score of patients who died and those who survived (p=0.044).

Table 1. Sociodemographic characteristics of patients

	Survivor	No Survivor	p-value
Characteristic	n = 142	n = 51	
Age *median (IQR)*	46 (28.25)	65 (28)	**<0.001**
Gender (males) *n (%)*	112 (78.9)	36 (70.6)	0.23
ISS *median (IQR)*	17.5 (16)	22 (19)	**0.044**
Polytrauma *n (%)*	103 (72.5)	39 (73.6)	0.585
Isolated TBI *n (%)*	33 (23.2)	12 (23.5)	0.966

Bold values are statistically significant.
ISS- Injury Severity Score; Isolated TBI- Isolated traumatic brain injury

In **Table 2** we have presented clinical characteristics of patients. In our study we found statistically significant difference compering the patients who survived and those who did not in terms of Glasgow Coma Scale (p<0.001), the need of mechanical ventilation (p<0.001) and vasopressor support (p<0.001).

The laboratory characteristics of our patients are shown in **Table 3**. Statistically significant difference, between the group of survivors and those who died, was only in terms of Oxygen saturation measured in arterial blood gases (p=0.006)

A Cox regression analysis was performed to ascertain the prediction of patients' characteristics on in-hospital mortality. The multivariate Cox regression model was statistically significant, $\chi^2(4) = 57.803$, $p < 0.001$. **Table 2** shows the univariate and multivariate Cox regression of predictors of in-hospital mortality. GCS (Hazard ratio 0.924 95%CI 0.873 – 0.979), vasopressors (Hazard ratio 3.47 95%CI 1.373 – 8.787) and age (Hazard ratio 1.030 95%CI 1.014 – 1.047) independently predict in-hospital mortality.

Table 2. Clinical characteristics of patients

	Survivor	No Survivor	p-value
Characteristic	**n = 142**	**n = 51**	
GCS *median (IQR)*	15 (1)	9 (10)	**<0.001**
SAP *median (IQR)*	130 (34.5)	130 (70)	0.381
DAP *median (IQR)*	80 (21.75)	80 (37)	0.839
MAP *median (IQR)*	97 (25.5)	97 (41)	0.624
HR *median (IQR)*	94 (26)	87 (39)	0.266
P/F ratio *median (IQR)*	395.45 (272.73)	295.45 (292.27)	**0.008**
Vasopressors *n (%)*	26 (18.3)	45 (88.2)	**<0.001**
Mechanical ventilation *n (%)*	56 (39.4)	50 (98)	**<0.001**
Erythrocyte transfusion ≥ 10 unites *n (%)*	8 (5.6)	4 (7.8)	0.575
FFP transfusion ≥ 10 unites *n (%)*	8 (5.6)	5 (9.8)	0.308
Tr transfusion ≥ 10 unites *n (%)*	12 (8.5)	8 (15.7)	0.146
Cryoprecipitate transfusion ≥ 10 unites *n (%)*	28 (19.7)	10 (19.6)	0.968

Bold values are statistically significant.
GCS- Glasgow Coma Scale; SAP- Systolic arterial pressure; DAP- Diastolic arterial pressure; MAP-Mean arterial pressure; HR-Heart rate; P/F- Ratio of arterial oxygen partial pressure to fractional inspired oxygen; FFP transfusion-Fresh frozen plasma transfusion; Tr transfusion - Platelet transfusion

DISCUSSION

Trauma is still one of the leading causes of death for people under the age of 40 in Europe, despite differences in geography, lifestyle, sociopolitical factors, and economic environment, although mortality rates vary widely between countries (5). Other examples of trauma are non-fatal injuries that result in life-long disabilities and health consequences. Therefore, it is very important to identify predictors of lethal outcomes from trauma in the ICU.

In this study, we observed that lethal outcomes happened more often in elderly patients. This finding is supported by other studies, which noted that the age over 65 years is an independent risk factor for increased mortality in trauma, controlled for the same Injury Severity Score (ISS) (6–8). The breakdown of homeostatic mechanisms due to ageing may mask injuries and their severity, making clinical assessment and treatment more difficult. Medications such as beta-blockers, anticoagulants, and steroids can mask the compensatory phase of the shock response. Additionally, conditions like renal and hepatic impairment, chronic steroid use, or a history of malignancy can increase mortality risk in elderly trauma patients by up to fivefold (9).

Table 3. Laboratory characteristics of patients

	Survivor	No Survivor	p-value
Characteristic	**n = 142**	**n = 51**	
Le *median (IQR)*	13.85 (6.25)	15.1 (7.68)	0.48
NLR *median (IQR)*	13.67 (10.11)	14.13 (9.94)	0.309
Hgb *median (IQR)*	119 (27)	122 (24)	0.328
HCT *median (IQR)*	0.36 (0.08)	0.37 (0.07)	0.221
INR *median (IQR)*	1.07 (0.22)	1.11 (0.28)	0.844
aPTT *median (IQR)*	23.1 (4.62)	23 (3.87)	0.566
Fibrinogen *median (IQR)*	2.4 (0.95)	2.55 (1.3)	0.413
Cr *median (IQR)*	80.5 (31)	85.5 (38.25)	0.34
Gly *median (IQR)*	7.2 (3.33)	7.6 (2.93)	0.134
AST *median (IQR)*	65 (71)	66 (86.5)	0.313
ALT *median (IQR)*	47 (53.25)	45 (49)	0.801
pH *median (IQR)*	7.36 (0.11)	7.37 (0.11)	0.748
pCO_2 *median (IQR)*	4.98 (1.19)	4.87 (1.28)	0.941
sO_2 *median (IQR)*	99 (2.15)	98.05 (3.5)	**0.006**
HCO_3 *median (IQR)*	21.4 (5.15)	21.5 (5.2)	0.463
BD *median (IQR)*	-3.7 (5.75)	-3.4 (6.15)	0.809
LAC *median (IQR)*	2.1 (1.98)	2.4 (1.65)	0.291
CRP *median (IQR)*	2.1 (6.65)	2.4 (3.8)	0.585

Bold values are statistically significant.
Le- leukocytes; NLR-Neutrophil to Lymphocyte Ratio; Hgb-Hemoglobin; HCT-Hematocrit;INR- international normalized ratio; aPTT- Activated Partial Thromboplastin Time;Cr- Creatinine; Gly-Glycemia; AST- aspartate aminotransferase; ALT- alanine aminotransferase; pCO2- partial pressure of carbon dioxide ;sO2- Oxygen saturation;HCO3- bicarbonate- Base deficit; LAC-Lactate; CRP- C-reactive protein

There is evidence for gender differences in the morbidity and mortality following trauma. Male gender and advanced age significantly increase the risk of infections and multiple organ failure following trauma and blood loss (10). Bösch et al. suggested the beneficial effects of estrogen for the central nervous system, cardiopulmonary system, liver, kidneys, and overall survival. Also, estrogen enhances humoral and cell-mediated immune responses that could be beneficial in case of major trauma because of the increased activity of macrophages (11).

The severity of trauma is directly correlated to death rates among traumatized patients. The assessment can be made by determining various parameters that are combined into point scales widely used today. One of the most important is the Glasgow Coma Scale (GCS) (12). Among others, GCS was one of the scores that we used in the assessment of our patients. Lower scores on the scale were parameters that were distinguished as a risk factor for late death in trauma patients. Ian Maconochie et al. (13) pointed out an association between the score values and the possible outcome in patients who had suffered a head injury. They found out that death occurs in one-third of patients due to severe injury and lower values of GCS (GCS < 8), while in 20%, it will lead to permanent disability.

Another significant score that is used for evaluating trauma patients is the injury severity score (ISS). As for its role as a predictor of lethal outcomes in trauma, the ISS has demonstrated utility in assessing the overall severity of trauma and has been associated with mortality risk. Higher ISS values generally indicate a more extensive and severe injury burden, which may correlate with an increased risk of mortality. ISS has limitations because multiple injuries within the same body region are only assigned a single score and this may underestimate the severity for the trauma patients. However, it's important to note that the ISS alone may not provide a comprehensive prediction of lethal outcomes, as other factors such as age, pre-existing health conditions, and the timeliness and quality of medical care also play significant roles (14-16).

Tracheal intubation of severely injured patients is mandatory on some occasions, such as severe craniocerebral trauma, multiple rib fractures, and severe shock. A higher ISS score and a lower GCS score are predictors of the duration of mechanical ventilation and the length of hospitalization (17,18). However, mechanical ventilation can bring some complications, such as ventilator-associated pneumonia, which is a known independent risk factor for mortality in the ICU (19). There are several explanations for this, where it is pointed out that traumatized patients suffer persistent inflammation, immunosuppression, and catabolism

Table 4. Univariate and multivariate Cox regression of predictors of in-hospital mortality

	Univariate			Multivariate		
Characteristic	**Hazard ratio**	**CI**	**p - value**	**Hazard ratio**	**CI**	**p- value**
Age	1.032	1.016 – 1.048	**<0.001**	1.030	1.014 – 1.047	**<0.001**
ISS	1.007	0.983 – 1.032	0.572			
sO_2	0.947	0.895 – 1.001	0.056			
GCS	0.916	0.868 – 0.967	**0.002**	0.924	0.873 – 0.979	**0.007**
P/F ratio	0.999	0.997 - 1	0.159			
Vasopressors	8.146	3.45– 19.24	**<0.001**	3.47	1.373 – 8.787	**0.009**
Mechanical ventilation	19.877	2.726– 144.90	**0.003**	5.053	0.597 – 42.787	0.137

Bold values are statistically significant.
ISS- Injury Severity Score; sO2- Oxygen saturation; GCS- Glasgow Coma Scale; P/F ratio- Ratio of arterial oxygen partial pressure to fractional inspired oxygen;

syndrome (PICS). Consequently, they can be more vulnerable to multi-drug-resistant nosocomial infection than other critically ill patients in the ICU, despite equal exposure to invasive devices and to the particular local distribution of microbiota (22). Also, patients with traumatic injuries could experience two types of ARDS. Early-onset ARDS takes place during the first 48 hours after hospital admission due to blood polytransfusion, and late-onset ARDS occurs later, being often associated with multiple organic failures and pneumonia (23). The results of our work support these findings. It has been shown that patients requiring mechanical ventilation have a higher likelihood of poorer outcomes.

Due to massive bleeding, which follows trauma, hemorrhagic shock may occur. The first step in shock resuscitation is to restore mean arterial pressure and systemic blood flow to prevent regional hypoperfusion and tissue hypoxia. Fluid resuscitation is the first strategy applied to restore mean arterial pressure in hemorrhagic shock. However, vasopressor agents may also be needed (24). Although these medications effectively improve hemodynamic parameters, they are also associated with important side effects such as increased myocardial oxygen consumption, myocardial ischemia, and arrhythmias (25). There are numerous studies, as well as ours, that concluded that the use of vasopressors is associated with increased mortality in patients with trauma (26–28). It can be explained in terms of the fact that most severely injured people deny this kind of therapy and that it also has significant side effects that can lead to a lethal outcome.

Acute traumatic coagulopathy is identified in 10 – 34% of traumatizing patients, and it has been associated with increased mortality rates (29). Fibrinogen plays an important role in coagulation by forming stable blood clots. Low fibrinogen levels or inefficient fibrinogen utilization may adversely impact patient outcomes. There are some identified factors that are affecting the level of fibrinogen in major trauma. First of all, lower levels are seen in massive bleeding because of increased utilization. In hypothermia, the synthesis of fibrinogen is affected, and acidemia following hypoperfusion could lead to an increased breakdown of fibrinogen. It is important to say that crystalloid fluids and synthetic colloids can lead to relative hypofibrinogenemia, impacting its function (30, 31). Current European guidelines recommend fibrinogen substitution with cryoprecipitate, fresh frozen plasma, or fibrinogen concentrate at fibrinogen concentrations less than 1.5 to 2.0 g/l during uncontrolled bleeding (24). Surprisingly, our study raises the inconsistent finding that fibrinogen isn't an independent risk factor for lethal outcomes.

Coagulopathy leads to increased transfusion requirements, significantly affecting both morbidity and mortality. Mortality rates rise in the initial hours after trauma patients with uncontrolled hemorrhage due to the "lethal triad"—a combination of coagulopathy, acidosis, and hypothermia—reinforcing each other in a detrimental cycle. The majority of trauma patients develop coagulopathy within two hours. Recognizing coagulopathy early is crucial, prompting the rapid activation of the massive transfusion protocol (MTP) with the hope of preventing death by interrupting the lethal triad before it becomes irreversible. Most deaths associated with MTP occur within the first 6 hours of trauma, with some studies reporting a fourfold increase in mortality when coagulopathy is present. Astonishingly, our results did not designate with these findings. Given that trauma-induced hemorrhage is a leading preventable cause of death worldwide, trauma-induced coagulopathy (TIC) is addressed by promptly administering fresh frozen plasma (FFP), platelets, and other high-dose blood components. Specific massive transfusion protocols are designed to deliver high volumes of blood products in a standardized manner, often using a 1:1:1 ratio of packed red blood cells (PRBC), platelets, and FFP, closely resembling whole blood, especially since whole blood may not be widely available (32). However, no studies to date have addressed the cause of death after MTP (33).

Some limitations of this study should be mentioned. The sample size of this study is relatively small, and being a single-center retrospective study further limits its ability to detect differences between groups. Residual confounding due to unmeasured confounders such as comorbidities and infections. The reason for this is their absence in the health information system. Also, one of the limitations is that at the time we did not do viscoelastic tests for every patient in need of transfusion. We relied on monitor coagulation parameters, clinical response to interventions, and ongoing bleeding. Furthermore, due to the retrospective nature of the study, we did not conduct dynamic assessments of variables. Including this data might reveal more information and strengthen the validity of our research. However, our research was conducted at a Level 1 Trauma Center, the leading academic emergency referral center in our country, serving not only central Serbia but also several neighboring countries.

CONCLUSION

This study added to the increasing body of research that suggests risk factors for unfavorable clinical outcomes after severe trauma. It may be essential to properly and promptly differentiate individuals with lower prognoses, which can lead to prompt and more aggressive treatment of these patients and might cut in-hospital mortality. Age, vasopressors and Glasgow Coma Scale, in particular, may be helpful indicators of in-hospital mortality of traumatized patients treated in the ICU. Additional prospective multicenter research is required on this topic.

Author contributions

Sanja Ratković and Adi Hadžibegović have equal contribution in writing.

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UZRAST, GLAZGOVSKA SKALA KOME I VAZOPRESORI KAO PREDIKTORI SMRTNOG ISHODA KOD PACIJENATA SA TRAUMOM LEČENIH U JEDINICI INTENZIVNOG LEČENJA

Sanja Ratković [1,2], Adi Hadžibegović [2], Sofija Mirosavljević [2], Boris Kajmaković [1,2], Jovana Stanisavljević [1,2], Isidora Jovanović [2], Tijana Todorčević [2], Jelena Vrućinić – Kozić[2], Marija Milenković [1,2], Ksenija Petrović [2], Marija Rajković [1,2], Ivan Rović [2], Đuro Šijan [2], Milica Rajković [2], Bojan Jovanović [1,2]

Sažetak

Uvod: Trauma predstavlja jedan od najznačajnijih javnozdravstvenih problema širom sveta. Ona je jedan od vodećih uzroka smrtnosti, posebno u populaciji mladih, ali sa značajno većim udelom nefatalnih povreda koje rezultiraju doživotnim invaliditetom i zdravstvenim posledicama. Pravilna i blagovremena identifikacija pacijenata sa većim rizikom od mortaliteta je ključna za bolje ishode. Cilj ove studije je da ispita potencijalne prediktore smrtnog ishoda kod pacijenata koji su doživeli traumu, a leče se u jedinici intenzivnog lečenja.

Metode: Retrospektivna kohortna studija je sprovedena u traumatološkoj, 12-krevetnoj intenzivnoj intenzivnoj pomoći Univerzitetskog urgentnog centra Kliničkog centra Srbije, Beograd. Svi uzastopni pacijenti sa tupim traumama primljeni su u intenzivnu intenzivnu terapiju između avgusta 2021. i avgusta 2022. Primarni ishodi od interesa bili su bolnička smrtnost od svih uzroka. Vrednost p < 0,05 smatrana je statistički značajnom.

Rezultati: *GCS* (koeficijent opasnosti 0,924 95%CI 0,873 – 0,979), vazopresori (koeficijent opasnosti 3,47 95%CI 1,373 – 8,787) i starost (koeficijent opasnosti 1,030 95%CI 1,030 95%CI 1,0147 individualno) su se istakli kao najznačajniji nezavisni prediktori smrtnog ishoda.

Zaključak: Ova studija ukazuje na faktore rizika za nepovoljne kliničke ishode nakon teške traume.To može biti od izuzetnog značaja da bi se na vreme izdvojili pojedinci sa lošom prognozom, kako bi se što pre započela adekvatna intenzivna terapija i time smanjila smrtnost. Starost, vazopresori i mehanička ventilacija nezavisno mogu biti prediktori letalnog ishoda kod pacijenata koji su preživeli traumu, a leče se u jedinici intenzivnog lečenja.

Ključne reči: *GCS*, starost, vazopresori, intenzivno lečenje

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ORIGINAL ARTICLE

Same-day carotid artery stenting and aortic valve surgery: a minimally invasive option for high-risk patients

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Summary

Introduction: The etiology of aortic valve stenosis (AS) is multifactorial; hypertension, hyperlipidemia, and diabetes mellitus are the most common risk factors for the development of the disease. The same factors increase the incidence of atherosclerosis in the peripheral arterial vessels. Hemodynamic disturbance in both diseases increases the risk of cerebrovascular symptomatology. Due to the overlapping of the symptoms in patients with concomitant aortic valve stenosis and carotid artery disease, the indication for treatment is not always straightforward. There are different strategies for treatment; same-day or simultaneous surgery, staged procedure, transcatheter technique, or medical treatment.

Aim: The aim of our study is to observe the feasibility and safety of same-day SAVR and CAS in patients with concomitant severe aortic valve and carotid artery stenosis.

Material and methods: A prospective non-randomized study performed from August 2015 to August 2023 included thirty-four patients who underwent same-day SAVR (simple or in combination with other cardiac surgery procedures) and CAS intervention.

Results: The study included 34 patients with concomitant carotid and aortic disease. The majority of patients had SAVR with CABG procedure. In total, MACCE was reported in 3 patients.

Conclusion: The guidelines for treatment strategy are unclear due to a lack of studies about this subject. Surgical aortic valve replacement (SAVR) and carotid artery endarterectomy (CEA) done simultaneously, can yield favorable results but could be excessively invasive for high-risk patients. In these cases, surgical aortic valve replacement and carotid artery stenting (CAS) are feasible, less invasive option.

Keywords: carotid artery stenting, aortic valve stenosis, surgical aortic valve replacement

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INTRODUCTION

The incidence of aortic valve stenosis (AS) in the population above the age of 65 is more than 2 % (1). The etiology of AS is multifactorial; hypertension, hyperlipidemia, and diabetes mellitus are the most common risk factors for the disease (2). The same factors increase the incidence of atherosclerosis in the peripheral arterial vessels. The prevalence of extracranial internal carotid artery (ICA) stenosis in patients with severe aortic stenosis (AS) reaches up to 33% of patients having carotid stenosis >50% (3). Hemodynamic disturbance in both diseases increases the risk of cerebrovascular symptomatology. Severe AS decreases cardiac output, and consequently produces syncope in patients with peripheral vascular dilatation (4, 5). Reduction of the blood patency through the stenotic carotid artery can result in loss of consciousness and syncope (6, 7, 8). Due to the overlapping symptoms in patients with concomitant aortic stenosis (AS) and carotid artery disease, determining the appropriate treatment is not straightforward. There are different strategies for treatment; same-day or simultaneous surgery, staged procedure, transcatheter technique, or medical treatment (9). Treatment guidelines remain unclear due to the lack of sufficient studies on this topic (9). Surgical aortic valve replacement (SAVR) and carotid artery endarterectomy (CEA) can yield favorable results but could be excessively invasive for high-risk patients. In these cases, surgical aortic valve implantation (SAVR) and carotid artery stenting (CAS) are feasible, less invasive options.

The aim of our study is the feasibility and safety of same-day SAVR and CAS in patients with concomitant severe aortic valve and carotid artery stenosis.

MATERIAL AND METHODS

A prospective non-randomized study performed from August 2015 to August 2023 included thirty-four patients who underwent same-day SAVR (simple or in combination with other cardiac surgery procedures) and CAS intervention.

The inclusion criteria: Severe aortic valve stenosis indicated for SAVR in the elective patients with concomitant significant carotid artery stenosis suitable for CAS procedure.

Exclusion criteria were: Cardiac reoperation, emergent and urgent cases, carotid artery stenosis is not suitable for CAS, history of bleeding disorder.

All participants were exanimated by a standard perioperative protocol of our Institute.

The cardiologist performed physical and echocardiographic examinations. The presence of significant aortic valve stenosis was evidenced by measuring the aortic valve area (AVA) less than 1cm^2, mean pressure gradient more than 40 mmHg, and peak jet velocity more than 4 m/s. Also, the functions of the left and right ventricles and other valves were checked. Coronary angiography was performed in all patients to exclude significant coronary artery disease.

The preoperative physical exam was performed in all patients. The CA disease was revealed by a history of cerebrovascular events or carotid bruit on the auscultatory exam. The patients were considered asymptomatic if they had no history of TIA and stroke 120 days before the procedure.

The angiologist performed a color duplex scan to evaluate carotid artery stenosis, plaque characteristics, and carotid blood flow velocity before the procedure. Additionally, a computed tomography (CT) angiography scan confirmed the degree of CA stenosis, characteristics of the carotid plaque, and anatomy of the cerebral circulation.

The stenosis was measured using the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.

The indication for carotid revascularization was artery diameter reduction of more than 80% in asymptomatic or >50% in the symptomatic patients by the NASCET criteria. In patients with bilateral CA disease, a choice of the artery to treat was made according to the plaque's severity and morphology.

The vascular surgeon and radiologist provided the final approval for CAS according to the plaque's anatomic characteristics for saving stent implantation.

Unfavorable characteristics were tortuosity of the carotid vessels, extreme calcification, pinhole stenosis, total artery occlusion, circumferential calcification (more than two-thirds of the vessel circumference), significant vessel angulations, and severe aortic arch calcification.

In patients with bilateral CAD, a choice of the artery to treat was made according to the clinical criteria, severity the morphology of the plaque, or both.

Carotid artery stenting procedure protocol

CAS was performed in the catheterization laboratory under local anesthesia before cardiac procedures. After the procedure, neurological status was evaluated to detect a newly created cerebrovascular disturbance. All patients received 100mg Aspirin starting two days before the procedure. The percutaneous transfemoral approach was used. Heparin was administered at a dose of 1mg/kg. The distal cerebral protection device (Emboshield Abbot Vascular and Spider) was used in all patients. Predilatation of the stenosis was done before the placement and final stent expansion. Balloon expandable stents (Xact Abbot Vascular, Cristallo Invatec, and Carotid WALLSTENT Boston Scientific) were deployed into the common carotid artery. The results of the CAS were considered successful if residual stenosis was ≤ 20%, and if complications such as stroke or TIA did not occur. Within 1 hour of completion of the procedure, patients were transferred to the

cardiac surgery operating theatre. During that period, patients received intravenous heparin via infusion pump according to activated clotting time (ACT) value, which was measured on an hourly basis. The aim was to maintain ACT around 200 seconds (10).

Aortic valve replacement

Approximately 15 minutes after the CAS procedure the patient was transferred into the operation theater. During this period their neurological function was checked.

The surgical procedure was performed through the conventional sternotomy under general heparinization (ACT >480s). Standard ascending aorta cannulation and venous cannulation were performed, and cardio-pulmonary bypass was performed with a standard non-pulsatile technique. The crystalloid or cold blood cardioplegia was used. The aortic valve replacement was performed through the transversal aortotomy using the mechanical or biological stented prosthesis. After completion of the intervention and weaning from the cardiopulmonary bypass, a complete reversal of heparin was done by infusion of full dose protamine and antifibrinolytic agent (tranexamic acid).

Periprocedural pharmacological protocol

Dual antiplatelet therapy was administered early after the procedure, providing that chest tube bleeding was less than 50 cc for three consecutive hours. Six hours after the cardiac procedure, clopidogrel 300 mg is given as a loading dose in the intensive care unit (ICU) via nasogastric tube, followed by 75mg/day for one month postoperatively.

The anticoagulation was started on the first postoperative day and titrated according to the international normalized ratio (INR). Implanted biological prostheses need three months of anticoagulation treatment, while patients with mechanical prostheses take a long-life therapy.

Aspirin 100 mg/day was continued from the first morning after the procedure for the remainder of the patient's life.

RESULTS

The study included 34 patients with concomitant carotid and aortic disease. Most of the patients were males, elderly, dominantly with NYHA 2 and 3. The majority had hypertension and hyperlipoproteinemia, and a half of them were diabetics **(Table 1)**.

The ejection fraction was near the lower bound, majority had MR 0 or 1. A small number of patients had CV events before this hospitalization, but half of the patients had symptoms of carotid disease, mostly bilateral. The majority of patients had stenosis above 80% in an examined artery, and below 70% in a contralateral artery **(Table 2)**.

Table 1. Preoperative characteristics 1

	N (%) / mean±sd / med(IQR)
Age (yrs)	70.1±5.2
Gender male	21 (61.8%)
NYHA	
1	2 (5.9%)
2	14 (41.2%)
3	18 (52.9%)
HTA	33 (97.1%)
HLP	26 (76.5%)
Heredity	25 (73.5%)
DM	14 (41.2%)
PVD	8 (23.5%)
CRF	2 (5.9%)
COPB	1 (2.9%)
Previous MI	3 (8.8%)
Type of MI	
NSTEMI	2 (5,8%)
STEMI	1 (2,9%)
Time of MI >90 days	3 (8,8%)
Heart failure	5 (14.7%)
EuroScore II	2.84 (4.78)

Table 2. Preoperative characteristics 2

	N (%) or mean±sd
EF (%)	48.4±12.0
MR	
0	9 (26.5%)
1	18 (52.9%)
2	5 (14.7%)
3	2 (5.9%)
CV events	6 (17.6%)
CVI	3 (8.8%)
TIA	3 (8.8%)
Preop. TIA	4 (11.8%)
Preop. CVI	2 (5.9%)
Carotid disease sympt.	11 (44%)
Type of carotid disease	
Unilateral	6 (17.6%)
Bilateral	28 (82.4%)
Stenosis degree	85.2±7.5
Stenosis range	
60-69	0 (0%)
70-79	4 (11.8%)
80-89	17 (50%)
90-100	13 (38.2%)
Count. lat. stenosis degree	49.8±21.7
Count. lat. stenosis range (%)	
<50	13 (38.2%)
50-70	17 (50%)
70-99	3 (8.8%)
100	1 (2.9%)

The majority of patients had SAVR with CABG procedure, no complications during the procedure were reported, and three patients had CVI in the postoperative course (one after REDO SAVR, one after SAVR+CABG and one after simple SAVR procedure- 2,9% each). Inotropes were applied in half of patients **(Table 3)**.

Table 3. Intraoperative characteristics

	N (%) / mean±sd / med(IQR)
Cardiac procedure type SAVR +	
CAPB	19 (55.9%)
TVP	1 (2.3%)
MVR	1 (2.3%)
REDO SAVR	2 (5.9%)
Clamp time	77.5±35.3
Pump time	103.5±44.5
Complications during CAS	0
Postop. TIA	0
Postop. CVI	3 (8.8%)
Neurodeficiency	3 (8.8%)
Deficit type	
ischemia	3
Inotrops	16 (47.1%)
Drainage 6h	250 (300)
Drainage 24h	500 (375)
Extubation time	11.5±3.6

Revision of hemostasis was applied in several patients. Several patients had atrial fibrillation, pleural edema, and urinary infection. None of the patients were returned to ICU, and none of them died after the procedure **(Table 4)**.

Table 4. Postoperative characteristics

	N (%) / mean±sd / med(IQR)
Revision of haemostasis	6 (17.6%)
Disorientation	6 (17.6%)
Periop. MI	0
AF	7 (20.6%)
Th AF – amiodaron	7
Wound infection	0
Mediastinitis	0
Urinary infection	1 (2.9%)
Pleural effusion	7 (20.6%)
ICU return	0
Death outcome	0
ICU stay (days)	2 (2)
In hospital stay (days)	8 (8)

In total MACE was reported in 3 patients, and all 3 had CVI in the early postoperative period. Other adverse events such as MI and death were not registered **(Table 5)**.

Table 5. Clinical outcomes within 30 days after SAVR and CAS

Major events 30 days	**N (34)**
Stroke	3
Transient ischemic attack	0
Myocardial infarction	0
Death	0
Death/Stroke/MI	3

DISCUSSION

The risk of major adverse clinical events like transient ischemic attack (TIA), stroke (CVI), myocardial infarction (MI), and death in the periprocedural period (30 days) after SAVR surgery is around 5,7% for simple aortic valve surgery (11), and that risk significantly increases in patients with carotid artery disease, who underwent aortic valve replacement (12). Consequently, treatment of concomitant carotid and cardiac disease (aortic valve disease or coronary artery disease) is very important to reduce adverse events, but clear guidelines do not exist (13). There are three different strategies for the treatment of significant carotid stenosis, medical therapy, carotid artery stenting, and carotid endarterectomy, and the choice of technique and time of treatment concomitant carotid and heart disease is still a topic of discussion (14, 15). Correction of the carotid disease before open heart disease (staged procedure) reduces the incidence of cerebrovascular events but increases the probability of myocardial infarction, due to this complication same-day or simultaneous treatment was implemented (16,17). On the other hand, some studies showed that simultaneous CEA and CABG surgery increases the risk of death and serious morbidity (17,18). There is a described significant hemodynamic depression during a CAS procedure in patients with concomitant severe aortic valve and carotid diseases. The deployment of balloon-expandable stents increased rates of persistent hemodynamic instability due to carotid sinus stimulation during the procedure. Pressure drop in patients with significant aortic stenosis could produce significant myocardial ischemic attack with rhythm disturbance (19). There were no adverse events during stenting in our study population, which is encouraging, especially when it comes to high-risk patients in whom simultaneous surgery procedures increase postoperative adverse events. Brigitte Gansera et al. showed results of simultaneous carotid endarterectomy and cardiac surgery with a total of 5.2% mortality in the 30-day follow-up. Cerebrovascular events (transient ischemic attack and stroke) have been registered in 1.8% and 2.6% of patients (20). Compared to the presented results in the literature, our strategy for this group of patients reached similar results. Karolina Dzierwa et al. in their study had very satisfactory results in which they investigated same-day CAS and OHS (21). In their study, MACE did not occur during or immediately after CAS, and the percentage of 4.3% of MACE after OHS relates to very high-risk patients. Their study showed that the same-day approach could be a good modality of treatment. In our study, we registered 3 cerebrovascular events. One CVI occurred after REDO SAVR, one after SAVR+CABG, and one after simple SAVR, which is 2.9% for each one. We did not register other major cardiovascular adverse events such as MI or death 30 days after the procedure. Minimally invasive SAVR and transcatheter aortic valve implantation in combination with CAS could be excellent treatment options in high-risk patients. Excluding the cardio-pulmonary bypass, decreasing the aortic manipulation, and shortening the cross-clamp time are the advantages of the

minimally invasive approaches (22,23). There is a lack of studies that show the results of same-day treatment of the concomitant carotid and aortic valve stenosis.

CONCLUSION

Patients with severe, concomitant carotid and cardiac aortic valve diseases require cautious assessment and a multidisciplinary approach. Although CAS precedes open heart surgery (OHS) is not without risks, it is a very good choice in preventing fatal outcomes during SAVR. To reduce the risk of fatal outcomes, the preferred approach for treating patients with aortic stenosis, carotid artery stenosis, or both involves minimally invasive procedures such as TAVI or CAS. However, in high-risk patients, the treatment approach may involve same-day or simultaneous procedures, combining traditional methods such as SAVR and CEA with less invasive techniques like TAVI and CAS. There are no definitive guidelines in the literature regarding the best method of treatment; however, this study may contribute to more informed decision-making in the future for patients with concomitant carotid and heart disease.

Ethical Approval: Not applicable

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Author Contributions:

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HIRURŠKA ZAMENA AORTNE VALVULE ISTOG DANA NAKON STENTIRANJA KAROTIDNE ARTERIJE: MANJE INVAZIVNA PROCEDURA KOD VISOKORIZIČNIH PACIJENATA

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Sažetak

Uvod: Etiologija stenoze aortne valvule (SOAS) je multifaktorijalna; hipertenzija, hiperlipidemija i dijabetes melitus su najčešći faktori rizika za nastanak ovog oboljenja. Ovi faktori rizika povećavaju i učestalost ateroskleroze u perifernim arterijskim krvnim sudovima. Hemodinamski poremećaj kod oba oboljenja povećava rizik od cerebrovaskularnih događaja. Zbog preklapanja simptoma kod pacijenata sa udruženom stenozom aortne valvule i karotidnom bolešću, nije lako doneti odluku o indikaciji za adekvatnim tretmanom. Postoji nekoliko strategija lečenja: hibridna procedura, simultana hirurgija, etapna procedura, transkateterska tehnika ili medikamentozno lečenje.

Cilj: Cilj studije je ispitivanje izvodljivosti i sigurnosti hibridne procedure SAVR i CAS kod pacijenata sa udruženom aortnom stenozom i stenozom karotidnih arterija.

Materijal i metode: Prospektivna nerandomizovana studija je izvedena na našem Institutu u periodu od avgusta 2015. godine do avgusta 2023. godine i pacijenti su bili podvrgnuti hibridnoj procedure (istog dana je urađena hirurgija aortne valvule i implantacija stenta u karotidnoj arteriji).

Rezultati: Studijom je obuhvaćeno 34 pacijenta sa udruženom karotidnom bolešću i stenozom aortne valvule. Osim same hirurgije aortne valvule, u najvećem broju slučajeva pacijentima je rađena i konkomitantna hirurška revaskularizacija miokarda. Ukupno su evidentirana 3 neželjena kardiovaskularna događaja.

Zaključak: Nema mnogo istraživanja na ovu temu, te nema jasnih preporuka o strategiji lečenja. Simultano hirurško lečenje aortne valvule i karotidne arterije se izvodi uz prihvatljivo dobre rezultate, ali može biti previše invazivno za visokorizične pacijente. U tom slučaju treba razmotriti hiruršku zamenu aortnog zalistka i CAS kao manje invazivnu opciju lečenja.

Ključne reči: stentiranje karotidne arterije, stenoza aortne valvule, hirurška zamena aortne valvule

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ORIGINAL ARTICLE

Impact of peripheral nerve blocks on inflammatory response following knee arthroplasty

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Summary

Introduction: The increased inflammatory response after knee arthroplasty (TKA) is a result of bone and soft tissue trauma whose extensive reactions contribute to postoperative morbidity and mortality.

Methods: After elective TKA, 200 patients were included in this prospective cohort study. In one group of patients the adductor block and IPACK block were applied, while in the second group there were no blocks.

Results: In the group with blocks fewer patients experienced pain at rest with lower intensity (1.18±0.76 vs. 3.35±1.18 p<0.001). In the group without blocks, pain was more intense when coughing (1.7±0.52 vs. 3.72±1.61 p<0.001) and during active movements of the operated leg (1.67±0.83 vs. 3.78±1.94 p<0.001). In the first 24 hours after surgery, in the group with blocks, 22% of patients needed opioids in a dose of 9.64±3.21, while all patients in the group without blocks needed opioids in a dose of 30.94±11.47. Postoperatively, a statistically significant difference between the groups was observed in WBC, CRP, ESR, and albumin levels on the 1st, 3rd, and 5th days. Three months after TKA, the KOOS score was statistically higher in the group with blocks (92.6±11.73 vs 85.65±17.49 p<0.001).

Conclusion: The combination of nerve blocks provides adequate postoperative analgesia enabling early rehabilitation, reducing morphine consumption, reducing the count of WBC, CRP, ESR, and albumin (1st, 3rd, and 5th day postoperatively), and positively affecting the functional status three months after surgery. Identification and influence on factors that reduce the local and systemic inflammatory response is vital in improving recovery after TKA.

Keywords: knee arthroplasty, inflammatory response, nerve blocks, analgesia

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INTRODUCTION

Total knee arthroplasty (TKA) is the most common orthopedic procedure, aimed to reduce pain and improve quality of life in end-stage knee osteoarthritis (1). Systemic inflammation following major surgery is proportional to the degree of injury and it results from the activation of innate immune response. Inflammation is essential to limit exposure to harmful cellular debris and pathogens, promote healing and reflect changes in the cellular, neuroendocrine, protein, and cytokine systems (1–3). At the site of surgical injury, damage-associated molecular patterns (DAMPs) such as heat shock proteins, S100 proteins, high-mobility group protein B, nucleic acids, DNA, and adenosine triphosphate are responsible for triggering the inflammatory-immune response (4–6). They activate the cells of the innate immune system that induce the production and release of proinflammatory cytokines and chemokines (e.g. interleukin (IL)-6; tumor necrosis factor-α (TNF-α); IL-1β; IL-8; IL-12; type 1 interferons); leukotrienes (e.g. leukotriene B4); and DAMPs (e.g. high-mobility group box protein 1) promoting inflammation (4–6). Inflammation is a normal response to tissue damage, whose extensive reactions contribute to postoperative morbidity and mortality (4). The increased inflammatory response after TKA is a result of bone and soft tissue trauma (3–5).

Peripheral nerve blocks are a part of the multimodal analgesia regime after TKA. They provide adequate analgesia without muscle weakness and prevent the appearance of chronic pain (7–10). The use of peripheral nerve blocks following TKA has become more accepted for postoperative pain control, but there is no report of their effects on the inflammatory response. Surgical trauma in the postoperative period changes the level of different biomarkers of the inflammatory response. In clinical practice, the level of white blood cells (WBC), and C-reactive protein (CRP) are one of the most commonly used markers of acute inflammation(4–6).

This study aimed to determine the impact of a combination of adductor and IPACK block on inflammatory response and the appearance of complications after TKA.

MATERIALS AND METHODS

Two hundred patients underwent elective TKA at the Clinic for Orthopedic Surgery and Traumatology, University Clinical Centre of Serbia, after the Ethics Committee approval (No 340/1- July 21, 2021), and obtained written informed consent **(Figure 1)**.

This prospective cohort study includes patients aged 40-90 years, ASA I-III, with same type of implant. The patients were excluded in case of incomplete data, opioid use within 30 days before surgery, or other neurological illness that may compromise postoperative rehabilitation (drug or alcohol abuse, mental illness etc.).

TKA was performed in a bloodless field using a tourniquet in spinal or general anesthesia. Postoperatively, a combination of two peripheral nerve blocks was performed in one group of patients as part of a multimodal analgesia regime. This combination includes adductor canal block (ACB) and infiltration in the space between the popliteal artery and the capsule of the posterior knee (IPACK block), a local anesthetic for each block was 15 ml of 0.33% levobupivacaine.

ACB was performed after the identification of the sartorius muscle at midpoint of the adductor canal using the linear probe (10–12 MHz). A local anesthetic was administered laterally to the femoral artery.

The IPACK block was performed with a curved (2–5 MHz) transducer positioned, 2-3 cm above to patella over the medial thigh slightly flexed at the knee. Using the in-plane technique, the needle was inserted anteromedially into the space between the popliteal artery and the femur, followed by the injection of local anesthetic.

All patients received non-opioid analgesics (paracetamol 1 g iv. and ketorolac 30 mg iv. every eight hours alternately).

The Numerical Rating Scale (NRS) was used to measure pain intensity, at different time points in the first 24 hours postoperatively (0- no pain; 10-the worst pain imaginable). Morphine of 1 mg an intravenous bolus was given every 10 minutes if NRS was higher than three in resting or higher than five during activity or coughing. Dose of opioids in the first 24 hours postoperatively were converted into a standardized morphine milligram equivalent (MME).

Laboratory test

All parameters were tested in the same laboratory, preoperatively, on the first, third, and fifth day after surgery and included the count of white blood cells (WBC), red blood cells (RBC), hemoglobin (Hgb), hematocrit (HCT), plates (PLT), C reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen and albumin.

The level of CRP was evaluated by immunoturbidimetric assay for the in vitro quantitative determination on Roche/Hitachi Cobas c systems and results are expressed as the mean in mg/L. Spectrophotometric determination of albumin was done on Roche/Hitachi Cobas c systems and expressed in g/L. All blood samples were anticoagulated by EDTA and processed in a Sysmex blood analyzer (TOA Medical Electronics, Kobe, Japan) to determine the complete blood cell counts and differential counts of leucocytes. ESR was done using ESR Analyzer Therma LINEAR modified by Westergeen and expressed in mm/h. Fibrinogen was done by Clauss on Stago Starmax and expressed in g/L.

The *Knee Injury and Osteoarthritis Outcome Score* (KOOS) was used to assess patient-relevant outcomes three months after knee surgery. KOOS includes

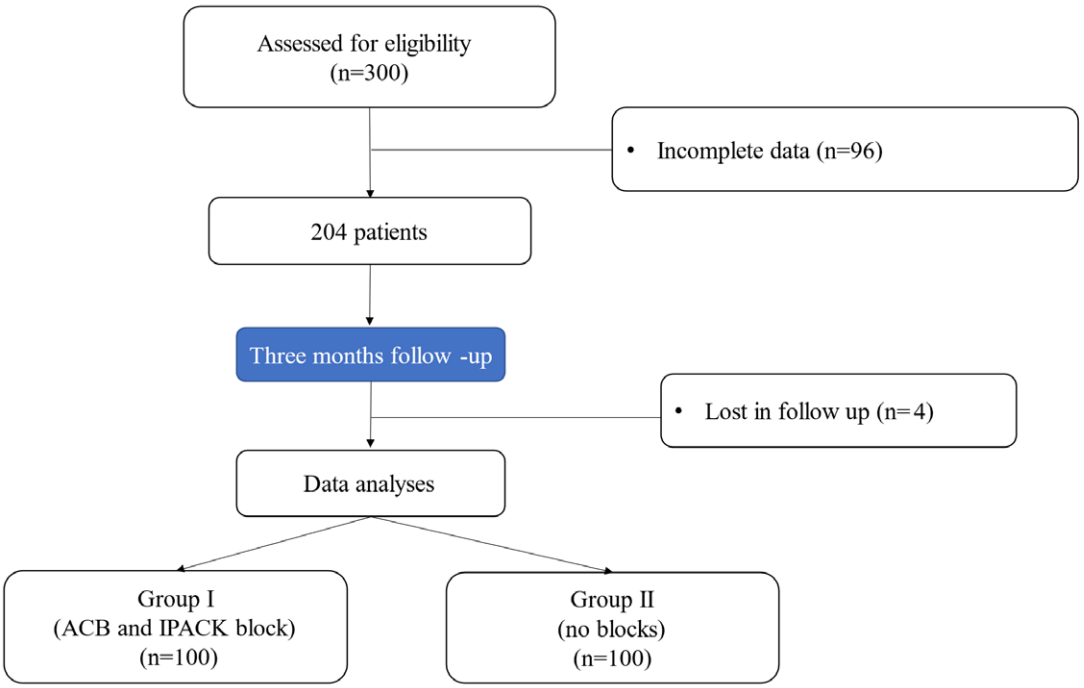

Figure 1. Patient selection and study flow

scale of *Symptoms and stiffness, Pain, Function, daily living, Function, sports, and recreational activities* and *Quality of Life*. The KOOS was expressed as the percentage of total score (0 – severe knee problems; 100 – no knee problems).

Postoperative complications included nausea, sleepiness, vomiting, itching, and drainage or swelling of the wound, deep venous thrombosis, and other complications three months postoperatively were registered.

Statistical Analysis

Statistical Analysis was performed with SPSS v28 (Statistical Package for Social Sciences, SPSS Inc, Chicago, Illinois). Data were expressed as mean ± standard deviation (SD). Normal distribution was tested using the Kolmogorov-Smirnov test. Depending on the nature of parameters, to test differences between groups the Pearson X^2 test, Fisher exact test, Kruskal Wallis test and Wilcoxon rank sum test was used. Two-tailed tests were used. Significance level was set at $p < 0.05$.

RESULTS

Three months after TKA, there were complete medical data for 200 patients (100 with blocks (ACB and IPACK block) in the first group and 100 in the second). Ninety-six patients had incomplete data, and four were lost during the three-month follow-up **(Figure 1)**.

The groups did not differ in the patient's age **(Table 1)**. There were more female patients in both groups (58% vs 62%), but with no difference between groups. In the group with blocks, 56% were ASA III, while in the group without blocks, 50% were ASA II. There was no difference between groups in BMI and the type of anesthesia. High pain intensity lasting more than three months prior to surgery was observed in 96% of patients undergoing knee surgery compared to 97% of patients overall **(Table 1)**.

Table 1. Patient characteristics

Characteristics	Blocks	No blocks	p value
Age (y)			
Mean (SD)	66.85(9.1)	70.5(6.46)	0.109
Sex - n (%)			
Male	42(42%)	38(38%)	0.665
Female	58 (58%)	62(62%)	
Weight (kg)			
Mean (SD)	81.2(12.67)	83.98(9.75)	0.194
Height (m)			
Mean (SD)	1.69(0.09)	1.7(0.09)	0.369
BMI (kg/m²)			
Mean (SD)	28.22(3.36)	28.62(2.97)	0.40
ASA physical status - n (%)			
ASA I	1 (1%)	1 (1%)	0.608
ASA II	43(43%)	50(50%)	
ASA III	56(56%)	49(49%)	
Type of anesthesia - n (%)			
General	35(35%)	30(30%)	0.545
Spinal	65(65%)	70(70%)	
In pain before surgery (during ≥3 months)			-
in the knee for surgery	96(96%)	97(97%)	0.700
in the knee & another place	4 (4%)	3(3%)	
***Pain before surgery*(NRS) – mean (SD)**	6.11(1.15)	6.33(1.15)	0.21
Total	**100(100%)**	**100(100%)**	-

BMI-body mass index; ASA- American Society of Anesthesiologists.

Table 2. Postoperative pain intensity and opioid consumption

Characteristics	In pain – n (%)			Pain (NRS) – mean (SD)		
	Blocks	No blocks	p value	Blocks	No blocks	p value
Pain after surgery, at rest						
Within 24h	82 (82)	100 (100)	**<0.001**	1.18 (0.76)	3.35 (1.18)	**<0.001**
Pain during activity						
In pain	56 (56)	100 (100)	**<0.001**	1.67 (0.83)	3.78 (1.94)	**<0.001**
Pain during coughing						
In pain	8 (8)	61 (65.48)	**<0.001**	1.7 (0.52)	3.72 (1.61)	**0.0013***
Opioids consumption						
Within 24h	22 (22)	100 (100)	**<0.001**	9.64 (3.21)	30.94 (11.47)	**<0.001**
Total	**100 (100)**	**100 (100)**	-	**100 (100)**	**100 (100)**	-

*p<0.05.

In the group receiving blocks, fewer patients experienced pain at rest, and the pain intensity was lower (1.18±0.76 vs. 3.35±1.18, p<0.001) **(Table 2)**. Also, there was a statistical difference between groups in pain when coughing (1.7±0.52 vs. 3.72±1.61 p<0.001) and during active movements of the operated leg (1.67±0.83 vs. 3.78±1.94 p<0.001) **(Table 2)**.

22% of patients needed opioids in the group with blocks in a dose of 9.64±3.21, while all patients in the group without blocks needed opioids in a dose of 30.94±11.47 **(Table 2)**.

There was no difference between groups in the number of WBC, RBC, Hgb, HCT, PLT, CRP, ESR, fibrinogen and albumin before surgery. Postoperatively, there was a statistically significant difference between the groups in WBC, CRP, ESR, and albumin levels **(Table 3, Figure 2)**.

KOOS three months after surgery, was higher in the group with blocks (92.6±11.73 vs 85.65±17.49 p<0.001) **(Table 4)**.

In the group without blocks nausea and sleepiness were more often **(Table 5)**. One patient had a foot drop, while no other postoperative complications were present in either group **(Table 5)** (11).

Table 3. Laboratory results

Laboratory test	Blocks (n=100)	No blocks (n=100)	
	$\bar{x}$(sd), med (min,max)	$\bar{x}$(sd), med (min,max)	p
before surgery			
WBC (x 10^9/L)	6.74 (1.99), 6.4 (3.7,12.8)	6.86 (1.59), 6.65 (4.2, 10.9)	0.656
RBC (x10^{12}/L)	4.49 (0.42), 4.46 (3.52, 5.63)	4.57 (0.4), 4.58 (3.65, 5.54)	0.271
HGB (g/L)	138.54 (13.9), 140 (109, 179)	138.65 (13.51), 139 (99,168)	0.956
Hct (%)	0.41 (0.04), 0.41 (0.32, 0.52)	0.41 (0.04), 0.41 (0.32, 0.49)	0.217
PLT (x10^9/L)	242.45 (60.4), 236 (117, 488)	231.99 (55.33), 235.5 (125, 393)	0.246
CRP (mg/L)	5.13 (7.06), 3 (0.3, 47.1)	6.01 (8.86), 2.4 (0.6, 65)	0.755
ESR (mm/h)	17.71 (12.07), 14 (2.3, 78)	18.71 (14.02), 14 (3.3, 80)	0.959
Fibrinogen (g/L)	3.71 (0.63), 3.62 (2.4, 5.8)	3.51 (0.86), 3.6 (1.2, 5.8)	0.142
Albumin (g/L)	40.85 (3.15), 41 (31, 47)	40.89 (2.46), 40 (34, 46)	0.719
1st day after surgery			
WBC(x 10^9/L)	8.71(2.45), 8.75 (3.6,15.6)	9.52 (2.72), 9.2 (4.8,17.8)	**0.044***
RBC (x10^{12}/L)	3.7 (0.48), 3.7 (2.62, 4.73)	3.77 (0.46), 3.76 (2.45, 4.76)	0.385
HGB (g/L)	113.7 (13.27), 113.5 (86, 152)	113.46 (13.73), 114(83, 154)	0.898
Hct (%)	0.34 (0.04), 0.33 (0.25,0.43)	0.33 (0.04), 0.33 (0.23, 0.46)	0.404
PLT (x10^9/L)	195.62 (46.93), 194 (76,324)	195.6 (49.5), 198 (99,325)	0.341
CRP(mg/L)	60.54 (30.9), 53.25 (3.6, 136.3)	76.76 (33.32), 72.75 (17.6, 171.1)	**0.001**
ESR (mm/h)	42.07 (19.84), 36 (3.5, 130)	51.6 (27.56), 45 (8,156)	**0.014***
Fibrinogen (g/L)	4.91 (0.92), 4.85 (3.4, 7.8)	4.91 (1.24), 4.75 (2.2, 8.6)	0.731
Albumin (g/L)	32.27 (3.22), 32 (26, 40)	30.87 (3.23), 31 (24, 39)	**0.005***

Laboratory test	Blocks (n=100)	No blocks (n=100)	
3rd day after surgery			
WBC (x 10⁹/L)	8.05 (2.43), 7.75 (4.2, 16.4)	8.48 (2.83), 7.95 (3.0, 17.8)	0.293
RBC (x10¹²/L)	3.41 (0.48), 3.4 (2.36, 4.51)	3.37 (0.51), 3.36 (2.27, 4.47)	0.552
HGB (g/L)	104.76 (13.83), 105 (71,139)	102.07 (15.01), 100 (75, 145)	0.233
Hct (%)	0.31 (0.04), 0.31 (0.21, 0.42)	0.30 (0.04), 0.30 (0.21, 0.43)	0.104
PLT (x10⁹/L)	215.65 (69.6), 205.5 (73, 477)	203.06 (64.04), 191 (101, 462)	0.227
CRP(mg/L)	79.69 (36.32), 73 (17.3, 250.9)	129.56 (63.61), 119.45 (12.7, 378)	**<0.001**
ESR (mm/h)	64.57 (19.91), 64.5 (10,110)	85.35 (28.84), 90 (4,176)	**0.003***
Fibrinogen (g/L)	6.0 (1.6), 6.1 (3.1, 9.0)	6.2 (1.29), 6.2 (2.4, 8.8)	0.276
Albumin (g/L)	33.39 (3.34), 33 (26,42)	31.33 (3.6), 31 (25, 40)	**<0.001**
5th day after surgery			
WBC(x 10⁹/L)	6.78 (1.79), 6.7 (3.2, 11.9)	7.74 (2.03), 7.5 (3.2, 12.6)	**0.038***
RBC(x10¹²/L)	3.37 (0.44), 3.36 (2.37, 4.4)	3.37 (0.43), 3.3 (2.64, 4.82)	0.987
HGB (g/L)	104.32 (12.85), 104.5 (80, 131)	103.23 (11.63), 102.5 (84, 138)	0.602
Hct (%)	0.31 (0.038), 0.31 (0.24, 0.39)	0.3 (0.035), 0.3 (0.25, 0.42)	0.238
PLT (x10⁹/L)	272.38 (78.9), 274 (103, 471)	269.45 (79.7), 262.5 (132, 534)	0.812
CRP(mg/L)	44.48 (35.08), 37.5 (2.3, 285)	58.59 (36.72), 49.3 (9.6, 190.3)	**0.005***
ESR (mm/h)	45.45 (22.8), 42.5 (7, 130)	67.04 (27.52), 65 (6, 116)	**<0.001**
Fibrinogen (g/L)	5.34 (1.13), 5.25 (2.6, 9.0)	5.37 (1.20), 5.35 (2.3, 8.1)	0.351
Albumin (g/L)	34.62 (3.38), 34.5 (28,44)	32.86 (3.37), 32 (27,42)	**<0.001**

WBC - white blood cells; RBC - red blood cells; Hgb - hemoglobin; Hct - hematocrit; PLT- plates; CRP- C reactive protein; ESR-erythrocyte sedimentation rate;*- p<0.05.

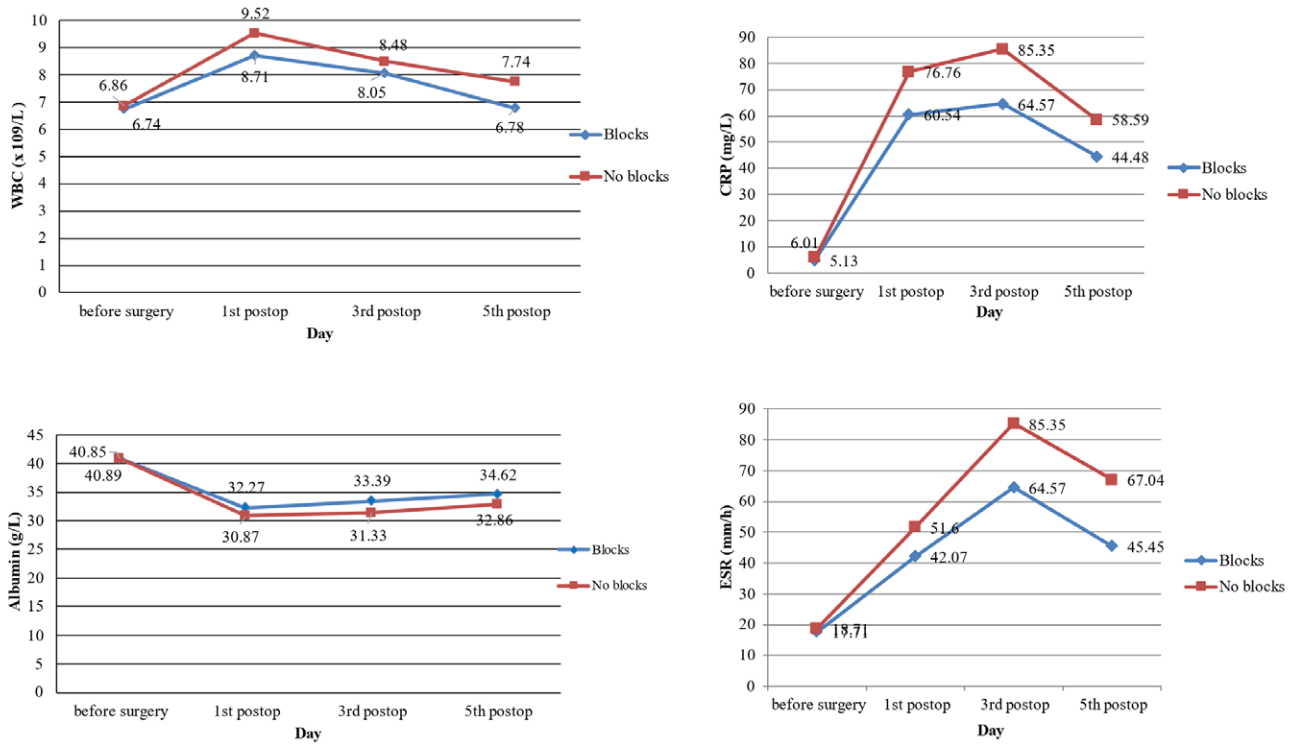

Figure 2. Laboratory results - WBC, CRP, ESR, albumin

Table 4. KOOS three months after knee arthroplasty

Characteristics	Blocks	No blocks	p value
KOOS (%)			
Mean (SD)	92.6 (11.73)	85.65 (17.49)	**<0.001**
Median (Range)	95 (40-100)	90 (25-100)	
Symptoms + Stiffness (%)			
Mean (SD)	92.07 (12.92)	88.5 (15.45)	**<0.001**
Median (Range)	98 (25-100)	94.5 (25-100)	
Pain (%)			
Mean (SD)	93.26 (11.03)	81.19 (19.93)	**<0.001**
Median (Range)	95.5 (31-100)	83 (22-100)	
Function, daily living (%)			
Mean (SD)	92.61 (12.02)	85.38 (18.65)	**<0.001**
Median (Range)	96 (35-100)	93 (25-100)	
Function, sports, and recreational activities (%)			
Mean (SD)	91.89 (12.49)	83.57 (20.16)	**<0.001**
Median (Range)	97.5 (35-100)	90 (10-100)	
Quality of life (%)			
Mean (SD)	95.8 (10.66)	89.68 (15.61)	**<0.001**
Median (Range)	100 (44-100)	97 (38-100)	
Total	**100 (100%)**	**100 (100%)**	-

Table 5. Postoperative complications

Characteristics	Blocks	No blocks	p-value
Postoperative complications			
Nausea, n (%)	0 (0%)	28(28%)	**<0.001**
Sleepiness, n (%)	4 (4%)	51(51%)	**<0.001**
Foot drop, n (%)	1 (1%)	0 (0%)	0.316
Wound drainage, n (%)	1 (1%)	1 (1%)	0.48
Urinary tract infection, n (%)	4(4%)	4(4%)	0.718
Chronic post-surgical pan, 3months after TKA			
Presence - n (%)	5 (5%)	21(21%)	**0.0016***
Pain- NRS			
Mean (SD)	3.7(0.43)	3.66(0.58)	0.19
Total, n (%)	**100 (100%)**	**100 (100%)**	-

NRS- Numerical Rating Scale; *- p<0.05*.

DISCUSSION

Osteoarthritis is the most common cause of TKA, and an inflammatory state already exists preoperatively in these patients as part of its pathophysiology (1,2). TKA as an invasive procedure is associated with stress response, which can be extensive. It comprises a neuroendocrine-metabolic reaction and an inflammatory-immune response (4,5,12). Tourniquet use contributes to this by ischemia-reperfusion injury which results in endothelial damage, increased adhesiveness, activation of leukocytes, and increased inflammatory response (4,5,13). However, stress response may vary depending on the anesthetic technique (12,14). Neuraxial anesthesia decreases neuroendocrine response to surgery by blocking all afferent neurogenic stimuli from the surgical field (12,14,15). Furthermore, anesthetic agents modulate cellular and humoral (gene expression and secretion) inflammatory responses (12,15).

Regional anesthesia, consecutive to tissue injury, modulates local and systemic response at different levels by various mechanisms (12,16). Many authors have confirmed the beneficial effect of local anesthetics in inhibiting an exaggerated inflammatory response by reduction in the metabolic activity and secretory function of leukocytes (16–18). Kim H.et al., suggested that spinal anesthesia, in contrast to general anesthesia, reduces the postoperative increase in CRP level without significant differences in other inflammatory markers (14).

However, inflammatory response after surgical trauma, serves to limit tissue damage and promote healing, by activation of polymorphonuclear neutrophil (PMN) and monocyte. Their activation leads to increasing different interleukins which induce the release of other cytokines (3,4,6). An increase in the level of IL6 correlated with post-operative complications after arthroplasty (4,19). Simultaneously, immature monocytes and granulocytes, which have anti-inflammatory effects, may create a potential window for increased susceptibility to infection

after TKA (4,16,20). Increased levels of anti-inflammatory molecules also contribute to this in post-operative period (16,21). Arthroplasty induced inhibition of T cell proliferation, with a significant reduction in CD4+ T cells (20,22). Heim C et al. confirmed increased neutrophil-to-lymphocyte ratios after TKA (23). Also, they showed that increased IL-10 enhances infectious complications in the presence of other risk factors and impaired long-term functional performance following TKA (23). However, studies have reported responses after TKA changes in leucocyte activation status (24, 25). Infection and inflammatory reactions are the most common reasons for revision knee surgery; therefore, it is essential to mitigate the intense inflammatory response following the procedure (23-25). Recently, Lutzner J. et al. compared the level of different cytokines after the implantation of a standard or hypoallergenic coated TKA. They also showed that increased inflammatory response is associated with worse functional results five years after TKA, disregarding the implant (26).

TKA aims to reduce pain and improve function. It is associated with intensive pain, especially in the first 24 hours after surgery. Stress reactions, as a consequence of bone and soft tissue trauma, increase the sensitivity of the nerves around the knee and may result in additional pain (1,7,12). Therefore, these patients are in pain more than three months before surgery as in our study group(1,2).

Peripheral nerve blocks are part of multimodal analgesia regime providing adequate analgesia without muscle weakness and preventing the appearance of chronic pain (7,8,10). Comparing to local infiltration analgesia (LIA) they provide longer analgesic duration (LIA) (10,27–29). ACB is the most popular block for preserving quadriceps strength and enhancing recovery. Its partial analgetic effects have to be combined with the technique that blocks the nerves in the posterior and lateral sides of the knee. IPACK block provides analgesia in the posterior aspect of the knee. In combination with ACB adequate analgesia is achieved in the anterior and posterior aspects of the knee without muscle weakness (30–32). Our study showed that this combination provided less pain intensity in the first 24h postoperatively and during active movements. Additionally, it reduces morphine consumption and improves KOOS value three months after surgery. This combination also reduces the count of WBC, CRP, ESR and albumin postoperatively. Martin et al., showed that nerve blocks inhibited clinical inflammation after total knee arthroplasty but did not change tissue and plasma cytokine concentrations (33).The degree of inflammation is considered as "the predicting factor" for recovery after TKA(34,35).

CONCLUSION

Peripheral nerve blocks, ACB and IPACK block, achieved adequate postoperative analgesia enabling early rehabilitation, reducing morphine consumption within 24 hours postoperatively, and positively affecting functional status three months after TKA. ACB and IPACK block reduces the count of WBC, CRP, ESR, and albumin (1st, 3^{rd,} and 5th day postoperatively). Identification and influence on factors that reduce the local and systemic inflammatory response is vital in improving recovery after TKA.

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Authors' contributions

- Study design: all authors
- Enrollment and data collection: Svetlana Srećković, Radmila Klačar, Ana Odalović, Dragana Vračević
- Data analysis and interpretation: all authors.
- First manuscript draft: Svetlana Srećković
- Revision of paper: all authors.

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UTICAJ PERIFERNIH NERVNIH BLOKOVA NA INFLAMATORNI ODGOVOR POSLE ARTROPLASTIKE KOLENA

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Sažetak

Pojačan inflamatorni odgovor nakon artroplastike kolena (TKA) rezultat je traume kosti i mekih tkiva, a njegova ekstenzivna reakcija doprinosi postoperativnom morbiditetu i mortalitetu. **Metode:** 200 pacijenata uključeno je u ovu prospektivnu kohortnu studiju nakon elektivne TKA. U prvoj grupi pacijenata primenjeni su aduktor kanal blok i IPACK blok, a u drugoj ne. **Rezultati:** Bol u mirovanju imalo je manje pacijenata u grupi sa blokom i bio je manjeg intenziteta (1,18±0,76 vs. 3,35±1,18 p<0,001). U grupi bez blokova bol je bio intenzivniji tokom kašlja (1,7±0,52 vs. 3,72±1,61 p<0,001) i pri aktivnim pokretima operisane noge (1,67±0,83 vs. 3,78±1,94 p<0,001). U prva 24 sata nakon operacije, u grupi sa blokovima, 22% pacijenata je koristilo opioide u dozi od 9,64±3,21 mg, dok su ih u grupi bez bloka svi pacijenti koristili u dozi od 30,94±11,47. Statistički značajna razlika između grupa je postojala u WBC, CRP, ESR i albuminima prvog, trećeg i petog postoperativnog dana. Tri meseca nakon TKA, KOOS skor je bio statistički viši u grupi sa blokovima (92,6±11,73 vs 85,65±17,49 p<0,001).

Zaključak: Kombinacijom nervnih blokova obezbeđuje se adekvatna postoperativna analgezija koja omogućava ranu rehabilitaciju, smanjuje potrošnju morfijuma, smanjuje broj WBC, CRP, ESR i albumina (1., 3. i 5. dan posle operacije) i pozitivno utiče na funkcionalni status tri meseca nakon operacije. Identifikacija i uticaj na faktore koji smanjuju lokalni i sistemski inflamatorni odgovor je od vitalnog značaja za poboljšanje oporavka nakon TKA.

Ključne reči: artroplastika kolena, inflamatorni odgovor, nervni blokovi, analgezija

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ORIGINAL ARTICLE

Reduced ovarian hyperstimulation syndrome risk with Follitropin-δ in ovarian stimulation

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Summary

Introduction: Ovarian stimulation (OS) during assisted reproductive technology (ART) carries the risk of ovarian hyperstimulation syndrome (OHSS). The risk is increased in polycystic ovary syndrome (PCOS). Recombinant DNA technologies have brought new generations of gonadotropins, such as Follitropin-δ. Individualized Follitropin-δ dosing, based on patient's body weight (BW) and Anti-Müellerian hormone (AMH), reduces OHSS risk.

Aim: To compare the prevalence of OHSS and the efficacy of OS with individualized Follitropin-δ and standard dosing with old generation gonadotropins in women with PCOS.

Material and methods: Case-control study encompassed 24 women stimulated with individualized Follitropin-δ dosing (Study Group) and 48 women with standard old generation gonadotropin dosing (Control Group). The inclusion criterion was PCOS. The exclusion criteria included other causes of infertility. Study participants were matched according to age, BW, AMH, and smoking status.

Results: Prevalence of moderate (0% vs. 5.9%) and severe (0% vs. 17.6%) OHSS were significantly lower in Study Group (p=0.009). Duration of OS (9.06±1.53 vs. 10.00±1.13 days, p=0.01) and total gonadotropin dose (1,117.95±234.90 vs. 1,940.33±501.20 IU, p<0.001) were significantly lower in Study group. The number of good quality embryos was significantly higher in Study group (3.33±1.13 vs. 2.20±0.96 embyos, p<0.001).

Conclusion: The prevalence of moderate and severe OHSS is lower in OS with individualized Follitropin-δ dosing compared to standard dosing with older generations of gonadotropins. The effectiveness of OS in the study groups did not differ significantly, except for the shorter duration of OS, a lower applied total gonadotropin dose and significantly higher number of good quality embryos, which were recorded in Study group.

Keywords: prevalence, good quality embryos, gonadotropin dose

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INTRODUCTION

Excessive multifollicular growth during ovarian stimulation (OS) in assisted reproductive technology (ART) is common in women with polycystic ovary syndrome (PCOS), often leading to ovarian hyperstimulation syndrome (OHSS), a challenging iatrogenic complication (1). OHSS stirs a general concern in ART, which disturbs both women's physical and mental health and increases the risks regarding adverse pregnancy outcomes (2). Results from the observational study highlight the significance of PCOS as a risk factor for OHSS, showing a marked difference in OHSS prevalence between women with and without PCOS. Among women with PCOS, 22.1% experienced OHSS, compared to less than 5% in those without PCOS (3). Consequently, prevention of OHSS in women with PCOS is very important for the safety of OS treatment.

The initiation of recombinant DNA technologies in the field of reproductive medicine caused a fast development of novel medications, and enabled transition from standardization to individualization regarding the choice and dosage of gonadotropins (4). This advancement in gonadotropin production also enabled the generation of proteins through biological processes, resulting in high-purity medications produced at large scales with consistent composition. Follitropin-δ, the newest and unique gonadotropin, is produced from a host cell line of human origin, while previous recombinant gonadotropins were derived from a host cell line of Chinese hamster. Additionally, it has a diverse pharmacokinetic profile from other gonadotropins because of higher levels of 2.6-linked sialic acid and tri- and tetra-sialylated glycans. This leads to more effective action of gonadotropin-δ compared to other gonadotropins (4), lower clearance (5), and a risk/benefit ratio considered to be positive including headache and OHSS (6). Furthermore, it comprises unique approach by individualizing the gonadotropin dosage based on body weight and ovarian reserve, allowing individualized therapeutic approach and decreasing the risk of OHSS (4).

Several years ago, Follitropin-δ was introduced in clinical practice in ART procedures in Serbia. Involvement in such practice is gradually increasing. However, real-world studies regarding Follitropin-δ, that reflect current practices with respect to how patients react to treatment in terms of safety, tolerance and efficacy in Serbia and South-East Europe are missing. Therefore, this observational match case-controlled study aimed to enhance medical knowledge regarding safety and efficacy of individualized Follitropin-δ in population of women with PCOS in Serbia. We aimed to evaluate the prevalence of OHSS and efficacy of OS in women treated with individualized Follitropin-δ dosing and in women who were treated with standard gonadotropin dosing.

MATERIAL AND METHODS

Subjects

Study participants were women who underwent ART at two clinics in Belgrade financed by the Republic Fund of Health Insurance of the Republic of Serbia. One clinic is a public university clinic and the other one is a private ART clinic. Both are located in Belgrade, the capital of the Republic of Serbia, both perform ART procedures financed by the Republic Fund of Health Insurance, and they are both considered to be referral centers for ART for the entire country. The inclusion criteria were: PCOS identified following Rotterdam criteria, fresh autologous cycle, age between 18 and 45 years. The exclusion criteria included obesity and any other infertility cause. The approval for this study was obtained from the Institutional review board (No. of decision 05006-2022-16004).

Methods

Retrospective observational analysis (matched case-controlled study) with carefully selected homogeneous group of patients assessed prevalence of OHSS and ART outcomes in women with PCOS stimulated with individualized Follitropin-δ dosing and with conventional gonadotropin dosing. After applying inclusion and exclusion criteria, anonymized data of two groups of women with PCOS undergoing OS were analyzed. The Study group encompassed women who received individualized Follitropin-δ dosing (individualized dosing group), the Control group received standard gonadotropin dosing (standard dosing group). In total, 24 women treated with Follitropin-δ were matched in terms of age, AMH, body weight, and smoking status with 48 patients who had been treated with standard gonadotrophin dosing.

The primary study outcome was the prevalence of OHSS, both regarding the prevalence of OHSS in general and regarding the prevalence of different severity of OHSS (mild, moderate, severe). The diagnosis of OHSS and various degrees of severity of OHSS were assessed by Golan criteria and classification (7). Secondary study outcomes were the duration of OS, the total dosage of applied gonadotropin, the total number of retrieved oocytes, the number of metaphase II oocytes (MII), the total number of obtained embryos, and the number of good quality embryos (GQE) and clinical pregnancy rate (CPR).

The approval for this study was obtained from the Institutional review board (No. of decision 05006-2022-16004).

Statistical analysis

Depending on the type of data, the data are presented as counts (percents) or mean+/–standard deviations. For comparisons between study groups, parametric tests

Table 1. Clinical characteristics of study participants

	Study group	Control group	p
Age (years)	32.67±3.21	32.63±3.14	0.958*
Infertility duration (years)	2.42±1.12	2.51±0.95	0.345*
Previous delivery/deliveries	0%	10.4%	0.162¶
Previous misscariages	20.8%	18.8%	1.000¶
Menarche (years)	12.60±1.39	13.37±1.79	0.069*
Cycle length (days)	33.13±9.05	32.40±7.35	0.719º
FSH - day 3 (IU/l)	5.97±1.43	5.70±1.75	0.515*
LH - day 3 (IU/l)	8.26±3.72	6.46±3.10	**0.033***
Estradiol - day 3 (IU/l)	139.77±62.48	179.37±88.78	0.068º
AMH (ng/ml)	5.78±.25	5.74±3.23	0.929º
Antral Follicle Count	25.67±1.46	25.42±1.22	0.446*
Right Ovary volume(cm3)	12.68±0.41	12.66±0.33	0.835*
Left Ovary volume (cm3)	12.76±0.44	12.71±0.34	0.572*

Data are expressed as mean±SD or as percentages. * – t-test was used to test the differences; ¶ - Fisher's exact test was used to test the differences; º - Mann-Whitney test was used to test the differences

Table 2. Outcomes of OS in study groups

	Study group	Control group	p
Duration of OS (days)	9.06±1.53	10.00±1.13	**0.01º**
Gonadotropin dose	1,117.95±234.90	1,940.33±501.20	**<0.001***
Serum E2 (pmol/l) trigger day	6512.60±1.39	7813.37±1.79	0.069*
No of periovulatory follicles	10.96±4.81	11.17±3,18	0.849*

Data are expressed as mean±SD or as percentages. * – t-test was used to test the differences; º - Mann-Whitney test was used to test the differences

(Student's t-test and Fisher's exact test) and non-parametric tests (Mann Whitney test, Chi-square test) were used. Multivariate logistic regression was employed as a statistical method to account for confounding factors. All data analyses were performed using the statistical software SPSS (IBM corp.). All p values less than 0.05 were considered significant.

RESULTS

Characteristics of women with PCOS treated with individualized Follitropin-δ and those treated with standard gonadotropin dosing are presented in **Table 1**. A significant difference between the groups was only found regarding serum LH levels on day 3 of the cycle, being lower in standard dosing group.

The outcome of OS treated with individualized Follitropin-δ or standard gonadotropin dosing are presented in **Table 2**. The duration of OS and applied gonadotropin dose were significantly lower in Study group.

Table 3 presents data on the outcomes of oocyte pick-up and ART results in the individualized Follitropin-δ dosing group compared to the standard gonadotropin dosing group. The number of germinal vesicles and atretic oocytes were significantly higher in standard gonado-

Table 3. ART outcomes in study groups

	Study group	Control group	P
Retrieved oocytes	10.50±5.09	10.25±3.24	0.828*
Metaphase II oocytes	5.79±3.06	5.06±2.57	0.291*
Metaphase I oocytes	1.71±2.39	1.46±1.73	0.618º
Germinal vesicle oocytes	0.37±0.92	1.10±1.51	**0.009º**
Atretic oocyte	0.04±0.20	0.88±1.06	**<0.001º**
Total No of Embryos	6.33±2.87	5.17±2.79	0.169º
No of Good Embryos	3.33±1.13	2.20±0.96	**<0.001º**
Clinical pregnancy rate	29.17%	34.8%	0.057¡

Data are expressed as mean±SD or as percentages. To test the differences: * – t-test was used t; º - Mann-Whitney test was used; ¡ - Chi-square test was used

Table 4. Prevalence of OHSS in study groups

	Study group	Control group	p
OHSS	7 (29.2%)	17 (37.0%)	0.515¡
Severe OHSS	0 (0.0%)	1 (5.9%)	
Moderate OHSS	0 (0.0%)	3 (17.6%)	**0.009** º
Mild OHSS rate	7 (100%)	14 (76.5%)	

Data are expressed as absolute numbers and as percentages (in brackets). To test the differences: º - Mann-Whitney test was used; ¡ - Chi-square test was used

tropin dosing while the number of obtained good quality embryos was significantly higher in individualized dosing group. **Table 4** presents the prevalence of OHSS, including overall cases and the distribution among different grades, within the study groups. Although the prevalence of OHSS in general did not differ significantly, the prevalence of different grades differed significantly, prevalences of moderate and severe forms were lower in individualized dosing group.

DISCUSSION

To the best of our knowledge, our study is the first to compare the prevalences of OHSS in the population of women with PCOS in Serbia and the region of South-East Europe stimulated with individualized Follitropin-δ dosing and with standard gonadotropin dosing. Results from our matched case-controlled study represent real-world data from Serbia during routine healthcare reproductive medicine care, generated through data obtained from electronic records from our clinics. Our data is in line with randomized control trials (RCT) evaluating this issue in general population of women undergoing ART in Japan (8) and also in the population of women with PCOS in Poland (9).

Regarding the efficacy of OS, we found significantly lower applied gonadotropin dose in women with individualized Follitropin-δ dosing, which is in accordance with the study performed by Gazzo et al. (10) and by Kovacs et al. (11). Furthermore, a significantly shorter duration of OS was present in individualized Follitropin-δ dosing group. This is in contrast with RCT performed by Qiao et al. (12). By default, participants in a randomized controlled trial (RCT) follow a strictly controlled treatment regimen based on a specified study protocol. In contrast, our study utilizes real-world data (RWD) derived from various electronic health and medical records, reflecting less regulated and more diverse treatment options. Furthermore, Qiao et al. performed a study in Asian population and the inclusion criteria considerably differed from our inclusion criteria, while they included women diagnosed with tubal and unexplained infertility as well as minimal and mild endometriosis. The aforementioned facts may explain the discrepancies between the results of their RCT and our matched case-control study. Still, when compared to other RWD, our duration of OS was shorter. Thus, mean duration of OS (9.06 days) was noticeably shorter than OS duration obtained from RWD DELTA study (13). This marked difference could be explained by the fact that in our study other causes of infertility rather than PCOS were excluded from the study, while in DELTA study all kinds of infertility causes other than anovulatory PCOS were included.

This study has some limitations. Follitropin-δ was introduced a few years ago, and the number of women stimulated with this new medication is gradually rising; however, the overall population of these women remains small. Besides, in order to avoid potential confounding factors that may influence ART outcomes, we applied very strict inclusion and exclusion criteria which resulted in narrowing down the selection of potential study participants. For the aforementioned reasons, the number of study participants is small and we acknowledge this as a study limitation. Furthermore, the study sample was small to evaluate different PCOS phenotypes among study participants, and that is another limitation of the study. Different PCOS phenotypes mirror the diversity of ovarian response to OS and risks in developing OHSS (14).

This study has its strengths as well. Rigorous exclusion and inclusion criteria lead to avoidance of possible confounding factors. Furthermore, external validity is another study strong point. As previously mentioned, both clinics involved in this study are considered to be referral centers for ART in the Republic of Serbia and neighboring countries. Therefore, women undergoing ART in those clinics could be considered as representative population of infertile women in the region.

CONCLUSION

Our study demonstrated excellent safety performances of OS with individualized Follitropin-δ dosing. These performances were better than OS with standard gonadotropin dosing, since the prevalence of moderate and severe OHSS is significantly higher in OS with standard gonadotropin dosing. In unison, ART outcomes between study groups did not differ significantly. The real-world data (RWD) on the safety profile of ovarian stimulation with individualized Follitropin-δ dosing in Serbia, provided by this observational matched case-control study, align with the findings of previously published clinical trials and global real-world studies. However, some data

regarding efficacy of OS are in contrast with RWD and RCT. Therefore, larger studies are needed to deliver more reliable data concerning the issues evaluated in this study.

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Disclosure of interest

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Author Contributions

- The conception or design of the work: Milan Perović, Nebojsa Zečević
- The acquisition, analysis, and interpretation of data: Milan Perović, Nebojša Zečević, Dragana Bojović-Jović, Tatjana Nožić Zečević, Ana Nikolić
- Preparing the manuscript draft: Milan Perović, Nebojsa Zečević, Dragana Bojović-Jović, Tatjana Nožić Zečević, Aleksandar Stojsavljević, Ana Nikolić
- Interpretation of revised version of manuscript: Milan Perović, Nebojša Zečević, Dragana Bojović-Jović, Tatjana Nožić Zečević, Aleksandar Stojsavljević, Ana Nikolić

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SMANJEN RIZIK OD HIPERSTIMULACIJE JAJNIKA USLED PRIMENE FILOTROPINA DELTA TOKOM STIMULACIJE JAJNIKA

Milan Perović[1, 2], Nebojsa Zečević[1, 2, 3], Dragana Bojović-Jović[1], Tatjana Nožić Zečević[1, 2], Aleksandar Stojsavljević[4], Gorana Nikolić[2, 5], Ana Nikolić[1]

Sažetak

Uvod: Stimulacija jajnika (OS) u sklopu vantelesne oplodnje (VTO) nosi rizik od sindroma ovarijalne hiperstimulacije (OHSS). Ovaj rizik je naročito izražen kod žena sa sindromom policističnih jajnika (PCOS). Rekombinantnim DNK tehnologijama stvorene su nove generacije gonadotropina, kao što je folitropin delta, koje individualizovanim doziranjem na osnovu vrednosti Anti-Milerovog hormona (AMH) i telesne mase (tm) pacijenta smanjuju rizik od OHSS-a.

Cilj: Upoređivanje prevalence OHSS-a i efikasnosti OS-a individualizovanim doziranjem folitropinom delta i standardnim doziranjem starijim generacijama gonadotropina u populaciji žena sa PCOS.

Metode: U studiji kontrole slučajeva radnu grupu činile su 24 žene stimulisane individualizovanim doziranjem folitropinom delta, a kontrolnu 48 žena koje su stimulisane standardnim doziranjem starijim generacijama gonadotropina. Studijski kriterijum za uključivanje bio je PCOS, a za isključivanje ostali uzroci infertiliteta. Ispitanice radne grupe uparene su sa ispitanicama kontrolne grupe na osnovu AMH, tm, godina starosti i pušačkog statusa.

Rezultati: U radnoj grupi prevalenca umerenih (0% vs. 5,9%) i težih (0% vs. 17,6%) formi OHSS-a značajno je manja (p=0,009) u odnosu na kontrolnu grupu. Trajanje OS (9,06±1,53 dana vs. 10,00±1,13 dana, p=0,01) i primenjena doza gonadotropina (1,117.95±234,90 vs. 1,940.33±501,20 IU, p<0,001) značajno su manji u radnoj grupi. Broj dobijenih embriona visokog kvaliteta veći je u radnoj grupi (3,33±1,13 vs. 2,20±0,96, p<0,001).

Zaključak: Prevalenca umerenih i težih formi OHSS-a manja je kod OS individualizovanim doziranjem folitropinom delta u odnosu na OS standardnim doziranjem starijim generacijama gonadotropina. Efikasnost OS u studijskim grupama nije se značajno razlikovala, osim kraćeg trajanja OS, manje ukupne primenjene doze gonadotropina i znatno većeg broja dobijenih visokokvalitetnih embriona, a koji su zabeleženi kod OS individualizovanim doziranjem folitropinom delta.

Ključne reči: prevalenca, kvalitetni embioni, doza gonadotropina

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ORIGINAL ARTICLE

Enhancing hip arthroplasty recovery with balneo-rehabilitation treatment

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Summary

Introduction: Balneo-rehabilitation treatment is a therapeutic approach that utilizes natural elements as a means of therapy. Hip arthroplasty is a surgical procedure that helps address hip joint dysfunction. This study aims to investigate whether the balneo-rehabilitation treatment can enhance the recovery of functional capabilities and improve the quality of life of patients who have undergone hip arthroplasty.

Material and Methods: The study included 100 patients who had undergone hip arthroplasty and participated in hydrokinesis exercises in thermal mineral water pools, alongside a standard dry-land rehabilitation program. The evaluation included assessments of hip joint range of motion and the strength of primary hip-moving muscles. Participants also rated the protocol's effectiveness based on improvements in quality-of-life parameters.

Results: The study results demonstrated that balneo-rehabilitation treatment significantly accelerated the recovery of functional abilities and enhanced the quality of life in patients following hip arthroplasty surgery.

Conclusion: Our results suggest that the balneo-rehabilitation treatment at the Special Hospital for Rehabilitation "Banja Kanjiža" accelerated recovery and improved the quality of life in patients following hip arthroplasty. Coordinated multicenter clinical trials and fundamental research are needed to verify the effectiveness of this treatment further.

Keywords: balneo-rehabilitation treatment, hip arthroplasty

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INTRODUCTION

Balneo-rehabilitation treatment (BRT) represents a therapeutic modality employing natural elements to elicit healing responses, encompassing a multifaceted approach involving ingestion, immersion in mineral water, thermal and hydrotherapy (HT), inhalation, application of healing mud, and various ancillary medical interventions (1). Physiological responses to these natural stimuli are categorized into general and specific reactions. General responses entail the organism's reaction to the thermal, chemical, and mechanical stimuli inherent in the balneo-rehabilitation treatment (2). In contrast, specific reactions are contingent upon the mode of application and the physicochemical attributes of the utilized natural agent (3). External application of balneological agents at the dermal level triggers the synthesis of active biological compounds, including beta-endorphins, acetylcholine, histamine, and serotonin, which, in turn, elicit systemic responses via neurohumoral pathways. These collective effects enhance the organism's functional capacity and intrinsic potential for self-recovery (4-5).

Thermal mineral waters exhibit temperatures exceeding 20°C and mineralization levels surpassing 1 g/l. Primarily used as a balneological agent, natural thermal mineral waters offer preventive and therapeutic benefits for a range of pathophysiological conditions. Therapeutically, they are administered via ingestion, immersion, inhalation, irrigation, electrophoresis, and sonophoresis of peloids (6-8). Immersion baths may be localized to specific body regions or encompass the entire body, with recommended durations typically ranging from 10 to 20 minutes, contingent upon the patient's overall health status, and conducted daily or every other day (9). Additionally, thermal mineral waters may be applied through rain, spraying, or pressurized hydromassage tubs, with temperatures commonly maintained within the range of 34 to 36°C, owing to its tolerability and sedative effects on the body. The minimum recommended therapy duration is seven days, extendable to up to 10 weeks as warranted (10). According to established balneological criteria, Banja Kanjiža's mineral water falls under group I/a within Quentin's classification, characterized by its sodium-hydrocarbonated composition, iodine, sulphide content, medium mineralization, and hyperthermic nature (11).

Fractures affecting the proximal femur segment are frequently denoted as hip fractures (12). These injuries typically arise from forces exerted upon the knee or foot, imparting impact upon the greater trochanter region during rotational or abduction movements of the extremity (13). Additionally, hip fractures can also result from underlying stress fractures (14). In the elderly, such fractures commonly ensue following falls from standing height onto a level surface, often characterized as low-energy fractures.

Hip arthroplasty stands as an efficacious surgical intervention for addressing hip dysfunction (15). Predominantly indicated for hip fractures and longstanding arthrosis, this procedure encompasses two primary approaches: hemiarthroplasty, reserved for patients lacking significant degenerative hip alterations, and total hip arthroplasty, typically undertaken in more physically active individuals with advancing degenerative changes (16). Hemiarthroplasty involves replacing the proximal portion of the femur with an implant, whereas total arthroplasty encompasses replacing both the proximal femur and the acetabulum. The selection between these surgical approaches following a femoral neck fracture remains subject to ongoing debate (17).

In most cases, patients who undergo hip arthroplasty get discharged from hospital after successful verticalisation and restoration of gait function. However, many patients continue to experience physical challenges and have not reached full recovery (18). In order to increase muscle strength, stretch, achieve an adequate range of motion, restore walking, and ensure proprioceptive recovery, patients are included in a rehabilitation program. There are several postoperative interventions, including early postoperative rehabilitation in hospital, inpatient rehabilitation or exercises at home, hydrotherapy, and fast-track protocols (19). Progressive resistance training (PRT) is one of the most frequent rehabilitation methods after hip replacement. It can also be introduced very early postoperatively due to muscle mass and strength loss accompanying the operation (20). In recent years, the so-called Enhanced Recovery After Surgery (ERAS) or Fast Track protocols - individualized multimodal peri- and postoperative approaches to rehabilitation - have been increasingly used to reduce the consequences after surgery, reduce pain, optimize and accelerate patient recovery and shorten the time spent in hospital (21). Another beneficial rehab method is hydrotherapy. Immersion in the aquatic environment reduces the impact of body weight on the joint, making it easier to move the extremities. Also, the water pressure protects the joint, gives the patient a sense of security when standing, and increases muscle strength, balance, and coordination (22). Despite the numerous rehabilitation options available, the most effective approach for achieving full functional recovery after hip arthroplasty remains uncertain, and there is limited information on how these methods affect the implant itself (23).

This study aims to assess the extent to which the balneo-rehabilitation treatment can augment the restoration of functional capabilities and enhance the quality of life in patients who have undergone hip arthroplasty surgery.

MATERIAL AND METHODS

Patients

Patients (n=100) included in this investigation were admitted to the Banja Kanjiža Special Rehabilitation Hospital from April 2020 to March 2021. The inclusion criteria were hip arthroplasty performed a maximum of five months before admission to the rehabilitation hospital, age between 55 and 80, eagerness to undergo a program of hydrokinesis exercises in pools with thermal mineral water, and a conventional dry-land therapeutic rehabilitation program. The Ethical Committee of the Banja Kanjiža approved this prospective study.

After obtaining the written consent of the subjects to participate in the study, the following parameters were collected: demographic data (gender, age, working ability), tobacco consumption habits, the presence of comorbidities (hypertension) and deformities (amputations), the cause of the hip arthroplasty, and how much time has passed since the surgical intervention was recorded. Body mass and height were measured, while body mass index (BMI) was calculated as well. During the course of the study, all patients continued with their regular therapy.

Research protocol

The subjects performed strength and endurance exercises, coordination and balance exercises, exercises for increasing the range of motion (stretching exercises) and aerobic exercises daily. Hydrokinesiotherapy with thermal mineral water was carried out in pools with thermal mineral water for three weeks. Patients exercised in pools once a day for 30 minutes six days a week, performing each exercise five times.

From the clinical parameters for each subject, the degree range of motion of the hip joint and the gross muscle strength of the most important muscles that move the hip joint were assessed. Measurements were carried out at the beginning of the study before therapy and at the end of the treatment. The gross muscle strength of the synergistic muscle groups involved in the movements of the hip joint (quadriceps, hip abductor, hip adductor) was assessed and categorized as: 0 - contraction neither visible nor palpable, 1 - contraction in trace and no movement of segments, 2 - motion full range with elimination of gravity, 3 - motion full range against gravity, 4 - motion full range against gravity and 5 - full range of motion against gravity with high resistance. The absence of progress in increasing the range of motion of the hip joint and increasing the degree of gross muscle strength was considered an indicator of therapy failure. After completing the therapeutic protocol, the respondents assessed the protocol's success by looking at the improvement of the mentioned quality of life parameters. They presented their general opinion on the success of the treatment.

Statistical analysis

Descriptive statistics was used for data processing. All numerical parameters are presented as mean value ± standard deviation, while categorical variables are presented as absolute and relative numbers. The non-parametric Wilcoxon test of equivalent pairs was used to test the significance of the difference, and Spearman's rank correlation was used to test the association. All data obtained during the research were processed using the computer statistical program SPSS 20.0 for Windows. In all tests, the accepted level of statistical significance is $p < 0.05$.

RESULTS

Demographic parameters

In this study, 39% of participants were male, while 61% were female. The majority of participants were classified as overweight, comprising 44% of the overall sample, while 61% reported a history of never smoking. Furthermore, 62% were diagnosed with hypertension. Through data analysis it was found that most patients in this study were older females who underwent surgery due to arthrosis of the hip joint **(Table 1)**.

Table 1. Demographic parameters of the experimental group and causes of hip arthropathy

Age (mean ± standard deviation, years)	68 ± 9			
Male n (%)	39 (39%)			
Female n (%)	61 (61%)			
BMI (kg/m^2) (%)	underweight	normal	overweight	obese
	2	27	44	27
Smokers (%)	Never	ex-smokers	active	
	61	24	15	
Hypertension (%)	62			
Amputation (%)	0			
Hip fracture	26 (n=25)			
Arthrosis of the hip	75 (n=77)			

Abbreviations: BMI – body mass index

Hip joint mobility

Based on data analysis **(Table 2)**, we determined that at the end of the therapy in 57% (n=58) of the subjects, there was an improvement in the degree of mobility of the hip joint, which reached a statistically significant level of difference ($p < 0.05$) in the registered categories compared to the initial ones.

At the start of the study, none of the subjects had a standard level of mobility; however, by the end of the therapy, 9% (n=9) of the participants had regained average mobility levels.

In 43% (n=44) of the subjects, the same categories of degree of hip joint mobility were registered at the beginning of the therapy.

Table 2. The degree of range of motion of the hip joint

Category	Before therapy	After therapy
I	1 (n=1)	9 (n=9)
II	13 (n=13)	51 (n=52)
III	82 (n=84)	39 (n=40)
IV	4 (n=4)	1 (n=1)
V	0 (n=0)	0 (n=0)

The table shows the variables as a percentage share in the given group (%) and absolute numbers (n - number of respondents). I – normal, II - easily limited (30% less than normal), III - medium limited (30-60% less than normal), IV - severe limitation (more than 60% less than normal), V – hypermobility.

Muscular strength

At the end of the therapy, we determined that in 72% (n=74) of the subjects, there was an increase in the intensity of gross muscle strength of synergistic muscle groups of hip joint movers, which reached a statistically significant level of difference ($p < 0.05$) in the registered categories compared to the initial ones. In 26% (n=28) of the subjects, the intensity levels of gross muscle strength in the synergistic muscle groups that move the hip joint remained unchanged from the beginning of therapy.

At the beginning of the study, none of the subjects registered a full range of motion against the gravitational force and significant resistance, while at the end of the therapy, 12% (n=12) of the subjects regained these values.

Table 3. Gross muscle strength of synergistic muscle groups involved in hip joint movements

Category	Before therapy	After therapy
I	0 (n=0)	0 (n=0)
II	2 (n=3)	0 (n=0)
III	88 (n=89)	28 (n=29)
IV	10 (n=10)	60 (n=61)

The table shows the variables as a percentage share in the given group (%) and absolute numbers (n - number of respondents). I - contraction is not visible or palpable, II - contraction in trace and no initiation of segments, III - full range of motion while eliminating the force of gravity, IV - full range of motion against gravity.

Quality of life

Upon arrival at the spa, only 3 (6%) patients were able to stand for as long as they wanted. At the end of the therapy, 31 (62%) patients did not have any pain related to the condition and were able to stand for as long as they wanted. Only one patient older than 70 years, body mass index 29, who, due to hip arthrosis, had come to the spa only 5 months after the surgical intervention, and after completing the therapeutic protocol, was able to stand for less than ten minutes **(Table 4)**.

Table 4. Ability to stand independently

	Category	Before therapy	After therapy
Ability to stand independently	I	6 (n=3)	62 (n=31)
	II	56 (n=28)	32 (n=16)
	III	22 (n=11)	2 (n=1)
	IV	*12 (n=6)*	*2 (n=1)*
Use of walking aids	I	12 (n=6)	34 (n=17)
	II	46 (n=23)	56 (n=28)
	III	32 (n=16)	8 (n=4)
	IV	10 (n=5)	2 (n=1)
Ability to dress independently	I	20 (n=10)	92 (n=46)
	II	78 (n=39)	6 (n=3)
	III	2 (n=1)	2 (n=1)

The table shows the variables as a percentage share in the given group (%) and absolute numbers (n - number of respondents). Ability to stand independently: I - stand as long as they want without pain, II - stand as long as they want with a feeling of pain, III - due to pain for less than 30 minutes, IV - due to pain less than 10 minutes. Use of walking aids: I - they do not use aids, II - they use 1 or 2 sticks, III - use 1 or 2 crutches, IV - a Walker. Ability to dress independently: A - can dress myself without difficulty, II - can dress myself with significant pain, III - I can't dress myself.

We found that upon arrival, only six patients (12%) were able to move without using a medical aid. After completing the therapeutic protocol, 17 patients (34%) were able to walk independently, while 23 patients (46%) transitioned to different mobility aids; those who initially used walkers switched to crutches, and those using crutches began using a cane, while 10 (20%) patients continued to use the same device. These findings indicate that there has been a significant improvement in the field of mobility, but additional weight is brought by the knowledge that the frequency of use of walking aids has also been significantly reduced. As we have already pointed out, only 6 (12%) patients did not use an aid upon arrival, while at the end of the therapy, another 11 (22%) patients were able to walk independently. Only 7 (14%) patients who completed the therapy continued to use a walking aid all the time, but we must point out that all of them were over 75 years of age. The largest number of patients, 27 of them (54%), significantly reduced the use of aids when moving

(Table 4). Also, we found that 90% of the respondents experienced a statistically significant change ($p < 0.05$) in the ability to dress independently after therapy compared to their abilities before therapy (Table 4).

After completing the therapy, all patients were able to walk significantly longer distances. As many as 14 (28%) patients were able to cover a distance that was 500% longer than the results they could achieve upon arrival at the spa (Table 5).

Table 5. An increase in the distance that the subjects could walk after the therapy

Lengthening category in relation to pretherapy distance	Respondent
I	0 (n=0)
II	12 (n=6)
III	28 (n=14)
IV	32 (n=16)
V	28 (n=14)

The table shows the variables as a percentage share in the given group (%) and absolute numbers (n - number of respondents. I - same or less than 50% extension, II - extension of more than 50% but less than 100%, III - elongation more than 100% but less than 300%, IV - elongation more than 300% but less than 500%, V - extension more than 500%.

DISCUSSION

Balneo-rehabilitation treatment, a treatment method that has been integrated into routine clinical practice across numerous European countries and globally (1), holds a significant place in the medical field. However, despite its extensive historical usage and cultural heritage, the scientific validity of balneo-rehabilitation treatment remains a topic of expert discourse, largely due to the imperative for evidence-based substantiation regarding the effects of balneological agents.

Among our cohort of 100 patients referred for spa rehabilitation, the majority were elderly females with a high prevalence of hypertension. The primary impetus for surgical intervention, precipitating subsequent referral for spa treatment within an average timeframe of three months, predominantly stemmed from hip joint arthrosis. Given that impaired independent mobility and standing significantly compromise the quality of life among individuals with hip joint dysfunction, our investigation sought to elucidate this critical facet of functional recovery. This entailed documenting the type and frequency of medical aids employed during ambulation, monitoring the duration of unassisted standing without difficulty, and assessing the distance travelled by patients.

Observing the realized enhancements in mobility and muscle strength, the anticipations regarding patients' progression in executing fundamental daily activities autonomously were substantiated. Kars et al. elucidated through a randomized clinical investigation that hydrokinesiotherapy engenders advancements in functional capacities, joint mobility, and pain alleviation among osteoarthritis patients (17). Similarly, Hinman et al. underscored the significant enhancements in muscle strength, functional abilities, joint mobility, and pain mitigation resulting from hydrokinesis therapy in osteoarthritis patients (24). Notably, a relatively limited number of clinical inquiries have comprehensively examined the manifold contributions of balneotherapy to the recuperation of patient's post-hip arthroplasty. Furthermore, Di Monaco et al. underscore the pivotal role of hydrokinesiotherapy in rehabilitating post-hip arthroplasty patients (25). Additionally, Papalia et al. highlighted the ongoing necessity for further exploration in the realm of evidence-based assertions regarding the beneficial effects of controlled physical activity, both on land and in aquatic environments, on the recovery of patients' post-surgical interventions at the hip and knee joint levels (26).

In a multicenter clinical investigation, Liebs et al. emphasized the importance of determining the optimal timing for integrating hydrokinesiotherapy into the rehabilitation protocol for patients undergoing knee and hip arthroplasty (27). Specifically, Giaquinto et al. determined that among the geriatric demographic, the administration of hydrokinesiotherapy, even six months post-surgical intervention on the hip joint, markedly contributed to functional rehabilitation and alleviation of subjective pain perception (28). Moreover, the findings elucidated by Musumeci et al. underscored the considerable significance of early incorporation of balneological intervention with thermal mineral water, showcasing notable enhancements in quality of life and functional recuperation, including muscle strength and joint mobility among patients who underwent hip joint arthroplasty procedures (29).

It is imperative to highlight the escalating global prevalence of obesity across all age demographics. This phenomenon significantly impacts not only the functional recuperation of patients following surgical intervention for hip dislocation but also poses a substantial risk factor for traumatic incidents predisposing to hip joint integrity compromise, particularly among the elderly. Within our study cohort, it was observed that individuals in the test group with elevated body mass index demonstrated comparatively less progress than other categories. Importantly, evidence from diverse global studies underscores the potential of balneotherapy and hydrotherapy in facilitating the attainment of appropriate body mass, with demonstrated safety profiles even among obese individuals (30-33).

The delineated advantages stemming from balneo-rehabilitation treatment procedures conducted within the Banja Kanjiža Special Hospital underscore the underutilized balneological potential inherent in our region. This assertion gains further weight when considering the established practices observed in neighboring Hungary, which shares a congruent geological origin and structure with our segment of the Pannonian region (34, 35).

To further solidify the position of balneology, it is imperative to undertake coordinated multicenter clin-

ical trials alongside fundamental research endeavors. Acknowledging the inherent complexity associated with such initiatives, particularly concerning the diverse physical and chemical properties of thermal mineral waters and their intricate interplay, challenges abound in isolating the effects of individual factors. Nevertheless, a strong commitment to utilizing our region's abundant natural healing resources, alongside the expertise of qualified healthcare professionals and well-equipped spa facilities, is essential. These efforts aim to benefit our local population and extend the therapeutic potential of balneological interventions to a global audience.

CONCLUSION

Our results suggest that the balneo-rehabilitation treatment at the Special Hospital for Rehabilitation "Banja Kanjiža" accelerated recovery and improved the quality of life of patients after hip arthroplasty. Furthermore, it is important to highlight the significant potential of using balneological agents for preventive purposes to maintain and enhance overall health while reducing the onset and progression of degenerative conditions. This preventive approach holds promise across diverse demographics, from children and adolescents to the elderly, offering holistic health benefits to the broader population. Coordinated multicenter clinical trials and fundamental research are needed to verify the effectiveness of this treatment further.

Author Contributions

Attila Klimó contributed to patient recruitment and initial manuscript drafting. Mina Bogetić and Marija Babić were responsible for data analysis and interpretation. Rada Jeremić and Predrag Brkić contributed to the study's conception, design, and provided manuscript review and editing.

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POBOLJŠANJE FUNKCIONALNOG OPORAVKA POSLE ARTROPLASTIKE KUKA PRIMENOM BALNEO-REHABILITACIONIH TRETMANA

Attila Klimó[1], Rada Jeremić[2], Marija Babić[3], Mina Bogetić[4], Predrag Brkić[2]

Sažetak

Uvod: Balneorehabilitacioni tretman je terapijski pristup koji koristi prirodne elemente kao sredstvo lečenja. Artroplastika kuka je hirurška procedura koja pomaže u rešavanju disfunkcije zgloba kuka. Ova studija ima za cilj da istraži da li balneorehabilitacioni tretman može poboljšati oporavak funkcionalnih sposobnosti i poboljšati kvalitet života pacijenata koji su bili podvrgnuti artroplastici kuka.

Materijal i metode: U studiju su uključeni pacijenti (n=100) koji su bili podvrgnuti artroplastici kuka i učestvovali u vežbama hidrokineze u bazenima sa termomineralnom vodom, pored konvencionalnog programa terapijske rehabilitacije na suvom. Evaluacija je uključivala procene opsega pokreta zgloba kuka i snage ključnih mišića pokretača zgloba kuka. Ispitanici su takođe ocenili uspeh protokola na osnovu parametra poboljšanja kvaliteta života.

Rezultati: Rezultati istraživanja su pokazali da je primena balneorehabilitacionog tretmana značajno ubrzala oporavak funkcionalnih sposobnosti i poboljšala kvalitet života pacijenata koji su bili podvrgnuti operaciji artroplastike kuka.

Zaključak: Na osnovu naših rezultata može se zaključiti da je balneorehabilitacioni tretman u Specijalnoj bolnici za rehabilitaciju „Banja Kanjiža" doveo do ubrzanja oporavka i poboljšanja kvalieteta života pacijenata nakon artroplastike kuka. Da bi se dalje proverila efikasnost balneorehabilitacionog tretmana, neophodna su koordinirana multicentrična klinička ispitivanja i fundamentalna istraživanja.

Ključne reči: balneorehabilitacioni tretman, artroplastika kuka

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ORIGINAL ARTICLE

Oxidative stress and obstetric complications in pregnant women with inherited thrombophilia with and without low molecular weight heparin therapy

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Summary

Introduction: Inherited thrombophilia (IT) presents genetic conditions associated with the risk of deep vascular thrombosis (DVT) and obstetric complications (OC) such as preeclampsia (PE), fetal growth restriction (FGR), stillbirth and placental abruption (PA).

The aim of our study was to evaluate the frequency of OC and oxidative stress (OS) in women with IT during pregnancies with and without low molecular weight therapy (LMWH), compared to women with healthy pregnancies.

Material and methods: We evaluated 60 pregnant women with IT diagnosed before ongoing pregnancy based on previous DVT or OC (study group) and 60 healthy pregnant women (control group). Blood samples were collected before delivery, along with placental tissue from all subjects, to determine the activity of CAT, GPX, GH, SH, GR, CuZnSOD, and MnSOD enzymes.

Results: After the introduction of LMWH therapy, the total number of OC decreased significantly in women with IT. Analyzing the association between OC and different kinds of IT, we found significant association only between Factor V Leiden mutation and Protein C deficiency with GH/PE. Levels of SH are higher in IT; CAT, GPH and GR are three times more active in patients with IT with LMWH therapy compared to control group.

Conclusion: Values of OS parameters in pregnant women with IT during delivery may confirm increased OS in those patients indicating that introduction of antioxidant therapy may be advisable.

Key words: thrombophilia, obstetric complication, oxidative stress

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INTRODUCTION

Inherited thrombophilia (IT) present genetic conditions associated with the risk of deep vascular thrombosis (DVT) and obstetric complications (OC) and they are presented as deficiency in anticoagulant proteins - antithrombin III (AT III), protein C (PC) or protein S (PS), as well as gene mutations for Factor V Leiden (FVL), Factor II 20210A (FII), plasminogen activator inhibitor 1 (PAI-1) or methytetrahydrofolate reductase (MTHFR). (1) Diagnosis of IT is often made based on history of OC, such as habitual abortion (HA), preeclampsia (PE), severe fetal growth restriction (FGR), stillbirth and placental abruption (PA).[1] Both VT and obstetric complications are more likely in AT3, PS or PC deficiency or FVL and FII mutations, while the significance of PAI-1 and MTHFR is questionable (2,3).

The etiology and pathogenesis of OC in IT is not clearly defined, which is one of the reasons for the controversial views on therapy (2). Increased coagulability, endothelial disfunction, vasoconstriction and placental ischemia combined with pathological placentation cause decreased placental perfusion and inadequate fetal-maternal circulation. Subsequent vasculopathy and secondary thrombosis may cause inadequate intervillous perfusion, placental infarction and OC, such as PE, FGR, stillbirth and PA (4). However, OC still occur in a certain number of pregnancies with IT on low-molecular weight heparin (LMWH) therapy. Therefore, other pathological factors for OC should be considered in pregnancies with IT.

Studies have found that normal pregnancy is characterized by mild pro-oxidative changes in the status of maternal blood when compared to non-pregnant patients. In pregnant women with PE, an increase in the concentration of reactive oxygen species as well as reduced activity of protective enzymes against oxidative damage has been proven, resulting in hypoperfusion of the placenta, which increases oxidative stress (OS) (5,6). OS, characterized by an overproduction of reactive oxygen species (ROS), can significantly impair the function of these cells, thus instigating a cascade of events leading to thrombus formation. Impaired antioxidant defenses compound the prothrombotic state by allowing the accumulation of ROS, thereby contributing to OS-induced endothelial dysfunction. Most of vascular complications of pregnancy can be attributed to IT (7). OS have been related to the development of different OC, such as PE, FGR, miscarriage, and others.

The aim of our study was to evaluate the frequency of OC and OS in women with IT during pregnancies without LMWH therapy, and pregnancies with LMWH therapy and in women with healthy pregnancies.

MATERIAL AND METHODS

We conducted a longitudinal study evaluating 60 women with diagnosed IT and 60 healthy pregnant controls ate the University Clinic for Gynecology and Obstetrics "Narodni front", Belgrade.

The study has been approved by the Ethics Committee of the Faculty of Medicine in Belgrade in accordance with internationally accepted ethical standards (The Helsinki Declaration of 1964, as revised in 1975, 1983 and 1989) and each participant signed the informed consent form.

In the study group IT was diagnosed before ongoing pregnancy based on previous VTE or OC. All patients had a history of previous pregnancy without LMWH therapy. The most frequent inherited thrombophilia in our study was PAI-1 mutation (N=24; 40%); followed by FVL mutation (N=16; 26.7%); FII 20210A mutation (N=10; 16.6%); DPS (N-6; 10%); and DPC (N-4; 6.7%). We analyzed only patients with PAI homozygote mutations (4G/4G), because authors suggest that PAI-1 4G/5G alone is not responsible for obstetric complications. Other analyzed patients with inherited thrombophilia had mutation in heterozygous form.

During ongoing pregnancy doses of LMWH had been stared during early first trimester, after confirming the presence of the fetal heart rate. All patients had prophylactic or intermediate dose LMWH on recommendation of the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy. Obstet Gynecol. 2018 Jul;132(1):e1-e17.[23] The control group consisted of healthy pregnant women without previous risk for IT, who had uncomplicated pregnancies.

All pregnancies were single, with known gestational age and without a congenital anomaly, or congenital infection. All the patients were non-smokers. All the patients received 1000 mg of vitamin C and 5 mg of folate each day until gestational week 16; after that all patients received multivitamin supplement that contained 100 mg of vitamin C each day.

In all patients (both study and control group) before delivery, after admittance to the Delivery ward or Operating room for Cesarean section (CS), blood samples were collected and samples were taken in two vacutainers (1 serum and 1 plasma with EDTA as an anticoagulant), centrifuged at 1500 g for 10 min at 4^{0}C; divided into appropriate aliquots of 200 μL and stored for analysis at the temperature of -80^{0}C. Erythrocytes and plasma were separated by centrifugation (10 min. at 5000 rpm, 4^{0}C). The separated erythrocytes were washed three times with physiological solution by centrifugation (10 min. at 5000 rpm, 4^{0}C), and thus prepared samples were frozen at -80°C. We took cotyledons from placentas immediately after birth for the analysis of the activity of antioxidative

Table 1. Characteristics of the study group in the ongoing pregnancy and control group

	Study group N = 60	Control group N = 60
Maternal age	33.1+/-4,8	35.3±4.3
Parity, N (%)		
1	12 (20%)	26 (43.33%)
2	27 (45%)	18 (30%)
>3	21 (35%)	16 (25.67%)
BMI	25.1±5.6	24.9±4.6
Gestational age at delivery (week)	36.81 +/- 11,03	39.3±9.4 *
Cesarean section, N (%)	37 (61.1)	7 (11,67) *
Neonatal body weight	2855.59 +/- 689.47	3406.6 ±843.2 *
1-minute Apgar score	8.51 +/- 1.57	9.01±1.34
5-minute Apgar score	9.23± 1.65	9.93±1.10

* p< 0.05
Abbreviation: BMI – body mass index

enzymes. The activity of the enzymes catalase (CAT), glutathione peroxidase (GPH), sulfhydryl groups (SH) and glutathione reductase (GR), copper-zinc-superoxide dismutase (CuZnSOD), manganese superoxide dismutase (MnSOD) was determined.

We collected data on maternal age; parity; pre-pregnancy body mass index (BMI), calculated as weight in kilograms (kg) divided by height in meters (m) squared; pregnancy complications, such as DVT, miscarriage, preterm delivery (PTD), gestational hypertension (GH), PE, FGR, PA and stillbirth; and delivery data – gestational age at delivery, delivery mode (vaginal or CS), neonatal body weight, 1-minute and 5-minte Apgar score. In the study group we also evaluated history of previous pregnancies without LMWH therapy, and collected data on pregnancy complication.

We compared data between study group on LMWH therapy in current pregnancy, previous pregnancy without LMWH therapy and control group.

Statistical analysis of the obtained data was conducted by using descriptive statistics (mean value, standard deviation (SD), standard error (SE), Min-Max variation range and median (Med) and mode (Mod) values). The normality of distribution was tested by Kolmogorov-Smirnov and Shapiro-Wilk test, Student's t-test (parametric test). The minimum condition for the existence of a statistically significant difference was when the probability (p, level of significance) was less than or equal to 0.05. Statistical data processing was performed using the computer programs MS Excel and Medcalc (MedCalc ver. 11.4 Software, Belgium).

RESULTS

There were no differences in maternal age, parity and BMI between the groups. Gestational age, and neonatal body weight were higher in control group, while CS was more frequent in IT. There was no difference in Apgar score **(Table 1)**.

Pregnancy complications in patients with IT with and without LMWH therapy, and in control group are shown in Table 2. Distribution of complications in relation to the types of IT without with and LMWH therapy is shown in Table 3. After the introduction of LMWH therapy, the total number of obstetrics complications had decreased statistically significantly (X2=10.08; p=0.039). We didn't prove statistical significance between DVT in pregnant women with IT in pregnancies without LMWH therapy in relation to pregnancy with LMWH therapy and control group (p= 0.027505). Pregnant women with IT with LMWH therapy had significantly lower frequency of PTD in relation to pregnancy without LMWH and in control group (X2=23.835; p<0.00012). We didn't prove statistical significance of frequency of PE (X2=0.831; sign test z-0.46, p-0.64), PA (X2-0.12; p=0.73) and FGR (p>0.005) between pregnancies without LMWH therapy in relation to pregnancies with LMWH therapy and control group. Statistical frequency of GH was higher in pregnant women with IT without therapy (Ks2=8.85; P=0.003) in relation to pregnant women with LMWH therapy and control group. The rate of miscarriages was higher in pregnancies before LMWH therapy in relation to pregnancies with LMWH therapy and control group (X2=76.7 with Yates correction; p<0.001). LMWH therapy statistically reduce the rate of stillbirth in relation to pregnancies before therapy and control group (X2=14.70 with Yates correction; p<0,001). **(Table 2 and Table 3)**

Erythrocyte CAT activity during labor in patients with IT with LMWH therapy is lower compared to controls (p=0.04). Changes in glutathione peroxidase (GPX) enzyme activity were not detected before delivery, neither in the group of pregnant women with IT nor in the group of healthy pregnant women. Erythrocyte CuZnSOD activity does not differ between controls and patients with IT (p-0.014) **(Graph 1)**.

Table 2. Obstetric complication in the study group in pregnancies without LMWH therapy and pregnancies with LMWH therapy and in the control group

	IT without LMWH therapy N = 60	IT with LMWH therapy N = 60	Control Group N = 60	p
DVT, N (%)	9 (15)	2 (3.3)	0 (0)	0.027505
Preterm delivery, N (%)	18 (30)	8 (13.3)	4 (6.7)	<0,00012
PE, N (%)	5 (8.3)	4 (6.3)	0 (0)	0,73
GH, N (%)	32 (53.3)	22 (36.6)	2 (3.33)	0,003.
FGR, N (N%)	26 (43.33)	22 (36.67)	0 (0)	>0,005
Miscarriage, N (%)	53 (88.33)	5 (8.3%)	0 (0)	<0,001
PA, N (%)	5(8.3)	4(6.3)	2	0,73
Stillbirth, N (%)	17 (28.3)	3 (1.7)	0 (0)	<0,001

Abbreviations: IT-Inherited thrombophilia; LMWH-Low Molecular Weight Heparin; DVT-Deep Vascular Thrombosis; PE-Preeclampsia; GH-Gestational Hypertension; FGR-Fetal Growth Restriction, PA-Placental Abruption

Table 3. Distribution of complications in relation to types of IT without with and LMWH therapy

		GH/PE	FGR	PTD	MC	SB	PA	DVT	TOTAL
FVL mutation	I	13	8	5	14	3	1	3	47
	II	10	3	2	1	1	1	2	20
FII 20210A mutation	I	7	5	3	10	4	2	2	31
	II	3	3	1	1	1	0	0	9
DPC	I	0	1	1	3	0	0	0	5
	II	3	2	0	1	0	0	0	6
PAI-1 mutation	I	17	11	7	20	9	2	3	69
	II	8	12	4	2	1	3	0	30
DPS	I	0	0	2	6	1	0	1	10
	II	2	2	1	0	0	0	0	5
TOTAL	I	37	26	18	53	17	5	9	165
	II	26	22	8	5	3	4	2	70
p		0.64	0.5	<0.001	<0.001	<0.001	0.73	0.035	

Abbreviations: FVL – Factor V Leiden; FII – Factor II; DPC – Protein C deficiency; PAI – Plasminogen Activator Inhibitor; DPS – Protein S deficiency; GH-Gestational Hypertension; PE-Preeclampsia; FGR-Fetal Growth Restriction; PTD – Preterm Delivery; MC – Miscarriage; SB – Stillbirth; PA-placental abruption; DVT-Deep Vascular Thrombosis

Analyzing the association between OC and different kinds of IT, we found significant association only between FVL and DPC with GH/PE.

Table 4. Association between FVL and DPC with GH/PE

		Comparative Measures		
		95% Confidence Intervals		
		Value	Lower	Upper
FVL	Odds Ratio	3.14	0.995	9.92
	Relative Risk	1.33*	0.950	1.86
DPC	Odds Ratio	8.05	0.788	8.22
	Relative Risk	1.14[a]	0.958	1.35

Abbreviations: GH- Gestational Hypertension; PE – Preeclampsia; FVL – Factor V Leiden; DPC – Protein C deficiency; [a]Rows compared

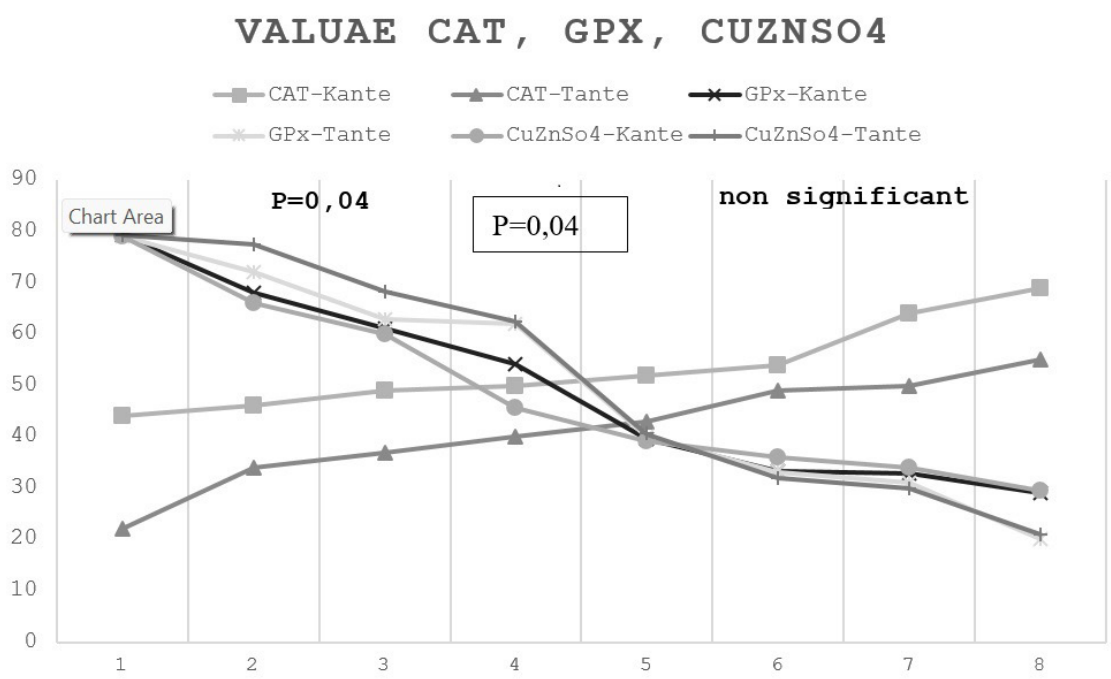
The level of SH groups in the plasma of patients with IT is higher compared to the values for controls **(Graph 2)**.

Ascorbyl radical is not detected in the plasma of control subjects before delivery (Kante) or in the plasma of patients with IT before delivery (Tante), indicating that there was no oxidative stress in both groups before delivery.

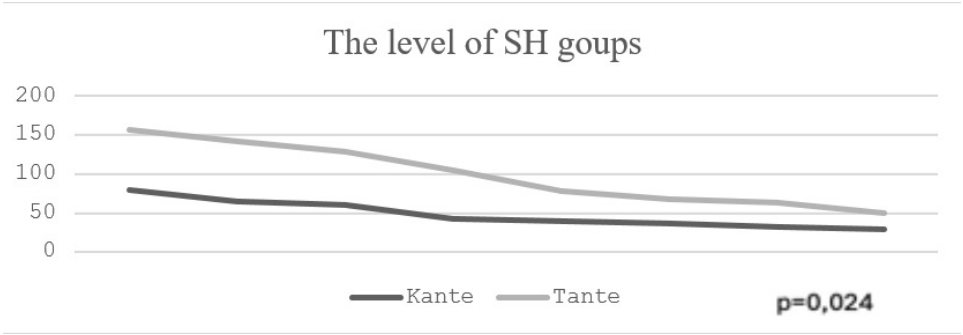
The results of enzyme activity in placental tissue show that the enzymes that use hydrogen peroxide (catalase, glutathione peroxidase and glutathione reductase), reducing the peroxide concentration, are three times more active patients with IT with LMWH therapy compared to control group. There was no difference in activity of MnSOD and CuZnSOD. This result indicates an increased hydrogen peroxide production in the placentas of patients with thrombophilia **(Graph 3)**.

DISCUSSION

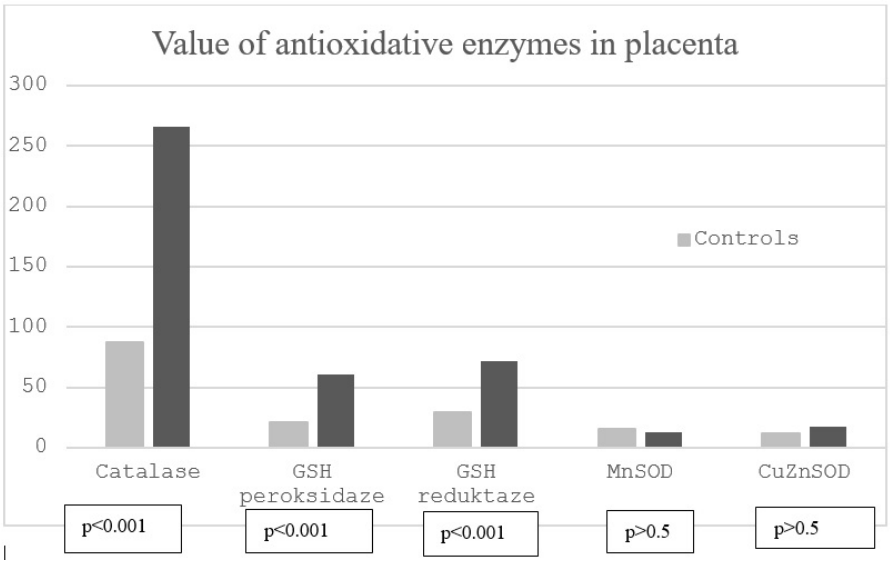
The most common IT in our study was PAI-1 mutation, followed by FVL mutation and FII G20210A mutation. Studies have shown different distribution of the most common IT among different populations; the most common appearance of PAI-1 and FVL mutations in Italian population;



Graph 1. Erythrocyte value of CAT, GPX and ZnCuSOD in patients with IT with LMWH therapy and control group before delivery
Abbreviations: CAT - Catalase activity; GPX - Glutathione peroxidase; ZnCuSOD - ZnCu superoxide dismutase; Tante – Patients with IT with LMWH therapy; Kante – Control group



Graph 2. Level of SH groups in plasma during delivery in pregnant women with IT with LMWH therapy and control group
Abbreviations: SH – sulfhydryl groups; Tante – Patients with IT with LMWH therapy; Kante – Control group



Graph 3. Activity of enzymes involved in the protection system against oxidative damage in placenta tissue of controls and patients with thrombophilia
Abbreviations: GSH – Glutathione; MnSOD – Manganese superoxide dismutase; CuZnSOD – Copper-zinc-superoxide dismutase

FVL, FII G20210A and MTHFR C677T mutations in Arab countries and MTFHR C677T and A1298C mutations, followed by the PAI-1 mutation in Romanian population (8-10). Variations in the prevalence of IT mutations among different populations can be attributed to different genetic profiles of the populations being studied. Therefore, determining the prevalence of these mutations in each population should assist in the development of thrombophilia screening protocols for the appropriate population.

CS was more frequent in patients with IT compared to controls. The most likely reason for completing a delivery by CS are OC and previous history. Other authors find that the increased frequency of CS is due to PTD and OC (FGR, PA, PE) (11).

In our study, the incidence of DVT in pregnancies prior to diagnosis of IT and prior to initiation of LMWH therapy had no statistical significance relative to the overall sample. A higher incidence of DVT in patients with IT, especially in pregnant women with FVL mutation, FII G20210A mutation, and DPS are reported (12,13). In our study, there was no statistically significant difference in the incidence of DVT in relation to the type of IT.

With the introduction of LMWH therapy, a statistically significantly lower number of early PTD (before 34 weeks) was registered. There was a statistically significant incidence of PTD between the LMWH treatment group compared to the control group. A higher incidence of PTD, especially late PTD, in patients with the FVL mutation is reported (11,12,14). In our group, the incidence of PTD was statistically significantly lower in patients with the FVL, F II G20210, and the PAI-1 mutations.

According to literature data, PA is more common in pregnant women with IT. There was no statistical significance in the occurrence of PA in pre- and post-LMWH therapy, indicating that LMWH therapy does not affect the occurrence of PA (12).

Most authors report an association between FGR and IT, especially the FVL mutation and DPS (8,15). The association between FGR and PAI-1 mutation has been reported as significant in case-controlled studies in general population of women with FGR (16, 17). On the contrary, Said et al. states that there was no association between the PAI-1 mutation and FGR (18). These discrepancies could be explained by huge differences regarding race and ethnicity between participants in conflicting studies.

The incidence of stillbirths has remained stable for decades, ranging from 4.9 to 10.4 per 1,000 births. In his study, Sarig found that pregnant women with IT had a higher incidence of sudden fetal death in the third trimester (66%) and particularly when associated with the FVL mutation. The most common IT in the stillbirth group was FII G20210A mutation. The number of stillbirths in pregnancies treated with LMWH was statistically significantly lower, only 1 patient had stillbirth with LMWH therapy, which justifies the use of LMWH in patients with a history of previous stillbirth (19).

GH/PE were the most common complication in group with IT. Most authors state that PE, early PE in particular, is associated with IT (10,20).

Thrombophilia, characterized by an increased tendency to form blood clots, presents a substantial risk during pregnancy, potentially impacting maternal and fetal outcomes. Specifically, endothelial dysfunction, driven by OS, emerges as a pivotal factor in thrombophilia, setting the stage for increased platelet activation and altered coagulation factors (21). Factors like FVL mutation, Prothrombin G20210A mutation, DPC and DPS contribute to the pro-thrombotic state observed in thrombophilia. Furthermore, inflammation, closely intertwined with OS, exacerbates the risk of blood clot formation. Inflammatory responses lead to endothelial activation, altered endothelial function, and increased adhesion molecules expression, disrupting the delicate balance between pro- and anti-coagulant factors. Chronic inflammatory conditions, such as autoimmune disorders, potentiate a persistent state of heightened clotting risk (21). Additionally, impaired antioxidant defenses compound the prothrombotic state by allowing the accumulation of reactive oxygen species, thereby contributing to OS-induced endothelial dysfunction. Understanding the interplay between these factors is crucial for tailored IT management, particularly in pregnancy. Treatment strategies encompass a multifaceted approach, including anticoagulant medications, lifestyle modifications, and targeted interventions to improve endothelial health. The complex nature of thrombophilia underscores the need for a collaborative healthcare approach, involving hematologists and high-risk pregnancy specialists.

The main reactive oxygen species in the blood of mothers with thrombophilia during childbirth is hydrogen peroxide (7,22). Superoxide dismutase is the main enzyme for the production of hydrogen peroxide in tissue. It can reach placental tissue from maternal or fetal circulation, amniotic fluid or uterine smooth muscle. The results of this research undoubtedly show that the placenta in IT patients is exposed to OS caused by an elevated concentration of hydrogen peroxide. Uncontrolled production of ROS is associated with the development of hypertension, which is the main symptom of PE (7,22).

AOS enzymes present in the placental tissue also protect the mother's blood from the increased amount of hydrogen peroxide produced in thrombophilia. If this defense loses effectiveness during pregnancy, prothrombotic conditions can lead to thrombosis. In the blood of pregnant women with thrombophilia on LMWH therapy, the level of some AOS enzymes (catalase, and the level of SH) was elevated compared to controls, which indicates a higher level of oxidative stress. Considering the lack of difference in the values of glutathione peroxidase, CuZnSOD, the question arises whether the administration of LMWH reduced the existence of oxidative stress in childbirth (7,22). After childbirth, when the placenta is rejected, its

protective function and filtering of the mother's blood is lost, and the production of hydrogen peroxide in the myometrium, endothelium and in the blood continues. In such conditions, thromboses can develop with a fatal outcome, which occur immediately after delivery (1,7).

CONCLUSIONS

Although many studies recommend only an expectant approach for patients with IT with possible prophylactic use of LMWH before and after delivery, our results indicate a positive effect of this therapy in reducing the frequency of PE, miscarriages and PTD. The most common intermediate thrombogenic thrombophilia are PAI gene mutations and F V Leiden mutations. Elevated values of catalase and SH and R-SH groups in the blood of pregnant women with thrombophilia during childbirth compared to controls may indicate increased OS in these pregnant women. The results of the activity of enzymes that reduce the concentration of peroxide with their activity are three times increased activity in the placenta tissue in subjects suffering from IT compared to control subjects. Therefore, the introduction of antioxidant therapy is also advisable in the therapy.

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None

Author Contributions:

- The conception of the study was done by Dragana Maglić, Vesna Mandić-Marković, and Jelena Bogdanović-Pristov.
- The acquisition, analysis, and interpretation of data were done by Jelena Bogdanović-Pristov,
- Milica Mandić, Jelena Vugdelić and Sabrina Škrijelj.
- Draft version of the Manuscript was prepared by Rastko Maglić, Olivera Džatić-Smiljković and Radomir Aničić.

Ethical approval

The study has been approved by the Ethics Committee of the Faculty of Medicine in Belgrade (Approval No. 1382/2) in accordance with internationally accepted ethical standards (The Helsinki Declaration of 1964, as revised in 1975, 1983 and 1989) and each participant signed the informed consent form.

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OKSIDATIVNI STRES I OPSTETRIČKE KOMPLIKACIJE KOD TRUDNICA SA NASLEDNOM TROMBOFILIJOM, SA I BEZ TERAPIJE HEPARINOM NISKE MOLEKULSKE TEŽINE

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Sažetak

Uvod: Urođena trombofilija (UT) predstavlja stanje udruženo sa rizikom od duboke vaskularne tromboze (DVT) i obstetričkih komplikacija (OK) kao što su preeklampsija (PE), zastoj u rastu ploda (IUZR), mrtvorođenost i abrupcija placente (PA).

Cilj studije: procena učestalosti OC i oksidativnog stresa (OS) kod žena sa IT tokom trudnoće sa i bez terapije niske molekulske težine (LMVH), u poređenju sa ženama sa zdravim trudnoćama.

Metodologija: U studiju je uključeno 60 trudnica sa UT dijagnostikovanom pre aktuelne trudnoće na osnovu prethodne DVT ili OK (ispitivana grupa) i 60 zdravih trudnica (kontrolna grupa). Kod svih ispitanica uzet je uzorak krvi pre porođaja, kao i uzorak placentnog tkiva i određena je aktivnost CAT, GPX, GH, SH, GR, CuZnSOD i MnSOD.

Rezultati: Nakon uvođenja NMH u terapiju žena sa UT značajno je smanjen broj OK. Analizom povezanosti OK i različitih tipova UT, nađena je značajna povezanost samo između mutacije faktora V Leiden i deficit proteina C sa gestacijskom hipertenzijom/preeklampsijom. Nivo SH je povišen kod UT; CAT, GPH i GR pokazuju tri puta veću aktivnost kod žena sa UT na terapiji NMH u poređenju sa kontrolnom grupom.

Zaključak: Vrednosti parametara OS kod trudnica sa UT tokom porođaja mogu da potvrde prisustvo OS i ukažu na opravdanost primene antioksidativne terapije.

Ključne reči: trombofilija, opstetričke komplikacije, oksidativni stres

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ORIGINAL ARTICLE

Erector spinae plane block for managing acute postmastectomy pain - single center experience from the Institute for Oncology and Radiology of Serbia

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Summary

Introdution: The most common oncological surgery in the female population is breast cancer surgery, according to the high incidence of breast cancer. Different intensities of postoperative pain usually follow mastectomy with axillary dissection. The erector spine plane (ESP) is a newly defined regional anesthesia technique for analgesia of the chest wall. In this study we report the success and the effect of ESPB on immediate postoperative analgesic pain in the Institute for Oncology and Radiology of Serbia.

In a study involving women scheduled for mastectomy with axillary dissection, we report the success and impact of ESPB on immediate postoperative pain management at the Institute for Oncology and Radiology of Serbia.

Methodology: Thiscase series study included 25 female patients with breast cancer indicated for unilateral mastectomy and axillary dissection in our center, between 18.01.2023 and 01.05.2023. who received ESP block with general anesthesia and their pain scores, analgesic requirements and nausea in the postoperative period. Data on pain scores and rescue analgesia requirements were collected at standardized intervals postoperatively.

Results: The average age of 25 women patients was 56.8 years. The mean heart rate was 72.08 at the beginning, and the value dropped to 65.32 beats/min during the intraoperative period. The pain intensity was highest in the 12th hour postoperatively and the incidence of patients with pain was the lowest, while at the 24th hour, we registered that significantly fewer patients received Rescue Analgesia.

Conlusion: Our results showed that the patients who received the ESP block had satisfactory postoperative pain control, as indicated by lower NRS scores.

Keywords: breast cancer surgery, postoperative pain management, regional anesthesia

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INTRODUCTION

The most common oncological surgery in the female population is breast cancer surgery, according to the high incidence of breast cancer (1). Different intensities of postoperative pain usually follow mastectomy with axillary dissection. Poor management of acute postoperative pain may lead to chronic pain, which affects approximately 25 to 60% of patients (2). Complex breast innervation in combination with extensive surgery requests good postoperative analgesia (3). Thoracic epidural (1), thoracic paravertebral block (4), pectoral blocks (5), and serratus plane block (6) are commonly used regional anesthesia techniques in breast surgery. Paravertebral block (PVB) is a challenging technique because of the anatomic proximity of the pleura and the central neuraxial system. The erector spine plane (ESP) is an alternative block, an interfascial block, and a newly defined regional anesthesia technique for analgesia of the chest wall.

The first description of the ESP block was in 2016 (7). ESP block has been used to treat acute and chronic pain in the torso and upper and lower limbs since this period (8, 9). The proposed mechanism of action is interpreted in many studies. Imaging studies show that only a tiny fraction of injectate enters paravertebral and epidural spaces within the first 30–60 min, and the vast majority remains within the erector spine muscle compartment (10, 11). Imaging studies in live subjects generally show injectate spread to the dorsal rami, para-vertebral space, neural foramina, and the epidural space, although the latter is less consistent (12). Penetration via diffusion into the paravertebral space continues over a prolonged period. This evidence is supported by a report in which preoperative sensory loss over two dermatomes progressed to six dermatomes in the postoperative period (13). ESPB provides all benefits associated with the gold standard thoracic epidural anesthesia for postoperative pain management and lacks hemodynamic side effects (14).

This study includes women scheduled for mastectomy with axillary dissection, evaluating the success of ESP block administered at the T4 level and its impact on immediate postoperative pain management.

METHODOLOGY

This is a case series study, which included 25 female patients with breast cancer indicated for unilateral mastectomy and axillary dissection who received ESP block with general anesthesia in our center between 18 January 2023 and 1 May 2023.

The study did not include patients who underwent any other type of peripheral block alone or in addition to ESP block with general anesthesia.

This initial patient cohort aims to illustrate the course of their postoperative analgesia, pain intensity, and incidence of nausea and vomiting within the first 24 hours. However, further investigation is needed.

DATA COLLECTION

A standard perioperative analgesia plan is applied to all patients who undergo a regional anesthesia technique at our institute, and a standardized regional anesthesia data collection form is used to collect all patient data. All patients undergoing regional anesthesia give informed consent for all procedures in anesthesia and the use of their data in medical studies.

In the preoperative period, prior to entering the operating room (OR), all patients received a standard protocol including Acetaminophen 1g (a mild analgesic unlikely to significantly impact postoperative pain intensity), Controloc 40 mg, Dexason 4 mg as an antiemetic, and prophylactic antibiotics.

After premedication, patients were positioned prone **(Figure 1)**, and the transverse process of the 4th thoracic vertebra was located using a Siemens Acuson P500 ultrasound. This was achieved by counting vertebrae from the spinous process of the 7th cervical vertebra. After antiseptic preparation of the skin with 10% povidone-iodine, an Erector Spinae Plane (ESP) block was performed under Ultra-sound guidance utilizing the in-plane technique **(Figure 2)**. Local infiltration with 1% Lidocaine was applied at the needle entry site before inserting a 21G, 100mm needle in alignment with the Ultra-sound probe until the contact with the transverse process was achieved. Following negative aspiration, 1 to 3 mL of saline solution was injected, confirming the elevation of

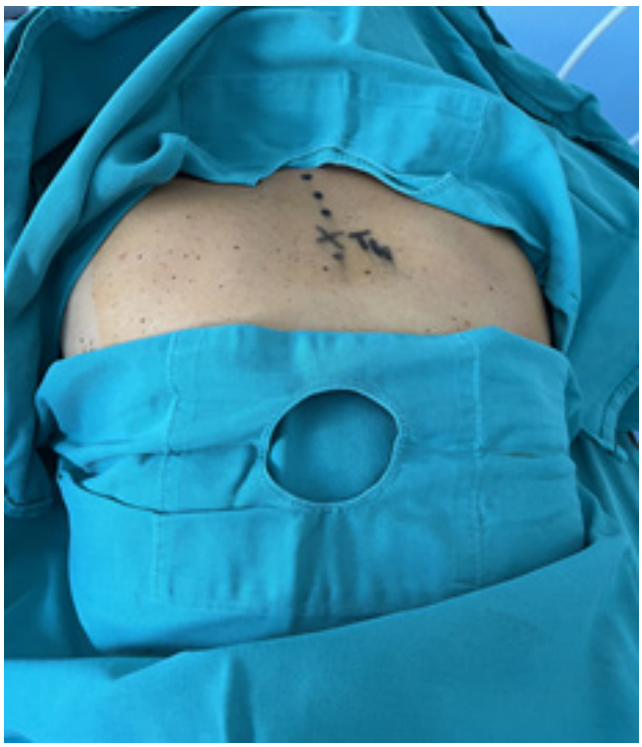


Figure 1. Prone position of the patient

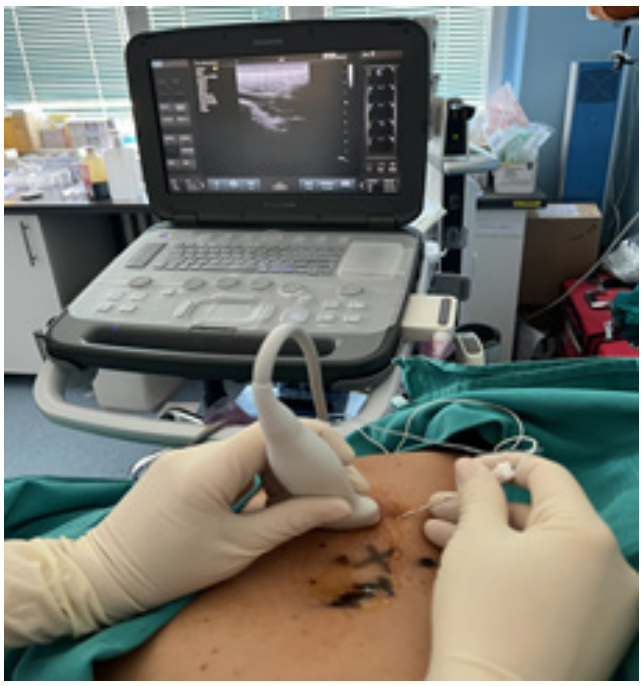


Figure 2. Needle position at the Transverse process at the T4 level

the fascia of the erector spinae muscle of the transverse process **(Figure 3)**. The ESP block was completed with a single-shot injection of 0.5% Bupivacaine, administered in a volume of 20 mL.

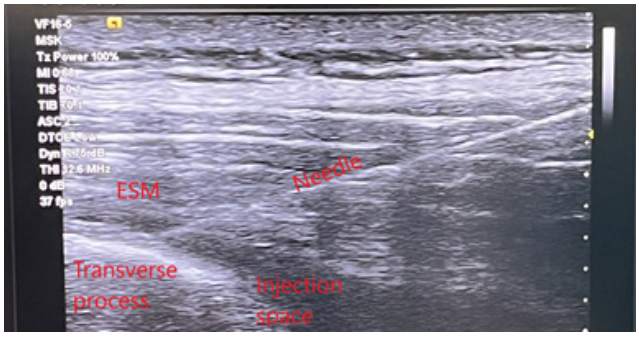


Figure 3. Ultrasound-guided ESB performance at the T4 level

After half an hour of ESP block, the patient entered the OR and anesthesia induction was performed. All patients were induced in general anesthesia using Fentanyl (1-2mcg/kg introduction dose) and Propofol; i-gel masks were applied for mechanical ventilation (volume control mode was used on GE Avance CS2 Pro device).Vitals (heart rate and blood pressure) were measured every five minutes. Anesthesia was maintained using sevofluran in combination with oxygen and air. Half an hour before the end of surgery, all patients received Ondansetron 4mg, as an antiemetic and Tramadol 100 mg (given that dose correction based on age is not required). After anesthesia weaning, we started recording pain intensity, using a numeric rating scale (NRS), and nausea and vomiting. For rescue analgesia (RA), we used a non-steroid anti-inflammatory drug, or Tramadol. For patients with NRS higher than 3, we applied Diclofenac 75mg; for those with NRS higher than 6, we used Tramadol of 100 mg. All analgesics and their application times were noted in detail in patient files.

All included patients were ASA 2 score patients, as we excluded patients with ASA 3 and higher scores. The following data were collected for all patients undergoing ESP block: age, hemodynamic data (mean arterial pressure and heart rate on induction, intraoperatively), Fentanyl amount intraoperatively, the general presence of pain, and NRS after weaning on the 6th, 12th, and 24th hour after surgery, the need for rescue analgesia and events like nausea in 6th, 12th, and 24th hour.

STATISTICS

Statistic software SPSS 23.0 was used for statistical data processing. The descriptive statistics used the following methods: central tendency (arithmetic mean value, median) and variability measures (standard deviation, minimal and maximal value). Fisher exact and Pearson's chi-square tests were used to examine the differences in the incidence of observed category characteristics between subjects in the group.

RESULTS

The average age of 25 female patients was 56.8 years, Med 55 (36 y-82 y), body mass index between 18.5 and 30, and in all patients, ASA score was 2. The results are shown in **Table 1**.

Table 1. Patients demographic data, Mean ± SD; Med (min-max)), n= 25

Age	56.80 ± 11.9: 55 (36 - 82)
BMI 18.5-30	100%
ASA 1/2/3	0/25/0 (0%/100%/0%)

ASA – American Society of Anesthesia, BMI-Body Mass Index

Table 2. Comparision of Hemodynamic parameters

MAP and HR	Mean ± SD; Med (min-max)	p
MAP Induction (mmHg)	84.3 ± 17.85 ; 84 (55-115)	0.11
MAP Intraoperative (mmHg)	77.72 ± 12.75; 77 (59-103)	
HR at induction (beats/min)	72.08 ± 13.25; 70 (60-120)	**< 0.05**
HR intraoperatively (beats/min)	65.32 ± 7.80; 60 (55-85)	

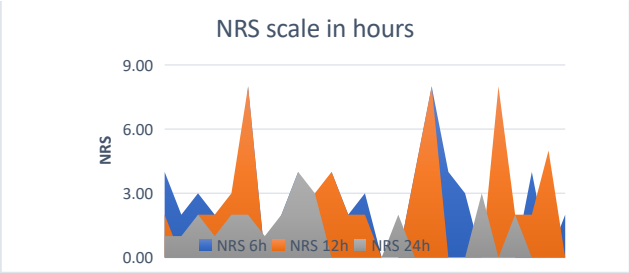
MAP- Mean Arterial pressure
HR- Heart rate

Hemodynamic results are shown in **Table 2**. At the beginning of anesthesia, the mean MAP was 84.3 mmHg with the lowest value of 55mmHg and the highest of 115mmHg, and in the intraoperative period, there was a slight drop in the mean MAP, which was 76.7mmHg, the lowest MAP was 59 and the highest was 103 mmHg. There is no statistically significant difference in mean MAP values between the induction and the intraoperative period. Heart rate **(Table 2)** was 72.08 at the begin-

ning, and there was a drop in value to 65.32 beats/min in the intraoperative period. A statistically significant difference was observed in HR values, with intraoperative HR being lower than HR at anesthesia induction ($p < 0.05$).

Table 3. Pain characteristics

Hours after surgery	6h	12h	24h
Incidence of pain n (%)	15 (60)	16 (64)	13 (52)
p	>0.05	>0.05	>0.05
NRS (0-10), Mean ± SD Med (Min-Max)	2.36 ± 2.34 2 (0 – 8)	2.36 ± 2.58 2 (0 – 8)	1.04 ± 1.21 1 (0 – 4)



Graph 1. NRS scale in hours

Characteristics of pain are shown in **Table 3**, **Graph 1**. In the first 6 hours upon surgery, we observed the lowest incidence of pain in 60% of patients. The mean NRS score was 2.36 Med 2, and the highest registered pain intensity was 8. The incidence of pain was highest in the 12th hour; the pain was present in 64% with a mean NRS score of 2.36, Med 2, and the highest intensity of pain was 8. In the 24th hour, the incidence of pain was 52%, the mean NRS score was 1.04, Med 1, and the highest pain level was 4.

Table 4. Rescue analgesia, nausea, and vomiting, n = 25

Hours after surgery	Rescue Analgesia	*p*	Nausea & Vomitus	*p*
6h	11 (44%)	0.549	4 (16%)	0.061
12h	13 (52%)	0.841	0	**0.001**
24h	4 (16%)	**<0.001**	0	**<0.001**

Graph 2. RA in 6th and 24th hours (RA - Rescue Analgesia)

The results of rescue analgesia use and events (nausea and vomiting) are shown in **Table 4** and **Graph 2**. Up to the 6th hour and at the 12th hour, there was no statistically significant difference between the number of patients who received RA and those who did not ($p > 0.05$). In the 24th hour, statistically significantly fewer patients received RA, four vs 21 ($p<0.001$). In the 6th hour, there were only four and the in the12th and 24th hour, we overlooked patients with nausea or vomitus, with statistical significance, retrospectively p 0.006, 0.001, <0.001, **Graph 2.**

DISCUSSION

Our study showed mild hemodynamic changes in mean MAP and HR, which decreased in the intraoperative period. In the study of Dubilet et al. (15), patients who were treated with an incisional ESP block in addition to standard pain control treatment after surgery presented significantly lower heart rate and systolic and diastolic blood pressure parameters compared to the control group (p from 0.03 to <0.001). We registered an intraoperative decrease in mean MAP that did not have statistical significance. However, the mean HR dropped significantly from 72 to 65/min in the intraoperative phase ($p< 0.05$). The local anesthetic is thought to spread within this potential space and diffuse into abutting structures, such as the paravertebral and epidural spaces (containing spinal nerves, dorsal rami, and ventral rami) (16), lateral cutaneous nerves (contained by the serratus anterior and intercostal muscles) (13), and even the quadratus lumborum (at low thoracic and lumbar levels) (17). So, we assumed that such hemodynamic changes could be related to the local anesthetic effect that gradually diffused from the erector spinae compartment to the paravertebral and neuraxial space. Still, severe hemodynamic changes are rare. According to this assumption, some imaging and dissection studies indicate that only a tiny fraction of injectate enters paravertebral and epidural spaces within the first 30–60 minutes. Most injectate remains within the erector spinae muscle compartment (10, 11). Penetration via diffusion into the paravertebral space may continue over a prolonged period (7). The erector spinae plane block (ESPB) is a simple fascial plane block alternative to an epidural block and PVB, with fewer side effects (18). It appears to be an effective analgesic technique at many levels and functions as an alternative when the PVB or epidural block is contraindicated (19). We certainly do not exclude the fact that perhaps only good analgesia impacted hemodynamics.

In our study, the highest incidence of pain was after 12 hours in 64% of patients, which corresponds to the duration of the block and the time of weakening of the drug's effect. Within each 6-, 12-, and 24-hour period individually, there was no significant difference in the number of patients who experienced pain and those who did not (15, 20).

The average pain intensity in all intervals was less than 3, considered mild pain. Postoperatively, the intensity of pain was weak up to 12 h, while after 24 h, the intensity of pain was even lower.

The need for RA was significantly higher up to the 12th hour, while at the 24th hour, we registered that significantly fewer patients received RA. While in the study of Dubilet et al. patients treated with a preincisional ESP block demon-

strated significantly lower VAS scores at 60 minutes 4, 8, and 12 hours following the surgery, compared to the control group of patients with conventional postoperative analgesia ($p < 0.001$). In contrast to our study, at 24 h following surgery, VAS score levels were significantly lower in patients in the control compared to the ESP group ($p < 0.001$ and 0.01).

We believe that the ESP block applied preoperatively provided good patient results, considering that the average pain value in all hours was low according to the NRS scale, while in 24 hours, it was below 2. According to the results of the consumption of RA in our study, up to 24 hours, the ESP block achieved its most potent effect between the 12th and 24th hour.

The frequency of nausea and vomiting is low, and there is a significant difference in the number of patients reporting these complaints across all time intervals. Given that breast surgery and female gender are significant risk factors for the occurrence of nausea, we believe that the good impact of the ESP block in terms of reducing the use of opiates postoperatively and lowering pain intensity postoperatively in all phases probably influenced the absence of a very unpleasant event in the form of vomiting.

We believe that our findings from this study could serve as a foundation for further research into the management of postmastectomy pain and contribute to the development of innovative treatment strategies for acute pain and the prevention of chronic pain.

CONCLUSION

In this study, we performed Ultrasound-guided unilateral preincision ESP blocks alongside the standard pain protocol for postoperative analgesia. Our results showed that the study

group who received the ESP block along with the standard protocol had reasonable postoperative pain control, as indicated by lower NRS scores and lower incidence rates of postoperative nausea and vomiting.

These were our observations and assumptions based on the data obtained, for more concrete conclusions a larger-scale study is needed.

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ERECTOR SPINAE PLANE BLOK KAO TRETMAN AKUTNOG BOLA NAKON MASTEKTOMIJE - ISKUSTVO JEDNOG CENTRA INSTITUTA ZA ONKOLOGIJU I RADIOLOGIJU SRBIJE

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Sažetak

Uvod: Najčešća onkološka operacija u ženskoj populaciji je operacija raka dojke, u skladu sa visokom incencijom istog. Različiti intenziteti postoperativnog bola obično prate mastektomiju sa disekcijom aksile. *Erector spinae plane* (ESP) kao alternativni blok, je interfascijalni blok, novodefinisana tehnika regionalne anestezije za analgeziju zida grudnog koša.

U ovoj studiji, koja uključuje žene predložene za mastektomiju sa disekcijom aksile na Institutu za onkologiju i radiologiju Srbije, ispitujemo efekte ESP bloka na neposredan postoperativni bol.

Metodologija: Ovom serijom slučajeva obuhvaćeno je 25 pacijentkinja sa karcinomom dojke indikovanih za unilateralnu mastektomiju sa disekcijom aksile, koje su primile ESP blok uz opštu anesteziju u našem centru u periodu od 18.01.2023. do 01.05.2023.

Rezultati: Prosečna starost pacijentkinja bila je 56,8 godina. Prosečna srčana frekvencija bila je 72,08 otkucaja u minuti i došlo je do pada vrednosti na 65,32 otkucaja u minuti u intraoperativnom periodu. Intenzitet bola bio je najviši ali učestalost pacijentkinja sa bolom najmanji u dvanaestom satu, dok smo u dvadesetčetvrtom satu registrovali da je značajno manji broj pacijentkinja primio dodatnu analgeziju.

Zaključak: Naši rezultati su pokazali da su pacijentkinje iz ispitivane grupe, koje su primile ESP blok uz standardni protokol, imale zadovoljavajuću kontrolu postoperativnog bola, na šta ukazuju niži NSB skorovi. Ovi rezultati zahtevaju dalje studije kojima bi se potvrdila definitivna efikasnost ESP bloka u postoperativnoj kontroli bola nakon mastektomije.

Ključne reči: hirurgija raka dojke, kontrola postoperativnog bola, regionalna anestezija

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REVIEW ARTICLE

Inflammatory manifestations of herpesviridae infection in the anterior segment of the eye

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Summary

Introduction: *Herpesviridae* is a large family of double-stranded DNA viruses with eight types known to infect humans: Herpes simplex virus (HSV) type 1 and 2, Varicella zoster virus (VZV), Cytomegalovirus (CMV), Epstein Barr virus (EBV), Human herpesvirus (HHV) 6, 7 and 8. Herpetic eye disease can affect the anterior and/or posterior segment of the eye. In this article we focused on the anterior segment manifestations.

Methods: A review of research articles with key words scleritis, keratitis, anterior uveitis, herpetic, HSV, VZV, CMV, and EBV published in PubMed database until April 30th, 2024 was done.

Results: HSV1, VZV, and CMV are well known to cause inflammation in the anterior segment of the eye**,** which includes episcleritis, scleritis, keratitis, and anterior uveitis or their combination. However, there are reports of anterior segment inflammation caused by EBV, HSV2, or HHV6. The disease usually has a recurrent or chronic course and persistent inflammation can cause severe damage to the ocular tissues, which can significantly impair vision. Although some types of ocular inflammation can be effectively treated with antiviral agents during active phase of the disease (HSV1, HSV2, VZV, CMV), so far there is no final treatment which would permanently prevent the recurrences. The main complications include corneal scarring, scleral thinning, glaucoma, synechiae, iris atrophy, and cataract.

Conclusion: Due to its recurrent or chronic course, the herpetic inflammation of the anterior segment of the eye remains a challenge for clinicians. While typical clinical clues may sometimes lead an ophthalmologist to suspect a herpetic cause of the inflammation, a definitive diagnosis—especially in atypical cases—can only be confirmed by PCR verification of the viral genome from ocular tissues or, in cases of uveitis, by detecting local specific antibody production in the aqueous humor using the Goldmann-Witmer coefficient.

Key words: Herpetic eye disease, scleritis, keratitis, anterior uveitis, Herpesviridae, HSV, VZV, CMV

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INTRODUCTION

Herpesviridae represent a large family of ubiquitous viruses with more than 130 subtypes identified. The virion consists of a lipoprotein envelope, tegument, nucleocapsid, and double stranded DNA with up to 200 genes. In this family, eight members can infect humans including: Herpes simplex virus (HSV) type 1 and 2, Varicella zoster virus (VZV), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Human herpesvirus (HHV) 6, 7 and 8. All of them, except for HHV-8 have been documented using PCR in samples from ocular tissues or fluids with inflammatory manifestations.

Herpetic eye disease can affect anterior and/or posterior segment of the eye. Anterior segment disease can manifest in many ways such as episcleritis/ scleritis, keratitis, anterior uveitis, or their combination (keratouveitis, sclerokeratitis, sclerouveitis, or sclerokeratouveitis), while posterior manifestations include necrotizing (acute retinal necrosis and posterior outer retinal necrosis) and non-necrotizing retinitis (1).

In this article, authors will focus on the anterior segment manifestations of different members of *Herpesvirdae* family, their epidemiology, clinical presentation, complications, differential diagnosis, and treatment options.

METHODS

A review of research articles with key words scleritis, keratitis, anterior uveitis, herpetic, HSV, VZV , CMV, EBV published in PubMed database until March 31st 2024 was done. To ensure the most accurate description of the disease's clinical presentation and complications, only clinical studies that confirmed the virus through polymerase chain reaction (PCR) or the detection of specific local antibody production using the Goldmann-Witmer coefficient were included in the review.

EPIDEMIOLOGY

HSV type 1 is ubiquitous viral agent that usually infects the host by droplet transmission, or less often by direct inoculation. Primary infection typically occurs early in life and is most often asymptomatic, with nearly two-thirds of cases going unrecognized (2). Rarely, primary infection can manifest in the eyelids (blepharitis with vesicles and ulcerations on the eyelids), with or without conjunctivitis. However, inflammation of the cornea in the form of dendritic keratitis, or less commonly disciform keratitis, can occur. The prevalence of HSV1 seropositivity increases in general population with age and was documented in 80-90% of persons above 40 years of age (3,4). After the primary infection the neurotropic HSV 1 enters a dormant phase in the sensory trigeminal ganglion. Later during life, it can be reactivated under the condition of immunosuppression, hormonal changes, exposure to radiation, respiratory infection, psychological stress, etc. (5)

HSV type 2 is a cause of genital herpes and is a sexually transmitted disease. Rarely transmission can also occur during labor from a mother to a child (causing neonatal conjunctivitis), or secretions can be transmitted directly to the eye. The prevalence of HSV2 seropositivity is 10-15% in general population (6).

Primary VZV infection (varicella or chickenpox) is transmitted via contaminated air or in direct contact with infected fluids. It usually infects children and young adults and high seropositivity of 80-90% was documented in unvaccinated young population (7,8). After the primary infection, virus resides in a latent phase in sensory ganglia. The reactivation of VZV infection (shingles) can occur in the corresponding dermatome with herpetic neuralgia and maculopapular rash in the area of branches of the ophthalmic nerve (n, frontalis, n. nasociliaris, n lacrimalis) leading to herpes zoster ophthalmicus (HZO). HZO is typically unilateral and usually occurs in elderly patients. Risk factors for HZO are older age and immunodeficiency conditions (HIV, autoimmune diseases, use of corticosteroid or other immunosuppressive therapy, tissue and organ transplantation, chemotherapy, physical and emotional stress) (9).

EBV or HHV-4 is ubiquitous, B lymphotropic virus with seropositivity in general population of up to 90-95% in adult age (10). The infection occurs via contact with infected saliva or genital secretions. It can manifest as infectious mononucleosis in young adulthood or with mild flu-like symptoms.

CMV or HHV-5 is one of the most common viruses worldwide. The infection occurs during childhood or in adolescence, but can also be transmitted vertically during pregnancy leading to multiple organ malformations in a newborn, including eyes.

Human herpesvirus (HHV) 6 includes two subtypes HHV-6A and 6B. Subtype 6A is more neurovirulent and is associated with neuroinflammatory disease. Subtype 6B (along with HHV-7) can cause exanthema subitum in infants and is transmitted via direct contact. The virus can be reactivated in patients with severe immunosuppression.

HHV-7 often acts together with HHV-6, and the viruses are sometimes referred to by their genus, *Roseolovirus*. Similarly to HHV-6, HHV-7 can cause exanthema subitum. However, primary infection is often asymptomatic, although it can manifest as acute febrile respiratory disease, fever, rash, vomiting, or diarrhea.

HHV-8 similarly to other members of *Herpesviridae* family infects the host early in life, and then becomes latent. It is associated with Kaposi sarcoma and is known to be an oncovirus, associated with tumorigenesis (11).

PATHOGENESIS

Herpesviridae family belong to neurotrophic viruses with tendency to infect sensory nerves (12). Usually following the acute infection with members of Herpesviridae family (HSV-1, VZV and HHV-6), the virus enters a latent phase in the sensory ganglia of the body and for the ocular tissue it is located in the trigeminal (Gasser's) ganglion (13,14). Later during life if the loss of immunity occurs, the reactivation of the viral infection can affect the corresponding dermatome (often seen in VZV as herpes zoster or shingles or in HSV as localized vesicles on erythematous skin lesions). However, recently HSV-1 latency was documented in corneal tissue as well, challenging the standard pathogenesis hypothesis (15).

CLINICAL MANIFESTATIONS

Anterior segment manifestations of Herpesviridae infection include: conjunctival and lid manifestations (blepharoconjunctivitis), corneal manifestations (keratitis), scleral manifestations (episcleritis and scleritis) and inflammation of the iris (anterior uveitis).

The symptoms in patients with anterior segment inflammation typically include: mild to moderate pain, ciliary hyperemia, photoaversion, and sometimes blurred vision.

Blepharoconjunctivitis

HSV-1 blepharoconjunctivitis

Blepharoconjunctivits is a well-known manifestation of primary infection with HSV-1 and usually occurs in children younger than 5 years of age (16). The main manifestations include cutaneous vesicular eruption on the lids and lid margins, follicular conjunctivitis with watery discharge, and preauricular lymphadenopathy. The lesions are infectious for ten days and spontaneously resolve in 15-20 days. In some rarer cases, blepharoconjunctivitis may recur later during life due to reactivation of latent virus in trigeminal ganglion. The lid skin lesions and follicular conjunctivitis are similar to the primary infection and are infectious for only 2-3 days and last for only a week.

VZV blepharoconjunctivitis

During the primary infection with VZV in childhood (chickenpox), vesicular skin lesions may occur in the lids, lid margins and can be followed by follicular conjunctivitis and preauricular lymphadenopathy. The lesions spontaneously resolve in one to two weeks (17). The exceptions are immunosuppressed individuals like children on immunosuppressive therapy due to autoimmune conditions such as juvenile idiopathic arthritis or with primary immunodeficiency which may have more severe course and require systemic therapy with acyclovir.

During the reactivation of VZV later in life (HZO), vesicular rash may occur in the area of the innervation of ophthalmic nerve on the upper eyelid, forehead and tip of the nose, and always respects the middle line of the face. If the branch of nasociliary nerve is affected (Hutchinson's sign) there is a high risk of eye involvement with manifestations such as VZV conjunctivitis, or corneal (VZV keratitis), scleral (VZV scleritis) or even intraocular manifestations (more often anterior uveitis or very rarely acute retinal necrosis). It always requires systemic antiviral therapy with acyclovir 800 mg 5 times daily for seven to ten days. Patients with immunodeficiency of any cause may require prolonged therapy. Dermatologist usually prescribes local therapy for vesicular skin changes, since they tend to develop secondary bacterial infection if not treated properly.

Keratitis

HSV keratitis

Herpes simplex keratitis is caused by recurrent infection of the cornea with HSV-1 and is the most common infectious cause of corneal ulcers and blindness worldwide, especially in industrialized countries (5,18). The global incidence is 1 to 1.5 million new, 9 million recurrent cases, including 40,000 new cases of monocular significant visual impairment or blindness each year (19,20).

The majority of HSV cases manifest as unilateral, although rare bilateral PCR confirmed cases of keratoconjunctivitis (21), keratitis (22–25), and endothelitis (26) have been reported. However, in a study from the Moorfields Eye Hospital, London conducted between 1973 and 1980, 19% of cases had bilateral presentation (27), while in other studies, the incidence of bilateral involvement was lower (1.3-12%), and risk factors included: congenital immunodeficiency, atopy, autoimmune diseases, rosacea, long-term use of corticosteroids or other immunosuppressive therapies, and organ transplantation (28). Studies have shown that the incidence of bilateral HSV keratitis in children ranges from 3.4 – 26%, and that the recurrence rate during the first year after the initial episode is higher than in adults (29–31).

The classification of herpetic keratitis based on the predominantly affected layer of the cornea is as follows: epithelial, stromal, and endothelial forms.

Epithelial HSV keratitis is typically self-limiting and occurs due to the cytopathogenic effect of the virus on the epithelial corneal cells and subsequent cell death. The most common form is dendritic, which is characterized by an epithelial defect in the form of twigs with terminal buds in which further replication of the virus takes place. If untreated or treated with corticosteroid therapy, they turn into amoeboid or geographic forms that cover a

large area with a stripped epithelial basement membrane. Therapy of epithelial form includes local antiviral therapy (acyclovir 3% ointment 5 times daily, for a maximum of 2 weeks) in order to close the defect, and also to reduce the incidence of recurrence both in the first episode and in each subsequent one. There is a possibility of viral resistance to acyclovir, due to repeated episodes and frequent use of the therapy. Considering that other approved antivirals have the same mode of action (to target the viral DNA polymerase), resistant herpetic keratitis represents a therapeutic challenge (32). A large number of studies have shown that trifluridine is as effective as acyclovir, while ganciclovir has a slightly better effect (33). Nowadays, most ophthalmologists prescribe the oral form of acyclovir for the prevention and treatment of recurrent herpetic keratitis (34). Although the therapeutic effect has been proven individually for both local and oral application of antivirals, there is not enough evidence that the combined application leads to accelerated healing (35,36).

Stromal HSV keratitis occurs with or without an epithelial defect. If the defect is not present, it is considered interstitial keratitis. It is believed to represent a stromal immune response in the absence of active viral replication and may be focal, multifocal, or diffuse in appearance (37,38). If ulceration is present in stromal HSV keratitis, it is considered necrotizing. It is believed that in this form active replication of the virus is present in the stroma (39), which leads to intense inflammation that predisposes to scarring, vascularization of the cornea and in some cases perforation.

Endothelial HSV keratitis is called disciform. It occurs as a result of HSV infection of the endothelium (2). The typical clinical picture is characterized by discoid localized edema of the stroma, with keratic precipitates on the corneal endothelium in its projection, while the surrounding cornea is transparent. Rarely, diffuse and linear forms of stromal edema can be seen. There is no inflammatory reaction in the anterior chamber. Stromal and endothelial keratitis are treated locally and systemically with antivirals, but unlike epithelial forms where corticosteroid therapy is contraindicated, in these forms it is necessary. Corticosteroid therapy is gradually reduced during treatment, until it is discontinued, although in some patients, the minimum dose must be used for a longer period. Such patients become dependent on corticosteroid therapy over time, and are at a risk of developing cataract and glaucoma. Patients who are corticoresponders (those who develop increased intraocular pressure due to corticosteroid therapy) and those with stromal keratitis associated with an ulcerative defect present a particular challenge. In the latter group, the alternative is the application of systemic corticosteroid therapy, instead of local, while in corticoresponders a low-potency corticosteroids such as fluoromethalone are used. In the USA, where only trifluridine and ganciclovir are approved as topical antivirals, oral antivirals are preferred due to the limited stromal penetration and side effects associated with prolonged use. Trifluridine, in particular, may cause allergic conjunctivitis, toxic keratoconjunctivitis, and punctal stenosis (19). For stromal and endothelial forms of HSV keratitis, as well as epithelial relapses, the recommended initial dose of acyclovir of 400mg 5 times per day is suitable, while the maintenance dose is 400mg twice daily.

The diagnosis of HSV keratitis is almost always made based on clinical appearance, while supplementary diagnostics such as epithelial cell culture detection and PCR are rarely used. Decreased corneal sensitivity in unilateral keratitis is important for establishing the diagnosis, although it can also be observed in neurotrophic defects of neurological or neurosurgical cause (compression of nerves by a brain tumor or their damage during surgery), while bilaterally present decreased corneal sensitivity is present in patients with diabetes.

Differential diagnosis of the epithelial form of HSV keratitis includes: Acanthamoeba keratitis, VZV keratitis, EBV keratitis, adenoviral keratitis, Chlamiadia trachomatis keratitis, and bacterial epithelial keratitis when the stroma is not affected. Non-infectious causes that resemble the epithelial form are erosion in healing (primary and recurrent), neurotrophic keratopathy, exposure keratopathy, Thygeson keratitis, and limbal stem cell insufficiency. Neurotrophic keratopathy and persistent epithelial defect can also occur due to frequent episodes of HSV keratitis (metaherpes). Differential diagnosis of stromal forms of HSV keratitis without ulceration includes stromal keratitis caused by syphilis, VZV, EBV, rubella, measles, Cogan's syndrome, Lyme disease, and when ulceration is present any bacterial or fungal agent, acanthamoeba, VZV, chemical injury, autoimmune diseases, and exposure keratopathy. The differential diagnosis of the endothelial form includes keratouveitis, Posner Schlossman syndrome, CMV endothelial keratitis, and corneal graft rejection (19).

Complications of herpetic keratitis occur as a consequence of the evolution of the disease and the applied therapy. The disease has a tendency to recur and in the patients with higher number of previous relapses, there is a greater risk of recurrence (18). The dendritic form of keratitis shows the greatest tendency to relapse (56.3%), followed by the stromal form (29.5%), while in geographic lesions it is less common (9.8%). The persistent dry eye (40) and scarring of the cornea (leucoma) with or without vascularization is formed in the area of repeated stromal inflammation. Other complications include glaucoma and cataracts. Secondary bacterial infections occur in neglected cases, especially where there is no adequate monitoring of the use of corticosteroid drops. The repeated episodes of the stromal form (metaherpes), can lead to corneal perforation requiring tectonic keratoplasty. The success of graft transplantation, whether tectonic or for the purpose of visual rehabilitation in severe leukoma, largely depends on the vascularization of the cornea,

which is a risk for graft rejection, as well as on the relapse of HSV keratitis on the donated tissue (41). In order to prevent the deterioration of the graft, patients who are preparing for transplantation are on oral antivirals for a long period of time (one year) before and after the surgery (acyclovir 400 mg twice daily). It is desirable that the patient does not have a recurrence of HSV keratitis at least one year before the surgery.

VZV keratitis

Herpes zoster ophthalmicus (HZO) represents a set of clinical manifestations on the eye and adnexa that occur as a result of VZV involvement of the ophthalmic branch of the trigeminal nerve (especially the nasociliary nerve which is responsible for the innervation of the ocular structures). In patients with HZO, involvement of the eye is documented in 50% of cases (42) and includes conjunctivitis, episcleritis, keratitis, uveitis, and retinitis.

The typical presentation of HZO is unilateral neuralgia in the area of innervation of the ophthalmic nerve and eruption of vesicles and pustules on the skin of the corresponding dermatome. Eruption of vesicles may be preceded by fever, weakness and headache. The presence of a vesicle on the tip of the nose is called Hutchinson's sign and is a result of involvement of the nasociliary branch of the ophthalmic nerve (43). In immunocompromised patients, the disease can manifest bilaterally. When the eyelids are affected by vesicles, there is often associated blepharitis, episcleritis and conjunctivitis, and due to severe inflammation accompanied by extensive swelling of the eyelids, ptosis of the upper eyelid may be seen.

As with HSV keratitis, the disease can manifest as epithelial or stromal keratitis. The epithelial form manifests as punctate or pseudodendritic keratitis. In the first form, a punctate edematous lesion with positive fluorescein staining are present, and are in fact the site of active viral replication. Pseudodendrites resemble dendritic HSV keratitis, but there is no real defect, no terminal buds, and they stain minimally with fluorescein.

Stromal keratitis can be superficial or deep. It usually develops after the epithelial keratitis. The superficial form, known as nummular due to its distinctive granular appearance, is thought to result from an immune reaction to the virus in the stroma. A month after the acute phase, a deep stromal form of keratitis can develop, which is characterized by pronounced edema. This form can be associated with anterior uveitis. Keratitis can be accompanied by viral trabeculitis, with increased intraocular pressure. Furthermore, the damage of the corneal nerves due to prolonged inflammatory reaction can cause neurotrophic keratopathy. Complications may include dense leucoma and melting of the cornea in the area of neurotrophic keratopathy. Secondary bacterial infections in the setting of unrecognized or poorly controlled keratitis are common.

The diagnosis is made on the basis of the clinical picture, reduced corneal sensitivity, while additional diagnostics (cell culture, PCR) is rarely performed. In patients with bilateral occurrence of HZO or a disseminated form of the disease (multiple dermatome involvement), HIV testing is indicated (43).

Differential diagnosis in different stages of HZO disease include: HSV keratitis and dermatitis, viral, bacterial or allergic conjunctivitis, exposure keratitis, acute glaucoma, infectious and non-infectious ulceration of the cornea, corneal abrasion, impetigo, cellulitis, insect bite, contact dermatitis.

Therapy includes urgent (ideally in the first 72 hours) per oral acyclovir 800mg 5 times a day for 7 days, and then gradual reduction to a maintenance dose of 400 mg twice daily. Valacyclovir 1000mg or famciclovir 500 mg are also given 3 times a day for 7 days. In immunocompromised patients, acyclovir is administered intravenously at 10 mg/kg of body weight every 8 hours for at least 7 days, and foscanet at 90 mg/kg every 12 hours (for patients with acyclovir resistance). Local application of acyclovir has not been shown to be effective as in HSV keratitis (43).

In our clinical practice, it is common to recommend B complex vitamins and vitamin C along with antivirals. Topical antibiotics are used to prevent bacterial infection when keratitis is accompanied by an epithelial defect. Local corticosteroids are used in stromal keratitis, uveitis, trabeculitis, while the systemic use of corticosteroids is contraindicated in HZO due to possible exacerbation of the disease. In patients with increased intraocular pressure, antiglaucoma therapy is required until pressure control is achieved. In USA, the VZV vaccine is recommended for patients over 50 years of age (44,45).

EBV keratitis

EBV keratitis is thought to be mediated by both active viral replication and immunological processes in the corneal tissue (46). Three types of keratitis associated with EBV infection have been reported: subepithelial infiltrates resembling Thygeson's keratitis, bilateral interstitial nummular ring-shaped keratitis in young patients with systemic mononucleosis, and multifocal non-suppurative keratitis involving the full-thickness or deep layers of the peripheral cornea followed by corneal neovascularization (46,47).

Scleritis and episcleritis

Members of Herpesviridae family, namely HSV and VZV, have been documented in cases of chronic unilateral scleritis and episcleritis. However, they represent a rare cause of scleritis and episcleritis, but unilateral manifestation may be indicative of herpetic cause.

Episcleritis tends to be mild and self-limiting with painless dilatation of episcleral blood vessels, but in

chronic cases may progress to scleritis (48). Scleritis is most commonly chronic non necrotizing, diffuse or nodular, in both HSV(49) and VZV(50,51) cases. However, a necrotizing case of VZV scleritis has been reported (52). Scleritis presents with intensive pain which increases with eye movements, ciliary hyperemia, lacrimation and sometimes chemosis. Herpes zoster ophthalmicus may precede VZV scleritis. They typically respond promptly and completely resolve after therapy with acyclovir and may require long term prophylactic treatment with this drug (400 mg twice daily).

Epstein-Barr virus (EBV) has been documented in cases with salmon-colored conjunctival masses in patients after acute mononucleosis and lymphoproliferative disorders. Furthermore, EBV can cause hemorrhagic conjunctivitis (46). In rare cases, EBV has been documented in patients with chronic progressive nodular necrotizing scleritis (47). Those patients tend to respond to prolonged therapy with valacyclovir.

Anterior uveitis

Members of Herpesviridae which have been documented in patients with chronic anterior hypertensive uveitis are HSV, VZV and CMV (11,53,54). Some rare cases of EBV anterior uveitis have been documented using PCR of aqueous humor (53).

HSV anterior uveitis

HSV anterior uveitis tends to occur in younger population (between 30 and 50 years of age), and has a recurrent course. During the recurrences patients complain of pain, redness of the affected eye and blurred vision. Clinical signs include unilateral moderate to severe ciliary hyperemia, decreased corneal sensitivity, corneal pathology (such as dendritic or disciform keratitis and endothelitis 25-54%), (55–57) medium to large keratic precipitates (76-100%), (55,58,59) moderate to severe anterior chamber exudation, sometimes hyphaema may occur, and in chronic cases corneal scarring (12-33%), (57,59) sectorial atrophy of the iris stroma (49-71%), (59–61) and iris sphincter atrophy with irregular pupil are present. As complications, posterior synechiae may occur (in 25-41%), (55,58,59) increased intraocular pressure (in 38-86%), (57,61) and cataract (in 15-37%) (58,59).

The main differential diagnosis of anterior granulomatous uveitis includes: tuberculosis, sarcoidosis (62), sympatheitic ophthalmia (63), Voght Koyanagi Harada disease (64), multiple sclerosis, etc. However, herpetic anterior uveitis typically presents unilaterally, whereas other conditions usually manifest bilaterally.

The main complications include glaucoma, corneal opacities, cataract, posteror synechiae, and iris atrophy. Glaucoma is caused by acute trabeculitis or obstruction of trabeculum with inflammatory cells. In rarer chronic cases, glaucoma may be due to posterior synechiae with pupilar block or secondary scarring of the trabeculum (65).

The treatment of anterior uveitis includes administration of topical corticosteroids, cycloplegics and in cases of corneal involvement antivirals (acyclovir 3% ointment). For patients with secondary glaucoma usually antiglaucoma topical therapy along with cautious usage of low potent corticosteroids (like 0.1% fluorometholone) is sufficient for treatment of trabeculitis. Systemic antiviral therapy is mandatory and includes acyclovir 400 mg 5 times daily first one to two weeks with gradual decrease in dose and prolonged therapy with maintenance dose of 400 mg twice daily for at least two months.

VZV anterior uveitis

VZV anterior uveitis occurs most commonly in elder patients (50-70 years of age), often after HZO (immediately or months later). Symptoms are similar as in HSV anterior uveitis except that post-HZO neuralgia may be more severe. Clinical signs include unilateral moderate to severe ciliary hyperemia, extremely decreased corneal sensitivity, corneal pathology (such as pseudodendritic or nummular keratitis and endothelitis (0-20%)) (55,56,61), small to medium size keratic precipitates (70-100%) (56,59) which tend to become pigmented during the course of the disease (60), severe anterior chamber exudation, and sometimes hyphaema may occur, in chronic cases corneal scarring (9%) (57), and sectorial atrophy (10-76%) (55,59,61) of the iris may be seen. As complications, posterior synechiae may occur (in 0-40%), (55,58,66) increased intraocular pressure (in 40-85%) (55,57), and cataract (in 17-35%). (58–60)

The differential diagnosis includes other unilateral anterior uveitides of viral origin, such as HSV, CMV, EBV, and rubella.

The main complications are similar for all Herpetic anterior uveitides and include glaucoma, corneal opacities, cataract, posteror synechiae, and iris atrophy. Glaucoma has the same pathophysiology as in HSV anterior uveitis.

The treatment of anterior uveitis includes topical corticosteroids, cycloplegics and in cases of corneal involvement acyclovir 3% ointment. Glaucoma therapy is similar as for HSV anterior uveitis. Systemic antiviral therapy includes acyclovir 800 mg 5 times daily first week with gradual decrease in dose and prolonged therapy with maintenance dose of 400 mg twice daily.

CMV anterior uveitis

CMV anterior uveitis always has chronic course and has a clinical picture which resembles Fuchs' heterochromic uveitis. It affects adult patients (40-70 years of age). Patients mainly complain of floaters in visual field. Clinical signs include unilateral mild ciliary hyperemia, normal

corneal sensitivity, corneal pathology (such as endotheliitis (0-40%)) (55,56,58), small diffuse stellate keratic precipitates (39-100%) (55,56,58), mild anterior chamber exudation, in chronic cases diffuse iris atrophy (20-50%) (55,56,58) may be seen. The main complications include iris heterochromia, increased intraocular pressure (in 60-100%) (55,56,58), and cataract (in 29-100%) (57,58).

Complications are less severe then for other Herpetic anterior uveitides and include glaucoma, cataract and iris atrophy.

The treatment of anterior uveitis is controversial since there is no final consensus regarding the most effective therapy, and includes topical corticosteroids, cycloplegics, ganciclovir 0,15-2% gel, (67) and even intravitreal ganciclovir injections were reported as effective in long term clinical studies (68). Glaucoma therapy is similar for all Herpetic anterior uveitides. Furthermore, in some clinical studies per oral valganciclovir 900 mg twice daily for two weeks followed by 450 mg twice daily was proposed. However, there was a high rate of recurrence (up to 80%) after the discontinuation of the drug (69).

EBV anterior uveitis

Anterior uveitis is rarely associated with EBV infection and there are only a few PCR-confirmed cases in the literature (70,71). Patients mainly complain of floaters and diminution of vision. Anterior segment manifestations include mild ciliary hyperemia, keratic precipitates which may become pigmented with time, mild anterior chamber exudation, and vitritis which is resistant to therapy. Also, the treatment seems controversial since there is no specific antiviral medication for EBV. Some case series reported that a combination of systemic acyclovir and intravitreal ganciclovir injections may be efficacious in control of intraocular inflammation (71).

Other causes of anterior uveitis

Also, there are rare reports of chronic anterior segment inflammation caused by HSV2 (in young patients, usually granulomatous) (72) and HHV6 (associated with vitritis) (73).

Investigations

The clinical presentation can often be typical especially in cases with HZO, and for routine praxis can be sufficient to diagnose and treat a patient. However, the only method to precisely diagnose the cause of ocular inflammation is to determine the presence of viral DNA in tissue samples or fluids using the polymerase chain reaction (PCR) or to confirm the local production of antibodies to a certain pathogen using the Goldmann-Witmer coefficient (73).

CONCLUSION

The herpetic inflammation of the anterior segment of the eye still remains a challenge for the clinician due to the fact that it often has recurrent or chronic course. In some cases, there are typical clinical clues which lead an ophthalmologist to suspect the herpetic cause of the inflammation (chronic unilateral inflammation, typical forms of keratic precipitates, specific pattern of iris atrophy). However, a definitive diagnosis—particularly in atypical cases—can be established only by confirming the viral genome in ocular tissues using PCR or, in cases of uveitis, by detecting local production of antiviral antibodies in the aqueous humor using the Goldmann-Witmer coefficient. The therapy often includes prolonged usage of specific antiviral agents, although there is an increasing number of cases of viral resistance especially of HSV and VZV to acyclovir and CMV to ganciclovir which require alternative medications.

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ZAPALJENSKE MANIFESTACIJE INFEKCIJE VIRUSIMA HERPESVIRIDAE NA PREDNJEM SEGMENTU OKA

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Sažetak

Uvod: *Herpesviridae* predstvaljaju veliku familiju dvolančanih DNK virusa od kojih osam tipova inficira ljude: Herpes simplex virus (HSV) tip 1 i 2, Varicella zoster virus (VZV), Cytomegalovirus (CMV), Epstein Barr virus (EBV), Human herpesvirus (HHV) 6, 7 i 8. Herpetična bolest oka može zahvatiti prednji i/ili zadnji segment oka. U ovom radu biće prikazane manifestacije na prednjem segmentu oka.

Metodologija: U revijskom radu su analizirani naučni radovi publikovani u PubMed databazi do 30.4.2024. godine sa ključnim rečima: scleritis, keratitis, anterior uveitis, herpetic, HSV, VZV, CMV, EBV.

Rezultati: Dobro je poznato da HSV1, VZV i CMV uzrokuju inflamaciju prednjeg segmenta oka**,** i to skleritis, keratitis i prednji uveitis ili njihovu kombinaciju. Ipak, postoje prikazi slučajeva uzrokovanih EBV, HSV2 ili HHV6. Bolest obično ima hronični ili recidivirajući tok i dugotrajna inflamacija može uzrokovati ozbiljna oštećenja tkiva oka, koja mogu značajno oštetiti vid. Iako neki tipovi zapaljenja oka se mogu efikasno lečiti antivirusnim lekovima tokom aktivne faze bolesti (npr. HSV1, HSV2, VZV, CMV), za sada nema finalnog rešenja koje bi trajno sprečilo recidive bolesti. Glavne komplikacije uključuju ožiljke rožnjače, istanjenje sklere, glaukom, sinehije, atrofiju dužice i kataraktu.

Zaključak: Usled hroničnog i recidivirajućeg toka bolesti, herpetične zapaljenske manifestacije prednjeg segmenta oka još uvek predstavljaju izazov za kliničara. Iako u nekim slučajevima postoje tipični klinički znaci koji navode oftalmologa da posumnja na herpetični uzrok zapaljenja, finalna dijagnoza (posebno u atipičnim slučajevima) može se postaviti jedino potvrdom virusne DNK iz tkiva oka pomoću PCR metode ili u slučajevima uveitisa detekcijom lokalne produkcije specifičnih antivirusnih antitela u očnoj vodici pomoću Goldman-Vitmerovog koeficijenta.

Ključne reči: Herpetična bolest oka, skleritis, keratitis, prednji uveitis, Herpesviridae, HSV, VZV, CMV

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REVIEW ARTICLE

Graves' orbitopathy

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Summary

Graves' orbitopathy (GO) represents eye changes that most often occur in patients with autoimmune hyperthyroidism- Graves' disease (GD), although they can also occur much less frequently in euthyroid and hypothyroid patients. About 30% of patients with Graves' disease have GO, while less than 10% develop a more severe form that requires treatment. The choice of treatment should be based on the assessment of clinical activity and severity of GO. Activity represents the degree of inflammation while severity of GO reflects the degree of functional and cosmetic changes. Patients with mild orbitopathy usually recover spontaneously, so therapy is not always necessary. General measures to control risk factors and local treatments are usually sufficient. Treatment of active moderate-to-severe forms of GO still relies in most cases on high-dose systemic-intravenous glucocorticoids as monotherapy or in combination with mycophenolate. Second-line treatments for moderate-to-severe and active GO include the second course of i.v. methylprednisolone; oral prednisone combined with either cyclosporine or azathioprine; orbital radiotherapy combined with i.v. glucocorticoids; teprotumumab; rituximab and tocilizumab. Sight-threatening GO is treated with several high single doses of i.v. methylprednisolone per week and, if unresponsive, with urgent orbital decompression. Rehabilitative surgery (orbital decompression, squint, and eyelid surgery) is indicated for inactive residual GO manifestations.

Keywords: Graves' orbitopathy, Graves' disease, glucocorticoids, mycophenolate, orbital decompression

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INTRODUCTION

Graves' orbitopathy (GO) represents eye changes that most often occur in patients with autoimmune hyperthyroidism – Graves' disease (GD), although they can also occur much less frequently in euthyroid and hypothyroid patients (1). Considering that it limits the performance of usual daily activities, orbitopathy has a significant impact on the patients' quality of life. In order to start the treatment, it is necessary to perform an adequate assessment of the disease. Moderate-to-severe forms GO are a major therapeutic challenge because there is still no safe and highly effective therapy. European Group on GO (EUGOGO) was founded in 1999. with the idea of improving treatment of GO. To date, two EUGOGO guidelines for the management of GO have been published, the first in 2016, and in updated version in 2021.

PATHOGENESIS, EPIDEMIOLOGY, CLINICAL MANIFESTATIONS AND DIAGNOSIS OF GRAVES' ORBITOPATHY

The pathogenesis of Graves' ophthalmopathy (GO) is rooted in an autoimmune process occurring in the retrobulbar tissue (1). Autoimmune reactions ongoing in the orbit are probably initiated by autoreactive T lymphocytes which trigger a cascade of events including secretion of cytokines, proliferation of orbital fibroblastas, differentiation of preadypocytes into adipocytes, infiltration of extraocular muscles and secretion of glycosaminoglycans by the orbital fibroblasts (1,2).

As a consequence of the above, the intraorbital mass increases, which leads to the development of the typical clinical picture of GO (3). The most typical clinical sign is the retraction of the eyelids, which is present in over 90% of patients, then eyelid edema and exophthalmos, both bilateral or unilateral. Also, lagophthalmos may be present, as well as conjunctival redness, limited extraorbital muscle motility, double vision and compressive optic neuropathy. At the beginning of the disease, almost half of the patients have symptoms of irritation, complain of increased tearing, dry eyes, light sensitivity and feeling of discomfort (4). The clinical picture can sometimes be atypical with dominance of any of the listed clinical signs (5). It is believed that the clinical picture of GO became milder over time due to rapid diagnosis and initiation of treatment (6).

GO is a rare disease (estimated incidence: 0.54–0.9 cases/100 000/year in men, 2.67–3.3 cases/100 000/year in women) with more commonly mild and no progressive cases. Moderate-to-severe forms accounting for 5–6% of cases only (7). Some factors may influence the course of GO. Risk factors for the occurrence and progression of GO include smoking, thyroid dysfunction, radioiodine treatment for hyperthyroidism, and high TSHR antibody levels.

The diagnosis of GO is usually made clinically (8). Sometimes that is not easy, especially in unilateral or unusual cases. In these cases, orbital visualization plays a major role in diagnosis and differential diagnosis.

Both CT and MR imaging are in use and have their advantages. MR examinations play a significant role in the assessment of soft tissues and disease activity, while CT is superior in the evaluation of bones and has a special role in planning the surgical treatment of GO. Although generally occurring in hyperthyroid patients with Graves' disease, GO is occasionally seen in patients with autoimmune hypothyroidism and patients without thyroid dysfunction (9) which can make diagnosis even more difficult. Besides thyroid function test it is useful to determine thyroid autoantibodies. TSH receptor autoantibody are indispensable biomarker in the laboratory assessment of GO, especially TSAb measured using most sensitive cell-based bioassay (10).

ASSESSMENT AND CLASSIFICATION OF GRAVES' ORBITOPATHY

A significant proportion of patients with GO improve spontaneously. In patients receiving no specific treatment typical course of disease is described: GO undergoes an initial phase of florid inflammation (active disease) followed by a phase of stabilization (plateau phase) and a final phase of remission (burned-out or inactive disease) (11).

In order to decide on the treatment of GO, it is necessary to perform an adequate examination. The examination includes an assessment of the activity and severity. Disease activity represents the degree of inflammation, i.e. the presence of redness and swelling on the eyelids, conjunctiva and plica and the presence of retrobulbar pain.

The concept of severity relates to the features that result from the chronic changes in the extraocular muscles and soft tissues. Assessment of severity is based on various parameters, including soft tissue changes, exophthalmos, extraocular muscle dysfunction and diplopia, corneal involvement, and optic nerve involvement (13). Based on the performed examination, the severity of the disease is divided into mild, moderate to severe and sight threating GO. exophthalmos **(Table 1)**.

MANAGEMENT OF GO

Although management depends on severity and activity of GO, there are general measures that apply to all patients. They include control of risk factors and local treatment.

Control of risk factors. Both hyperthyroidism and hypothyroidism have a negative effect on orbitopathy. Disorders of thyroid function, hyperthyroidism and hypothyroidism adversely affect orbitopathy (14,15). For this

Table 1. Classification of severity of Graves' orbitopathy (GO)

Classification	Clinical features
Mild GO	• exophthalmos <3 mm above normal for gender and race • minor lid retraction <2 mm • mild soft-tissue involvement • no double vision or intermittent
Moderate to severe GO	• exophthalmos ≥3 mm above normal for gender and race • lid retraction ≥2 mm • moderate to severe soft-tissue involvement • inconstant or constant double vision
Sight-threatening (very severe) GO	• involvement and damage to the cornea and/or optic nerve

reason, it is extremely important to maintain thyroid hormones in normal values with adequate treatment.

The association between GO and smoking is well known: smoking increases the risk of GO in patients with GD, smokers have more severe GO, smokers have worse or delayed outcome of immunosuppressive treatments, development or progression of GO after radioactive iodine (RAI) treatment is more frequent in smokers (16). All patients with GO and GD should be urged to quit smoking.

Considering that RAI treatment carries a risk of aggravation and de novo occurrence of GO, oral prednisone prophylaxis should be given to radioactive iodine (RAI)-treated patients with risk factors (smokers, severe or unstable hyperthyroidism, high serum TSHR-Ab) (17).

Local treatment. GO patients often have dry eyes as a consequence of several factors such as exophthalmos, lagophthalmos, increased width of the palpebral fissure, blinking rate, lid lag and altered tear film osmolality. Therefore, patients are advised to use artificial tears during the day and ophthalmic gels with a possible taping of the lids or using swimming goggles at nighttime when severe lagophthalmos is present (18).

Management of mild GO

Patients with mild orbitopathy usually recover spontaneously, so therapy is not always necessary. General measures to control risk factors and local treatments are usually sufficient (18). So far, one randomized study has been published that showed a beneficial effect of selenium on current eye changes as well as the degree of progression. Based on that, according to the latest EUGOGO guidelines (19) selenium is recommended for patients with mild orbitopathy. Occasional patients with mild and active GO may require intervention with glucocorticoids if their quality of life is severely impaired by the disease (19) **(Figure 1)**.

Management of moderate-to-severe and active GO

Due to their anti-inflammatory and immunosuppressive effects, *glucocorticoids* have been the **first line of**

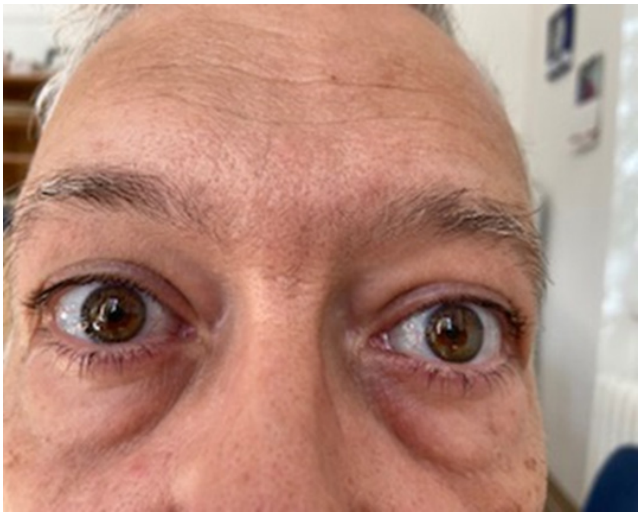

Figure1. Mild GO

treatment for moderately severe active orbitopathies for decades (19). In recent years, they have been combined with mycophenolate. According to current official recommendations, glucocorticoids are administered intravenously at weekly intervals for 12 weeks: six infusions of 0.5 g, followed by six infusions of 0.25 g. This protocol is well tolerated, it is effective in most patients and in the Clinic for Endocrinology of the University Clinical Center of Serbia it represents the first line of treatment.In more severe clinical cases a protocol with higher doses of corticosteroids is applied, with the starting dose of 0,75g for 6 weeks, followed by 0,5g for the next 6 weeks. Previous studies have shown that intravenous administration is more effective than oral administration and is better tolerated (21,22). Clinical and biochemical evaluation of patients is necessary before starting therapy because some conditions like viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, or psychiatric disorders represent absolute contraindications to i.v. glucocorticoid treatment (20, 23), while diabetes and hypertension should be well controlled before starting treatment (24).

In addition to the i.v. protocol, oral route is still used in many countries (25). In the Clinic for endocrinology in previous years we used Combined GC protocol which included 500mg of methylprednisolone in 500ml of saline solution for two alternative days. After that, the patients would continue to receive oral prednisone in decreasing doses for 4 weeks. In total, this therapy lasted for 6 months (26) and was successful in 65% of patients. Side effects were mostly mild, with weight gain, alterations in lipid profile, hirsutismus and myalgia that occurred most frequently (27) **(Figure 2)**.

Although it is known that intravenous glucocorticoids are better tolerated and have fewer side effects than oral (21-23) very serious complications have also been described during intravenous therapy (28-30).

Glucocorticoids can also be applied locally, as peribulbar, retrobulbar or subconjunctival injections in case of contraindications for systemic administration (31).

Figure 2. Moderate to severe GO

Immunosuppression with nonsteroidal agents has been studied either alone or as way to enhance the efficacy of GC. Mycophenolate mofetil (MMF) specifically targets activated T and B lymphocytes (32). In a randomized clinical trial MMF specifically comparing MMF in addition to IVGC vs IVGC alone, MMF showed benefit (33).

Second-line treatments for moderate-to-severe and active GO include the second course of i.v. methylprednisolone; oral prednisone combined with either cyclosporine or azathioprine and orbital radiotherapy combined with i.v. glucocorticoids particularly in the presence of diplopia and/or restriction of extraocular motility (19).

A number of immune cells and cytokines are thought to be involved in the pathogenesis of GO (34,35). Several monoclonal antibodies able to interfere with cytokine signaling are available for treatment of moderate-to-severe GO. Novel agents, such as rituximab. tocilizumab or teprotomumab or other biologicals, might represent a new way of approaching moderate-to-severe GO. However, they are not widely available and affordable. For the time being, evidence is missing regarding their effectiveness and safety.

Management of sight threatening GO

Sight threating GO (optic neuropathy) should be treated as soon as possible with high single doses of i.v. methylprednisolone (0.5–1 g of methylprednisolone daily for either three consecutive days or more preferably on every second day), and urgent orbital decompression should be performed if response is absent or poor within 1–2 weeks (19).

Management of inactive GO

Once GO has been inactivated by medical treatment, many patients require rehabilitative surgery for residual ocular manifestations (exophthalmos, lid retractions, eyelid, and periorbital puffiness, strabismus, and correlated symptoms such eye grittiness, retro/ periocular tension, and diplopia). They can be treated by a combination of decompression, ophthalmic plastic, and strabismus surgery (36).

CONCLUSION

Based on all the relevant clinical trials so far, intravenous glucocorticoids represent the most effective and safest method of treatment. Treatment should be carried out in combined thyroid-eye clinics or specialized centers providing both endocrine and ophthalmic expertise. Clinicians should monitor each individual patient receiving glucocorticoid therapy for response to treatment and adverse events. When drug-induced side effects outweigh benefits, clinicians should consider withdrawing glucocorticoid treatment in favor of another modality,

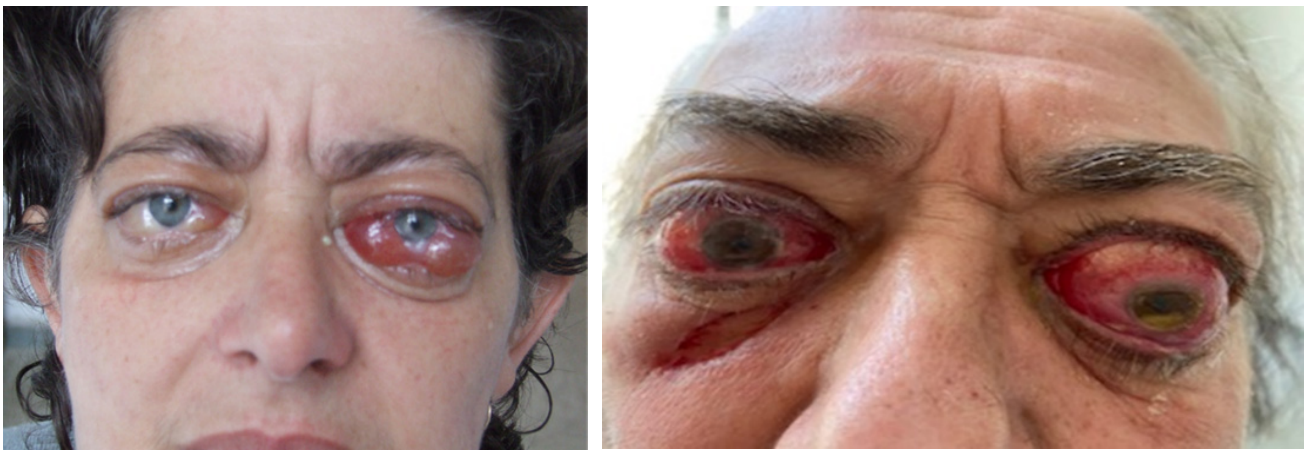

Figure 3. Sight threatening GO

or watchful monitoring. For second line treatment, biologicals, teprotumumab, tocilizumab or rituximab, hold great promise in the future management of GO and can be useful if patients are intolerant or resistant to standard immunosuppressive treatment.

In the University Clinical Center of Serbia, the treatment of GO is carried out in specialized endocrine-ophthalmic center in accordance with the current recommendations of the European Group of Graves Orbitopathy.

Author Contributions

Biljana Nedeljković Beleslin conceived and wrote the paper.

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GREJVSOVA ORBITOPATIJA

Biljana Nedeljković Beleslin[1,2]

Sažetak

Grejvsova orbitopatija (GO) je autoimino oboljenje orbite i glavna ekstratiroidna manifestacija Grejvsove bolesti. Oko 30% pacijenata sa Grejvsovom bolešću ima GO, dok manje od 10% razvije težu formu koja zahteva lečenje. Lečenje GO je multidisciplinarno. Izbor terapije se zasniva na proceni aktivnosti i težine bolesti Aktivnost predstavlja stepen inflamacije. Težina predstavlja stepen kozmetičkih i funkcionalnih poremećaja. Za blage i aktivne GO savetuje se kontrola faktora rizika, lokalna oftalmološka terapija i selen (posebno u oblastima deficitarnim selenom). Lečenje aktivnih srednje-do-teških formi GO u većini slučajeva se zasniva na primeni visokih doza intravenski primenjenih glukokortikoida kao monoterapijja ili u kombinaciji sa mikofenolatom. Druga linija lečenja obuhvata ponovljeni ciklus glukokortikoida intravenski, oralne glukokortikoide u kombinaciji sa ciklosporinom ili azatioprinom, radioterapiju u kombinaciji sa intravenskim glukokortikoidima, teprotumumab, rituksimab ili tocilizumab. U slučaju veoma teških, po vid ugrožavajućih GO se primenjuje više visokih, pojedinačnih doza metilprednizolona tokom nedelju dana. U slučaju da ne postoji povoljan odgovor na terapiju sprovodi se hitna hirurška dekompresija. Rekonstruktivna hirurgija (dekompresija, strabološka operacija ili operacija kapaka) je indikovana za neaktivne, posle medikamentne terapije zaostale, manifestacije GO.

Ključne reči: Grejvsova orbitopatija, Grejvsova bolest, glukokortikoidi, mofetil, orbitalna dekompresija

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REVIEW ARTICLE

Clinical manifestations of polycystic ovary syndrome

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Summary

Polycystic ovary syndrome, commonly abbreviated as PCOS, as the most common endocrine disorder in women of reproductive age, is a multifaceted disease characterized by various hormonal imbalances and a great degree of variation in its clinical presentation. This, coupled with its etiology and pathogenesis being incompletely understood, results in a broad disease spectrum that is challenging to accurately diagnose and manage. The primary clinical features which PCOS commonly manifests with include hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, though all three are not necessarily present in all PCOS patients.

Hyperandrogenism, manifesting as hirsutism, acne, and male-pattern alopecia, significantly affects both the physical and psychological wellbeing of these patients. Ovulatory dysfunction, presenting as irregular menstrual cycles due to oligo/anovulation, is an important element of PCOS's clinical presentation and leads to the infertility that some of these patients' experience. PCOS is commonly associated with insulin resistance and consequent hyperinsulinemia and metabolic disorders, seen in these patients. Subsequently, women affected with PCOS are at a greater risk of obesity, dyslipidemia, diabetes, and cardiovascular diseases, particularly later in life. The rate of mood disorders, namely depression and anxiety, is also increased in this population.

The complex nature of this syndrome makes difficulties in patient care, and its chronic nature emphasizes a proactive stance when it comes to treatment, but also a careful assessment of all the elements of the disease.

Keywords: PCOS, insulin resistance, hyperandrogenism, PCOM

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder occurring in women of the reproductive age (1). The syndrome was first described by Stein and Leventhal in 1935, who presented a series of cases that included seven female patients exhibiting enlargement of the ovaries and amenorrhea. The patients were treated with ovarian resection (2). The clinical presentation of the syndrome is heterogeneous, encompassing polycystic ovarian morphology, clinical and/or biochemical hyperandrogenism (HA), and ovulatory dysfunction accompanied with menstrual cycle irregularities and infertility (3).

The phenotypic expression of the syndrome is variable, and it changes throughout a woman's lifetime. This variation can occur because of aging or due to lifestyle changes. For example, reaching a healthy body weight can result in a "remission" of sorts (1). Due to this variability in phenotypic expression, over recent years PCOS has been defined as a syndrome instead of as a specific endocrine illness.

The consequences of this syndrome on the health of affected women persist throughout their lifespan and manifest in reproductive and psychological morbidity, cardiometabolic complications, an increased risk of malignancies, as well as diminished health-related quality of life (HRQoL) (3,4).

EPIDEMIOLOGY

A combination of considerable phenotypic variability, choice of patient population studied, as well as multiple different diagnostic criteria, all greatly influence the data on the prevalence of PCOS found in the literature. According to diagnostic criteria defined in 1990, the prevalence of PCOS among women of reproductive age is 5-9%, whereas, according to the Rotterdam criteria established in 2003, the prevalence ranges from 5.5 to 19.9% (5). Furthermore, according to the diagnostic criteria established in 2009, the prevalence ranges from10 to 15% (6).

In summary, the literature suggests the prevalence lies between 4 and 21% (5). It is important to note that in the general population, the incidence of PCOS increases proportionally with the rise in body mass index (BMI). The diagnosis of PCOS is most commonly made in the second or third decade of life, as it is at this time that the majority of patients begin to seek medical attention.

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of PCOS is incompletely understood. The initial clinical manifestations of PCOS appear in adolescence. It is currently thought to be a multifactorial disorder where endocrine, metabolic, genetic, epigenetic and environmental factors all play a role (7).

Namely, genetic loci linked to PCOS account for only 10% of its heritability. Furthermore, studies conducted in animal models point to a transgenerational inheritance pattern connected to intra-uterine epigenetic modulation that happens as a consequence of an aberrant intra-uterine milieu, specifically the presence of elevated androgen and Anti-Mullerian hormone (AMH) levels (8–10). Also, PCOS is more commonly found in the mothers and sisters of women who have been diagnosed with PCOS themselves (11). Apart from genetic factors, exogenous factors play a key role as well, most notably obesity, although obesity itself is oftentimes hereditary in nature. Obesity leads to changes in the functioning of the hypothalamus-pituitary-ovarian axis (12).

The three most significant theories of the origin of PCOS are:

1. The theory of aberrant ovarian steroidogenesis
2. The theory of insulin resistance (IR)
3. The theory of hypothalamus-pituitary-adrenal axis dysregulation (13)

In both ovulatory and anovulatory PCOS patients, ovarian theca cells overproduce androgens resulting in increased growth of immature ovarian follicles and a polycystic morphology of the ovaries. This is also the underlying cause of elevated concentrations of AMH, whose levels correlate with the number of preantral and small antral follicles. AMH is produced in the granulosa cells of small preantral follicles, and its serum levels are significantly elevated in PCOS patients with anovulatory cycles. Elevated levels of AMH reduce the number of follicle stimulating hormone (FSH) receptors, thereby inhibiting the FSH-induced stimulation of ovarian follicle growth leading to the absence of dominant follicle selection. Furthermore, elevated AMH levels decrease the sensitivity of ovarian follicles to FSH and block the conversion of androgens into estrogens through inhibition of the aromatase enzyme, which contributes to the development of HA (13). Hypersecretion of luteinizing hormone (LH) also leads to premature luteinization of granulosa cells and androgen hypersecretion which is additionally stimulated by hyperinsulinemia (14).

The second theory arose due to the strong link between IR and PCOS. It has been shown that in women with PCOS there are elevations in basal insulin secretion and the insulin secretory response to glucose is inadequate (15). A large number of studies point to hyperinsulinemia as a significant factor that drives IR. The synergistic action of insulin and LH exert an influence on theca cell androgen hypersecretion (16). Androgen excess, most notably of testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEAS) cause premature ovarian follicle atresia giving rise to multiple ovarian cysts and anovulatory cycles. Excessive androgen

production in the ovaries exacerbates obesity, especially visceral obesity, which worsens IR, leading to hyperinsulinemia. To come full circle, this hyperinsulinemia stimulates ovarian hypersecretion of androgens (15,16). This is further supported by the breadth of evidence supporting the use of insulin sensitizers in the treatment of PCOS. For example, drugs used commonly in the treatment of type 2 diabetes mellitus (DM2) such as metformin, the inositol stereoisomers myo-inositol and d-chiro-inositol, and more novel drugs such as pioglitazone, liraglutide and semaglutide, all either have indications or are being investigated for the treatment of PCOS, with the aim of boosting fertility and improving hormonal regulation (17–19).

The third theory points to a dysregulation on the level of the hypothalamus-pituitary-adrenal axis, with disordered secretion of gonadotropins causing elevated LH levels as well as normal or low levels of FSH (20). Anovulation is the consequence of the absence of the maturation of the dominant follicle. Because of anovulation, there is a reduction in progesterone, and progesterone surges become absent in the luteal phase of the cycle, preventing it from exerting its negative feedback effects at the level of the pituitary. The frequency of the pulsatile secretion of gonadotropin-releasing hormone (GnRH) is increased, causing an elevation in the frequency and amplitude of LH secretion (21). Elevated levels of LH stimulate ovarian androgen secretion while the relative lack of FSH lead to growth arrest of the dominant follicle and anovulation. This disruption in gonadotropin secretion, specifically the inverted FSH/LH ratio, is primarily found in PCOS patients of a healthy weight and is mostly normal in obese women (22). This disruption may in fact originate very early on in life, as exposure to higher levels of androgens during intrauterine development is thought to predispose towards PCOS (23).

Finally, several observational and interventional studies have demonstrated a possible role vitamin D deficiency plays in the metabolic, endocrine, as well as inflammatory aspects of PCOS. Supplementing with vitamin D might even prove to be a useful prevention strategy in those with a positive family history, though more research is needed (24).

PCOS PHENOTYPES

Although diagnostic criteria for PCOS aren't entirely standardized, four PCOS phenotypes have been defined based on clinical and hormonal characteristics:

1. Phenotype A: "Classic PCOS", characterized by clinical or biochemical HA, anovulation (ANOV) and polycystic ovarian morphology (PCOM)
2. Phenotype B: "Classic PCOS", characterized by HA and ANOV
3. Phenotype C: characterized by HA and PCOM (representing the ovulatory type of PCOS)
4. Phenotype D: characterized by ANOV and PCOM (representing the milder, non-hyperandrogenic PCOS phenotype) (25,26).

The classification of PCOS into phenotypes is important for epidemiological and clinical research on PCOS (27). In the majority of patients, after the fourth decade of life, the phenotypic expression becomes milder, which manifests as a decrease in the size of the ovaries, number of follicles, androgen levels, as well as greater menstrual cycle regularity (28). According to a meta-analysis performed in 2016, phenotype A is the most prevalent type (29). The prevalence of the different PCOS phenotypes is shown in **Figure 1** (30).

Women exhibiting the classic PCOS phenotypes, phenotypes A or B, have more pronounced menstrual cycle disturbances, hyperinsulinemia, and are more likely to have IR, metabolic syndrome, and a high BMI, including obesity. Values of AMH are also more commonly elevated in those women (26).

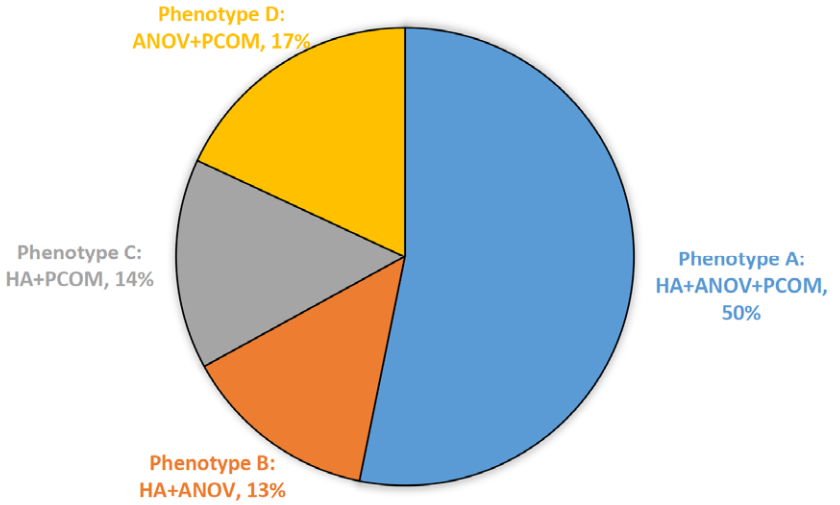

Figure 1. Prevalence of PCOS Phenotypes

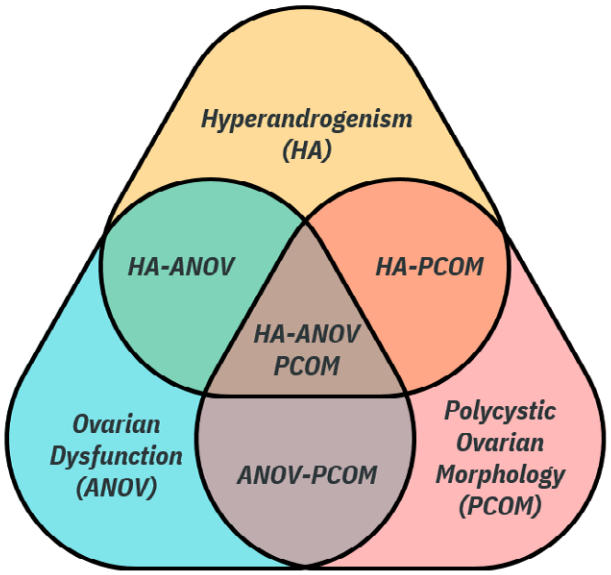

Figure 2. Clinical Characteristics and Phenotypes of PCOS

CLINICAL CHARACTERISTICS OF PCOS

The most important clinical characteristics of PCOS are HA with or without biochemical hyperandrogenism, ovarian dysfunction with or without menstrual cycle disturbances, and polycystic ovarian morphology, shown in **Figure 2**.

HYPERANDROGENISM

Clinical or biochemical hyperandrogenism (hyperandrogenemia-elevated androgen levels) occurs among 5-10% of women of reproductive age. The most common hyperandrogenic disorder is PCOS, which occurs in 80-85% of women with HA (31).

There is considerable heterogeneity among women with HA, and the phenotype itself can vary over time. Clinical manifestations of HA can be observed even without biochemical confirmation of elevated androgens, which is thought to be due to increased sensitivity of local tissues to androgens, as well as ethnic differences in phenotypic expression (32,33). On the other hand, biochemical HA can exist in PCOS patients even without an obvious clinical manifestation, especially in Asian populations (33).

Hirsutism is the most common clinical manifestation of HA. Other manifestations include acne, seborrhea, and androgenic alopecia, commonly known as male-pattern baldness. Hirsutism is defined as excessive growth of terminal hair in women, specifically those found in androgen sensitive areas. It appears in 5-8% of women of reproductive age (34). It happens because of elevated androgen serum levels and/or increased sensitivity of the pilosebaceous unit to androgens. It occurs in 65-75% of women with PCOS and represents the most common clinical criterion for diagnosing HA (32). Hirsutism is assessed using the Ferriman-Gallwey score (35). Scoring is performed by grading terminal hair growth on a scale from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth), assessed on a total of 11 specific body regions: the upper lip, chin, chest, upper and lower back, upper and lower abdomen, upper arms, forearms, groin, and legs (35). A modified score takes into account a total of nine body regions, excluding the legs and forearms, with a sum score of nine and above considered clinically evident hirsutism (34). When assessing HA based on hirsutism, it must be taken into account that the degree and distribution of HA do not necessarily correlate with levels of hyperandrogenemia (36).

Acne represents an inflammatory process in the pilosebaceous unit and occurs on the face, neck, back, and pectoral region. The incidence of acne in women with PCOS is between 15 and 25% and there are significant ethnic variations (37).

Androgenic alopecia represents the progressive loss of terminal hair on the scalp. Both androgens from the ovaries and those secreted by the adrenals are involved in its etiology. It occurs even in women with normal serum androgen levels and it is thought that genetic factors also play a role in its development (38).

Hyperandrogenemia exists in 60 to 80% of patients with PCOS (39). The androgens originate mostly from the ovaries, but there are often elevated concentrations of adrenal androgens as well. In most women with PCOS, elevated levels of circulating testosterone can be found. Changes in levels of albumin and sex hormone binding globulin (SHBG), both of which bind sex hormones, can influence testosterone levels. Hyperinsulinemia and obesity decrease the level of SHBG, and low levels serve as a marker of IR and androgen excess (40).

Biochemical HA is diagnosed by finding elevated concentrations of testosterone, androstenedione, 17OH progesterone, dehydroepiandrosterone (DHEA), DHEAS, an elevated serum Free Androgen Index (FAI), and decreased concentrations of SHBG (40).

OVULATORY DYSFUNCTION

Dysregulation of ovarian function in PCOS patients manifests with oligomenorrhea or amenorrhea as a consequence of oligo/anovulation. Rarely, patients develop polymenorrhea. A total of 75-85% of women with PCOS have irregular menstrual cycles (38). Irregularity of the menstrual cycle commonly manifests soon after menarche, or the menarche itself may occurs later in life. In some patients, the first menstruations are initially regular but later become irregular, often accompanied by an increase in body weight (41).

Women with PCOS may also have completely regular cycles, which doesn't exclude them from potential ovula-

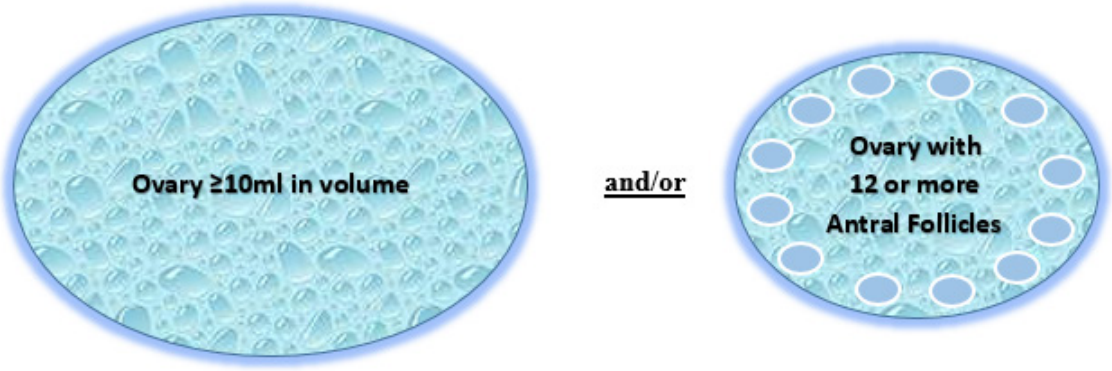

Figure 3. Diagnostic criteria for PCOM

tory dysfunction. Chronic anovulation may still be present, even in patients with completely regular menstrual cycles. It is estimated that PCOS can occur in 20-30% of women with regular menstrual periods, independently of their ovarian function (40).

Infertility in women with PCOS is most associated with chronic anovulation, but also with an increased propensity toward early spontaneous miscarriages. Additionally, PCOS related endometrial changes, lower oocyte quality, and obesity, may lead to a higher incidence of infertility in this population (41).

Recently conducted research shows IR is present in as many as 65-85% of women with PCOS and is more pronounced in patients who are also obese (38). IR represents a reduced ability of insulin to fulfill its metabolic activity consequently necessitating a higher level of secretion to exert its metabolic effect. Hyperinsulinemia develops secondarily, due to IR, and exists in 50 to 70% of women suffering from PCOS (42). Hyperinsulinemia negatively impacts follicular development. Elevated insulin levels can decrease the number of preovulatory follicles and cause anovulation (41).

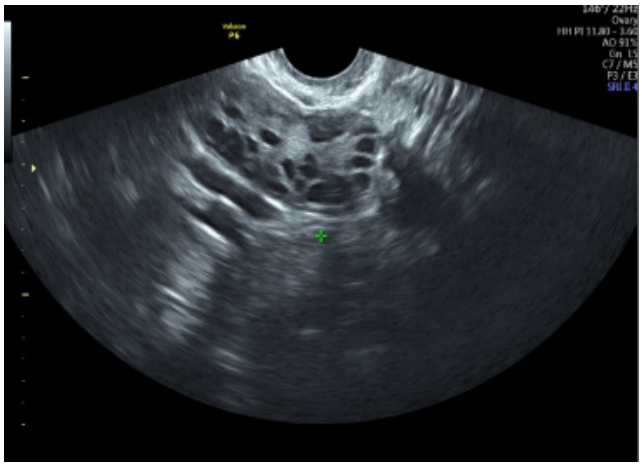

Figure 4. Ultrasonographic image showing PCOM

POLYCYSTIC OVARIAN MORPHOLOGY (PCOM)

In women with PCOS, the finding of enlarged ovaries is common, and the average volume of their ovaries is higher compared to women in the general population of the same age and body weight. Criteria used in defining PCOS includes the ovary/ovaries being larger than 10 ml and/or existence of ≥12 follicles 2-9 mm in diameter, as can be seen in **Figure 3** (43). Arguably, the condition for diagnosing PCOM is the presence of ≥25 antral follicles (44).

PCOM, although a common finding, is not crucial for the diagnosis of PCOS. PCOM is encountered in around 20% of healthy women with ovulatory cycles, during their reproductive years. The incidence in adolescents is even greater (45). During an ultrasound examination numerous peripherally arranged follicles surrounding the central stroma can be observed, shown in **Figure 4**.

In these patients, the growth of antral follicles concludes when the follicle is smaller than 10 mm and the emergence of dominant follicles does not occur. Follicular arrest is a consequence of HA in the ovary, as well as LH and insulin-mediated stimulation of follicular cells. When considering the diagnosis of PCOS, it is essential to bear in mind that polycystic ovarian morphology (PCOM) can be observed through transvaginal ultrasound in healthy women without PCOS, even more frequently in adolescent girls. Even with this in mind, it should be noted that the prevalence of PCOM in women with PCOS is approximately 80% (38).

MANIFESTATIONS OF PCOS AT DIFFERENT STAGES OF LIFE

During adolescence and the reproductive period, the clinical picture of PCOS is dominated by reproductive morbidity. Notable features include menstrual cycle disturbances, infertility, hirsutism, and acne. Obesity and DM2 can be found, but is not an obligatory component of the clinical picture (46). In the majority of cases, obesity is of the visceral type, which significantly influences the reproductive

and cardiometabolic morbidity of these patients (47).

Patients' fertility associated morbidity during the reproductive period is often due to the increased frequency of spontaneous miscarriages, occurrence of ovarian hyperstimulation syndrome during infertility treatment, gestational diabetes, and preeclampsia during pregnancy, often seen in this patient population (26). Premature delivery, before the 32nd week of gestation, are more common among women with PCOS. Newborns are also more frequently macrosomic, with a lower Apgar score, specifically less than 7 at 5 minutes of life, and are also at an increased risk of meconium aspiration syndrome (48).

Dyslipidemia, which manifests as elevated triglyceride levels, and decreased levels of high-density lipoprotein (HDL), happens as a consequence of IR and is found in 70% of patients with PCOS. Interestingly, levels of low-density lipoprotein (LDL) are also often decreased in these patients (28).

In general, PCOS patients have a lower HRQoL in all domains, but most often in those domains are affected by the clinical manifestations of the disorder. The HRQoL is especially negatively impacted by obesity, hirsutism, androgenic alopecia, acne, menstrual irregularities, and infertility (48). Furthermore, symptoms of depression, anxiety, as well as low self-esteem are frequent findings in this population (49). According to the literature, PCOS influences the daily life of more than 65% of patients affected by it, while fully half (50%) report that PCOS affects how they interact with their environment (40). Lower scores on HRQoL assessment scales significantly correlate with the severity IR (48).

With age and the gradual onset of menopause, the clinical presentation of PCOS changes. The regularity of the menstrual cycles improves, whereas the size of the ovaries, number of follicles, and serum androgen levels all decrease. The prevalence of classic PCOS phenotypes, phenotypes A and B, decreases in the 4th decade of life (28). However, according to current literature, there is no data available on the connection between the milder phenotypic expressions of PCOS in the peri- and post-menopause, and their long-term health outcomes. In later life, individuals with PCOS more commonly suffer from cardiovascular and cerebrovascular disease, pronounced obesity, metabolic syndrome, DM2, obstructive sleep apnea, endometrial hyperplasia and carcinoma, as well as anxiety and depression (28,48). The relative risk of developing cardiovascular disease is the highest among those with phenotype A and B, in whom it is estimated to be 1.3%. The risk of cardiovascular morbidity in these women persists throughout their lives and increases over time (48,50). The risk of venous thromboembolism in women with PCOS who have been treated with oral contraceptives is twice as high as in the general population (51).

Hyperinsulinemia and IR in later life can give rise to DM2 and cardiovascular disease. Menopause, in and of itself relates to IR and a propensity towards glucose intolerance and the development of DM2, which is then exacerbated by the higher incidence of this disease spectrum in women with PCOS. High insulin levels are also responsible for the development of obesity in these patients. These women are also at a higher risk of hypertension, metabolic syndrome, and obstructive sleep apnea (28,52).

Furthermore, as a consequence of their exposure to a large number of cumulative risk factors, specifically obesity, hyperinsulinemia, DM2 and menstrual irregularities coupled with chronic anovulation, PCOS patients have a higher risk of endometrial hyperplasia and endometrial cancer later in life (28). According to literature data, the risk of developing endometrial cancer is four times higher in these women compared to the general population (28). Although there is no definitive data on PCOS patients having a higher incidence of ovarian or breast cancer, chronic oligo/anovulation and the consequent prolonged exposure to estrogen theoretically increases the risk for the development of other estrogen-dependent tumors (28).

DIAGNOSIS

While PCOS represents the most common endocrinopathy of the reproductive period in women, variations in the phenotypic expression of the syndrome significantly complicate the diagnosis. Since 1990, several professional associations have put forth diagnostic criteria for the diagnosis of PCOS, with the aim of coming to a diagnostic standardization, and which have been collated in **Table 2**.

Initially, the US National Health Institute (NIH) defined diagnostic criteria for PCOS in 1990 as the following: clinical and/or biochemical HA with chronic anovulation, following the exclusion of other potential

Table 1. Clinical manifestations of PCOS throughout a woman's lifespan

Adolescence	Premenopause	Postmenopause
Insulin Resistance	Insulin resistance and DM2	Cardiovascular Morbidity
Obesity	Obesity	Obstructive Sleep Apnea
Hyperandrogenism	Hyperandrogenism	Endometrial Carcinoma
Oligoanovulation	Hypertension	Depression and Anxiety
	Dyslipidemia	
	Metabolic Syndrome	
	Obstructive Sleep Apnea	
	Depression and Anxiety	

Table 2. Criteria for establishing a PCOS diagnosis.

	1990 US NIH Criteria			
	2006 AE-PCOS Criteria			
	2003 Rotterdam Criteria			
	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Hyperandrogenism and/or Hyperandrogenemia	✓	✓	✓	X
Ovulatory Dysfunction	✓	✓	X	✓
PCOM	✓	X	✓	✓

AE-PCOS Androgen Excess and PCOS Society

causes of HA and anovulation (53). The drawback of this definition is that it only recognizes the classic PCOS phenotypes.

In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) established the "Rotterdam criteria". These expanded on the previously mentioned NIH criteria, but they also incorporated PCOM as a diagnostic criterion. Thus, according to the Rotterdam criteria, the conditions required for diagnosing PCOS are the presence of at least two out of the following three diagnostic signs: clinical and/or biochemical HA, chronic anovulation, and PCOM, with the prior exclusion of other pathological conditions with these symptoms (43).

The Androgen Excess Society (AE), together with the PCOS Society (PCOSS), defined a set of common diagnostic criteria for PCOS in 2009, emphasizing HA as one of the criteria for establishing the diagnosis of PCOS (48). No matter the diagnostic criteria, a prerequisite for the diagnosis is the exclusion of other conditions which may mimic the presentation of PCOS (54).

DIFFERENTIAL DIAGNOSIS

The diagnosis of PCOS is established by the exclusion of other causes of anovulation, such as thyroid diseases and hyperprolactinemia, and of other causes of HA, such as congenital adrenal hyperplasia, Cushing syndrome, severe IR syndromes, idiopathic hirsutism, androgen secreting tumors of the ovaries and adrenal glands (15,45,55).

TARGETING TREATMENT BASED ON A PHENOTYPIC APPROACH

The metabolic phenotype of PCOS, characterized by insulin resistance and an increased risk of type 2 diabetes, necessitates interventions focused on improving insulin sensitivity. Lifestyle modification, including diet and exercise, remains the cornerstone of treatment. Weight loss has been shown to improve metabolic parameters, and even a modest reduction in weight can significantly enhance insulin sensitivity and reduce hyperandrogenism (56). Pharmacological interventions, such as metformin, are also effective in improving insulin sensitivity and can be used particularly in women who do not respond adequately to lifestyle changes (57). Additionally, thiazolidinediones (TZDs) have shown promise in improving insulin sensitivity and menstrual regularity, although their use is limited due to adverse effects (58). In cases of severe obesity, bariatric surgery might be beneficial as it can significantly reduce weight and resolve metabolic disorders (39).

Managing hyperandrogenism in PCOS involves the use of medications that reduce androgen production or block androgen receptors. Combined oral contraceptives (COCs) are the first-line treatment for hyperandrogenism, effectively reducing hirsutism and acne by suppressing ovarian androgen production (59). Antiandrogens, such as spironolactone, flutamide, and cyproterone acetate, can be added to COCs for additional reduction in hirsutism (60). These medications act by blocking androgen receptors or inhibiting androgen production. In cases where COCs and antiandrogens are contraindicated or not tolerated, alternative treatments like finasteride, an inhibitor of 5-alpha-reductase, can be considered. Combining these treatments with insulin sensitizers like metformin may enhance metabolic benefits. In some cases, cosmetic procedures such as laser therapy may be employed to manage hirsutism (61).

The reproductive phenotype of PCOS is managed with the aim of inducing ovulation and achieving pregnancy. Clomiphene citrate (CC) remains the first-line pharmacological treatment for ovulation induction, with a success rate of approximately 80% for inducing ovulation and a 50% live birth rate (62). For women who are resistant to CC, letrozole, an aromatase inhibitor, has been shown to be more effective in inducing ovulation (63). Gonadotropins are used as a second-line treatment in women who do not respond to oral agents, but they require careful monitoring to reduce the risk of ovarian hyperstimulation syndrome (OHSS) (64). For women with PCOS undergoing assisted reproductive techniques (ART), lifestyle modifications

to achieve weight loss are recommended before starting treatment to improve outcomes (65).

CONCLUSION

PCOS can result in numerous health disorders in women and may present with a wide spectrum of symptoms and complications. These often appear at menarche, last throughout the reproductive period of life and continue into menopause. The continuous and persistent treatment of this syndrome is of major importance in those affected, not only for the sake of the reproductive health and fertility of these women, but also for their overall health and HRQoL improvement.

Author contributions

Conceptualization: RS and DM; Data acquisition: JZ, MOP, LR, and LN; Data interpretation and analysis: all authors; Preparing the draft of the manuscript: RS, JZ and LN; Revising and editing of the manuscript RS, DM, JBM and SO. Approval of the submitted manuscript version: all authors.

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KLINIČKE MANIFESTACIJE SINDROMA POLICISTIČNIH JAJNIKA

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Sažetak

Sindrom policističnih jajnika, odnosno PCOS, kao najčešće endokrino oboljenje kod žena u reproduktivnom periodu predstavlja kompleksno oboljenje koje se karakteriše različitim hormonskim poremećajima i brojnim varijacijama u kliničkoj slici. Dijagnoza i lečenje PCOS-a otežani su izrazito varijabilnom kliničkom slikom i nedovoljno poznatom etiologijom i patogenezom ovog poremećaja. Primarni klinički znaci PCOS-a obuhvataju hiperandrogenizam, ovulatornu disfunkciju i policističnu morfologiju jajnika, iako sva tri ne moraju biti prisutna kod svih pacijentkinja sa PCOS.

Hiperandrogenizam, koji se manifestuje kao hirzutizam, akne ili androgena alopecija, značajno utiče kako na fizičko, tako i na psihičko stanje ovih pacijentkinja. Ovulatorna disfunkcija, koja se manifestuje iregularnim menstruacionim ciklusima kao posledica oligo/anovulacije, predstavlja značajan element kliničke prezentacije PCOS-a i uzrokuje infertilitet koji se sreće kod pojedinih pacjentkinja. Takođe, insulinska rezistencija koja je karakteristična za PCOS dovodi do hiperinsulinemije i metaboličkih poremećaja koji se sreću kod ovih pacijentkinja. Posledično, žene sa PCOS imaju povećan rizik od gojaznosti, displipidemije, dijabetesa, i kardiovaskularnih bolesti, naročito u kasnijoj životnoj dobi. Učestalost poremećaja raspoloženja, pre svega depresije i anksioznosti takođe je značajno povećana u ovoj populaciji.

Kompleksnost sindroma otežava brigu o pacijentkinjama, a njegova hronična priroda ističe potrebu za proaktivnim pristupom lečenju i pažljivom procenom svih elemenata oboljenja.

Ključne reči: PCOS, insulinska rezistencija, hiperandrogenizam, PCOM

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REVIEW ARTICLE

Diagnostic histopathological tools in Hirschsprung disease and related disorders in childhood

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Summary

Diagnosing Hirschsprung disease (HD) and related disorders can be complex and demands a deep understanding of the mechanisms governing intestinal motility, which involves the enteric nervous system (ENS), interstitial cells of Cajal (ICCs), and the muscle layers of the intestine. The London classification identifies three groups of gastrointestinal neuromuscular disorders: neuropathies, myopathies, and ICC abnormalities. Hirschsprung disease, characterized by the absence of ganglion cells, is the most common intestinal neuropathy and it results from the impaired migration of neural crest cells during development. It affects about 1 in 5,000 live births and involves several genetic factors, notably the RET gene. HD typically affects the rectum and a part of the colon, with varying extents of aganglionosis. The diagnosis is based on the histopathological analysis of suction biopsies, the absence of ganglion cells, and the presence of thick submucosal nerves on a standard hematoxylin and eosin stain, supplemented by enzyme histochemistry (acetylcholinesterase method) or immunohistochemical methods (calretinin and other antibodies) staining. The treatment for HD involves surgical resection of affected bowel segments. Accurate intraoperative assessment of tissue margins is critical to preventing postoperative complications related to pseudoobstruction. Communication between surgeons and pathologists is essential to ensure successful treatment outcomes.

Other intestinal neuropathies include intestinal hypoganglionosis, hyperganglionosis, delayed maturation of ganglion cells, and gliopathies. Enteric myopathies are exceptionally rare conditions, with typical morphological changes such as atrophy of the muscularis propria, intracellular vacuolization of smooth muscle cells, and interstitial fibrosis. Disruption in ICC network and arrangement forms the morphological basis of slow transit constipation. Each of aforementioned disorders has unique characteristics and diagnostic challenges. Understanding and diagnosing these conditions often require a combination of histological, histochemical, immunohistochemical, and sometimes genetic analyses. The integration of these techniques is vital for accurate diagnosis and effective treatment planning.

In summary, the complexity of intestinal dysmotility disorders necessitates a thorough understanding of intestinal motility mechanisms and the utilization of advanced diagnostic methods to provide accurate diagnoses and effective treatments.

Key words: Hirschsprung disease, intestinal dysmotility, biopsy, immunohistochemical staining

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INTESTINAL DYSMOTILITY - INTRODUCTION

Diagnosis of Hirschsprung disease (HD) and allied disorders is often challenging. Accurate diagnosis requires comprehensive knowledge of all components involved in regulating intestinal motility, such as the enteric nervous system (ENS), network of interstitial cells of Cajal (ICCs), and the integrity and functionality of the muscular layers.

ENS is a part of autonomic nervous system, built from distinct types of cells which form a complex network (1). Its cells are derived from precursor cells of the vagal and sacral part of the neural crest. During embryonal development, these cells migrate along the primitive gut in the opposite directions, proliferate and differentiate into various cell types such as neurons, glial cells, and Schwann cells (2). Although precursor multipotent cells originate from two different segments of the neural crest, these two groups of cells give identical types of neurons and glial cells in the ENS. There are many different regulatory signaling pathways involved in ENS development where the RET (Rearranged during Transfection)/GDNF (Glial Derived Neurotrophic Factor) signaling pathway is detected as the most important and most studied. Recognition of a large number of signaling pathways involved in the ENS development and linked genetic and epigenetic factors has been important for better understanding of ENS developmental disorders, such as Hirschsprung disease and related disorders (3).

Two main parts of ENS are myenteric nervous plexus (MP) and submucosal nervous plexus (SP). MP is related to intestinal motility, while SP is important for regulation of blood supply and transepithelial ion transfer and has a minor role in the intestinal motility.

ICCs produce slow waves responsible for intestinal contraction (4). These cells are gracile, and immunohistochemistry is necessary for their detection and evaluation in daily practice. The most commonly used antibodies for this propose purpose are c-kit (CD117) and DOG1. A reduced number of ICCs is the main characteristic of some cases of chronic constipation and chronic intestinal pseudoobstruction (4, 5). Damage to ICCs or the disruption of c-kit immunohistochemical expression can be associated with other conditions. It has been observed in some cases of transient hypomotility following adequate HD surgery or in certain inflammatory conditions (6,7).

GASTROINTESTINAL NEUROMUSCULAR DISORDERS OF CHILDHOOD

According to the London classification of gastrointestinal neuromuscular disorders, three main groups of disorders are recognized: neuropathies, myopathies, and ICCs abnormalities (8). However, Kapur classified gastrointestinal neuromuscular disorders of childhood into five categories: enteric neuropathies, enteric myopathies, combined neuromuscular disorders, colonic desmosis and idiopathic disorders. In the group of enteric neuropathies five distinct disorders were recognized such as HD, hypoganglionosis, hyperganglionosis, delayed maturation of ganglion cells (DMGC) and gliopathies (9).

HIRSCHSPRUNG DISEASE

HD is bowel aganglionosis, which is a consequence of disrupted migration of pluripotent neural crest cells during the embryonal period, as previously mentioned. It is the most frequently diagnosed intestinal neuropathy (9,10). HD occurs in 1:5000 live births, with significant ethnic deviation (11). More than 11 genes can be involved in HD pathogenesis (12). The vast majority of HD patients have mutation of proto-oncogene RET (in about one-third of sporadic cases and a half of familial cases) (13). However, more than 100 different mutations of RET gene have been identified. HD can be sporadic, syndromic HD (within various syndromes such as Down syndrome, Waardenburg syndrome and others) and also, can be associated with other non-syndromic anomalies of heart, gastrointestinal tract, central nervous system, or genitourinary tract (11,12, 14).

Aganglionosis mainly affects the rectum and varying lengths of the large intestine, continuously. The most common HD type is short segment disease with rectum and sigmoid colon affection (80% HD). Less frequent HD forms are ultrashort HD (length of aganglionosis up to 3 cm), long segment disease (aganglionosis affects segment proximal to sigmoid colon or lienal flexure), total colonic aganglionosis (the absence of ganglion cells throughout the entire colon) and total intestinal aganglionosis (affected colon and terminal ileum). Male predominance (4:1) is characteristic of short HD segment, while long segment disease is equally present in both genders (11). For HD diagnosis, morphological findings are particularly important. Apart from the absence of ganglion cells, an important finding in affected bowel segment is overgrowth of extrinsic parasympathetic nerves. These nerves continually release acetylcholine, and this is associated with consequential smooth muscle contraction and pseudoobstruction. Elevated expression of actin alpha 2 of intestinal smooth muscle in the aganglionic segment leads to hyperactive contraction that also worsen pseudoobstruction (15). The number of more than two thick nerve bundles per high microscopic magnification is significant for HD diagnosis. Submucosal nerve bundles are typically thicker than 40 μm in diameter (16,17) **(Figure 1A)**. The funnel shaped segment (common lengths 1 to 3 cm) interposed between aganglionic and normoganglionic zone (NZ) is called transitional zone (TZ). Hypoganglionosis of MP and submucosal hypertrophic nerves are essential of TZ, while SP in TZ varies from agangli-

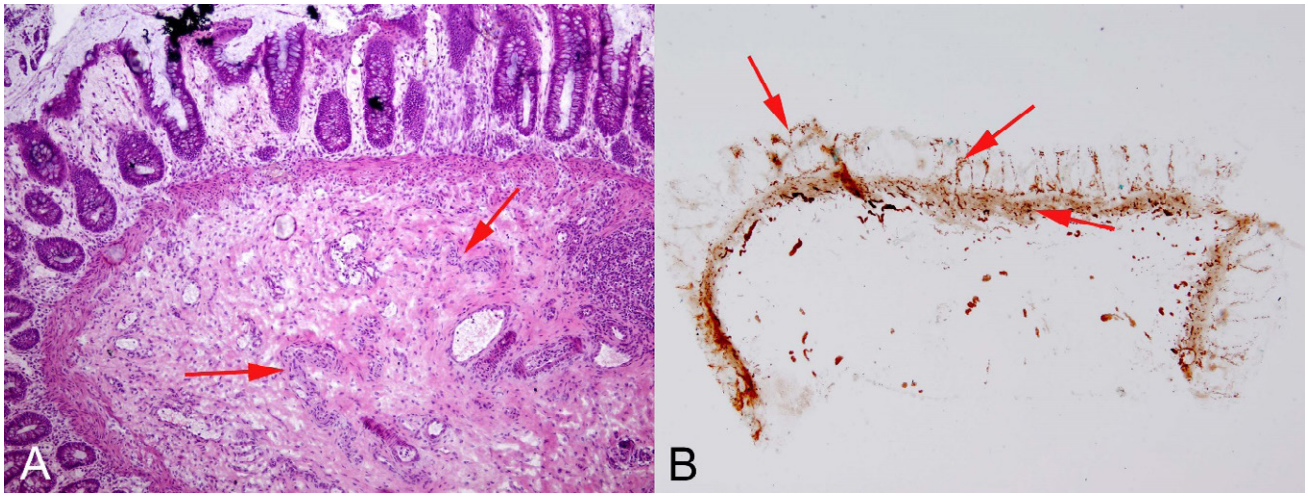

Figure 1. Typical morphology of HD: the absence of ganglion cells and thick nerves (arrows) in the rectal submucosa (A; H&E staining, 100x) and acetylcholine positive nerve fibers within mucosa and lamina muscularis mucosae (arrows) (B; AchE, 40x).

onic to hyperganglionic (12,18). Ectopic ganglia and abnormal "hybrid ganglia" with characteristics of extrinsic nerves could also be found within the transitional zone (19). On the other hand, in the long segment HD or total colonic/intestinal aganglionosis, nerve fibers are not prominent, and interstitial zone between two muscular layers may be inconspicuous, with close contact between the circular and longitudinal muscle layers (8,11,16). Multiple biopsies from different levels are necessary for the differentiation of long segment HD and total colonic/intestinal aganglionosis (21).

The gold standard in HD diagnosis involves histological analysis of suction biopsy samples containing mucosa and submucosa, or full-thickness biopsies of the rectum in children over 1 year old (8,12,20,22). Accurate diagnosis requires biopsy samples taken 2 to 3 cm above the dentate line to avoid the zone of physiological SP hypo- or aganglionosis (8,20). Suction biopsies should be taken from at least two sites in the rectum (23). HD diagnosis relies on detecting the absence of ganglion cells in serial hematoxylin and eosin stained (H&E) sections and/or visualizing hypertrophic and hyperplastic nerve fibers in serial frozen sections stained with acetylcholinesterase (AChE) technique **(Figure 1B)**. The AChE method is highly sensitive and requires meticulous section preparation (fresh tissue, proper orientation, serial cryostat sections, and always fresh substrate), as well as skilled pathologist interpretation (12). To mitigate these challenges, immunohistochemical staining methods are increasingly used for ganglion cell and nerve fibers detection in practice. Commonly applied antibodies in HD diagnostics include calretinin, S100, Glut-1, MAP-2, peripherin, synaptophysin, and PGP 9.5 (23,24) **(Figure 2A,B)**. Calretinin is most frequently utilized for its ability to detect ganglion cells and intrinsic nerve fibers in the mucosal lamina propria, enabling diagnostics even in superficial suction biopsies and when analysis is performed by unexperienced pathologist (25-28). The absence of calretinin immunostaining is a crucial feature for HD diagnosis (25,29).

Definitive therapy for HD involves surgical resection. There are several surgical techniques with different outcomes (30). The choice of surgical treatment is

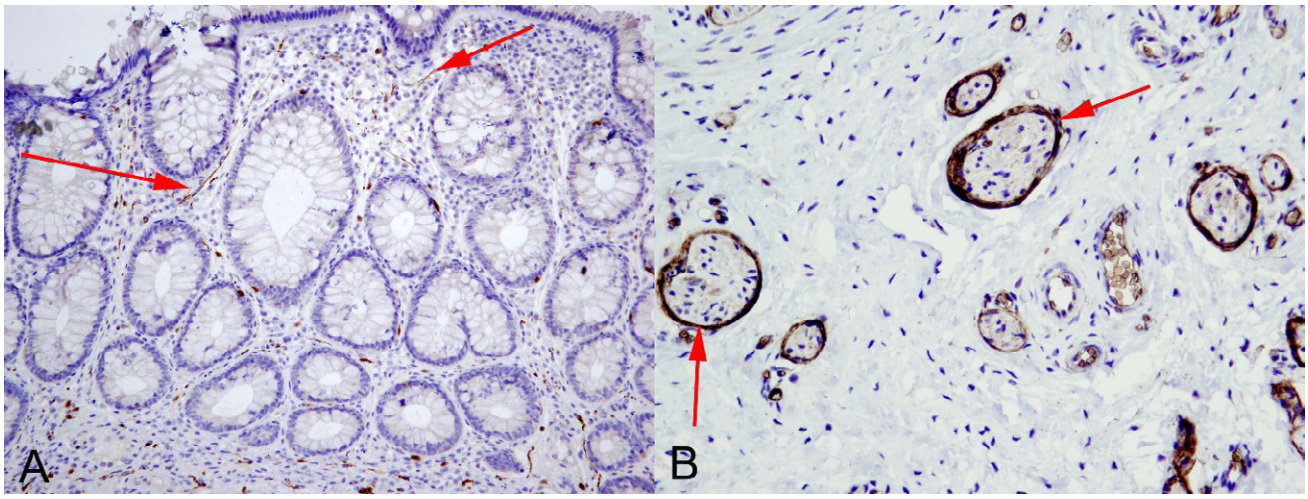

Figure 2. Immunohistochemical staining in HD diagnostics: calretinin positive intrinsic nerve fibers (arrows) in normoganglionic rectal mucosa (A; 200x) and Glut-1 positive perineurium of extrinsic nerves in HD (B; 200x)

conditioned by the length of affected bowel and general condition of the patient. The decision on the extent of bowel resection is based on intraoperative analysis of seromuscular or full-thickness biopsies. The presence of a TZ at the proximal surgical margin often leads to persistent pseudoobstruction, necessitating reoperation (18,23,31,32) or sometimes could be solved by botulinum toxin injections or some kinds of physiotherapy (33). To prevent retention of the TZ, it is recommended to resect at least 5 cm of ganglionic bowel and conduct frozen section examination of the entire proximal resection margin (23). Adopting a standardized and algorithmic approach can reduce anxiety and minimize diagnostic errors (29,31,32). Also, effective communication between the surgeon and the pathologist is crucial. When faced with diagnostic uncertainty, requesting additional tissue is a reasonable next step to ensure accurate diagnosis (31). Transplantation of human enteric nervous progenitor cells is a new approach in HD treatment that will probably play a significant role in the future (34). Pan et al. found that even Schwann cells from aganglionic bowel segment could be a potential autologous source of progenitor cells for regenerative therapy (35).

INTESTINAL HYPOGANGLIONOSIS

Isolated intestinal hypoganglionosis (IIH) is a rare condition (36). The conventional cutoff value for IIH in adults is <1 ganglion per 10 mm of bowel length, with an average of two ganglion cells or less per ganglion (37). Official criteria for pediatric cases are not established due to significant variability in the number of ganglion cells based on the age (37-39). According to Gastro International Working Group 2009, quantitative studies should be conducted by reference laboratories using their own control ranges, collected by the same observer using a standardized method (20,37). Typically, a full-thickness intestinal biopsy is necessary for diagnosis since the disorder predominantly affects the myenteric plexus in many cases. Immunohistochemistry with pan-neuronal markers can confirm hypoganglionosis. Reduced staining for calretinin and NeuN indicates a specific deficiency of intrinsic primary afferent neurons in this disorder (40).

HYPERGANGLIONOSIS

Hyperganglionosis includes diffuse intestinal ganglioneuromatosis and intestinal neuronal dysplasia (IND). Diffuse intestinal ganglioneuromatosis is a hamartomatous lesion of the ENS found in syndromes like multiple endocrine neoplasia type 2B or neurofibromatosis (8,9). In IND type A, there is an absence or significant hypoplasia of intestinal adrenergic nerves from extrinsic ganglia. In contrast, IND type B is characterized by an increased density of "giant" ganglia in the submucosal plexus, which contain at least eight ganglion cells (9,11,41).

DELAYED MATURATION OF GANGLION CELLS (DMGC)

DMGC is identified as the primary cause of constipation in infants during their first year of life. It is crucial that the maturation process of ganglion cells completes by the end of the fourth year of life to ensure proper gastrointestinal function and alleviate potential complications associated with delayed development during this critical period (36). The presence of immature ganglion cells in the ENS after the age of 4 is always a pathological finding, often associated with other ENS abnormalities (9).

GLIOPATHIES

Glial cells are crucial components of ENS ganglia. Traditionally, they were considered to have a supportive role within ganglia. Recent studies have highlighted their significant roles in maintaining ganglion cell homeostasis and neurotransmission. Moreover, they play an important role in intestinal inflammation, particularly in inflammatory bowel disease (IBD), where glial cells act as antigen-presenting cells (42). The Glial Cell Index (GCI) represents the ratio of glial cells to ganglion cells (37,43). Hoff et al. have identified GCI as a robust quantitative measure of the submucosal plexus (SP) and myenteric plexus (MP) within a species (43). Significant alterations in glial cell numbers and GCI have been observed in conditions like diverticular disease and IBD (44). Morphological abnormalities were noticed in aganglionic segment, TZ in HD and even in dilated proximal NZ segment of the bowel (45). Additionally, GCI could serve as a useful marker for TZ in HD (46). S100 and GFAP antibodies are commonly used for the identification of glial cells (43,44).

ENTERIC MYOPATHIES

Enteric myopathies are exceptionally rare conditions. For thorough histopathological evaluation, Masson-trichrome staining, Picrosirius red staining, and periodic acid-Schiff staining (PAS) are recommended. Typical morphological changes include atrophy of the muscularis propria, primarily affecting the longitudinal muscular layer, intracellular vacuolization of smooth muscle cells, and interstitial fibrosis. However, additional specific analyses are advised. Immunohistochemical staining for α-smooth muscle actin (α-SMA) is highly recommended. The loss of α-SMA expression in the circular muscular layer is observed in some cases of intestinal myopathies

(47). Aberrant α-SMA expression may also occur due to abnormalities of intracellular filaments (47). The use of an electron microscope can facilitate establishing the diagnosis **(Figure 3)** (48). Ultrastructural analysis is crucial and typically reveals myofilament degeneration, intracellular vacuolization, irregularity of membranes, variable cytoplasmic density, and increased interstitial collagen deposition (49-51). Morphological evaluation alone is insufficient for a definitive diagnosis, and genetic analyses are often recommended (49).

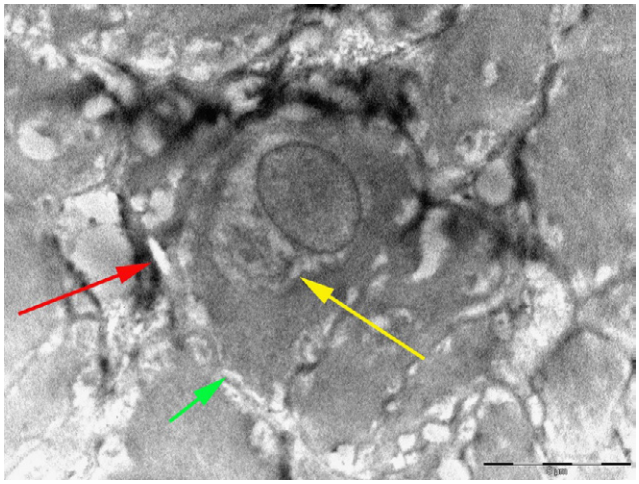

Figure 3. Ultrastructure of smooth muscle cell in visceral myopathy: perinuclear vacuoles (yellow arrow), subsarcolemmal vacuola (green arrow), collagen deposition (red arrow) (4000x).

DISORDERS OF INTERSTITIAL CELLS OF CAJAL (ICC)

ICC, identified by CD117 and DOG-1 immunopositivity, are located around MP ganglia where their density is highest, within the circular and longitudinal muscular layers, deep submucosa, and around submucosal ganglia. Disruption in ICC number and arrangement forms the morphological basis of slow transit constipation. Studies on ICC involvement in HD show conflicting results: while most authors indicate reduced ICC numbers exclusively in affected segments (52), some authors propose that lower ICC counts in the NZ of HD are linked to postsurgical complications, notably constipation (7,53,54). Decresed number of ICC is also described in cases of hypoganglionosis (55).

CONCLUSION

The diagnosis of intestinal dysmotility, particularly conditions like HD and related disorders, require a comprehensive approach integrating knowledge of all components involved in intestinal motility. Key diagnostic methods such as suction and full-thickness intestinal biopsy, along with immunohistochemical analyses, play pivotal roles in modern diagnostics of these conditions. The complexity of these disorders also requires standardization of diagnostic protocols and well-trained pathologists to ensure diagnostic precision, reduce errors, and facilitate accurate treatment for patients. Advances in understanding genetic and molecular mechanisms further enhance precise diagnosis and management of these challenging disorders.

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HISTOPATOLOŠKI ALATI U DIJAGNOZI HIRŠPRUNGOVE BOLESTI I SRODNIH OBOLJENJA

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Sažetak

Dijagnostika Hiršprungove bolesti (HB) i srodnih poremećaja može biti složena i zahteva dobro poznavanje mehanizama koji regulišu crevni motilitet, kao što su enterički nervni sistem (ENS), intersticijske Kahalove ćelije (IKĆ) i mišićni omotač creva. Londonska klasifikacija identifikuje tri grupe gastrointestinalnih neuromuskularnih poremećaja: neuropatije, miopatije i abnormalnosti IKĆ. Hiršprungova bolest koju odlikuje odsustvo ganglijskih ćelija, je najčešća crevna neuropatija i rezultat je poremećene migracije ćelija nervnog grebena tokom razvoja. Pogađa oko 1 od 5 000 živorođene dece i uključuje više gena, među kojima je najznačajniji *RET* gen. HB obično pogađa rektum i deo kolona, sa različitim stepenima aganglionoze. Dijagnoza se zasniva na histopatološkoj analizi sukcionih biopsija - odsustvu ganglijskih ćelija i prisustvu debelih submukoznih nerava na standardnom hematoksilin i eozin bojenom preparatu, dopunjenom enzimohistohemijskim bojenjem (metoda acetilholinesteraze) ili imunohistohemijskim (kalretinin i druga antitela) bojenjem. Lečenje HB podrazumeva hirurško resekciju aganglionarnog segmenta creva. Tačna intraoperativna procena tkivnih margina je ključna za prevenciju postoperativnih komplikacija uslovljenih pseudoobstrukcijom. Komunikacija između hirurga i patologa je od suštinskog značaja za postizanje uspešnog terapijskog ishoda.

Ostale crevne neuropatije uključuju intestinalnu hipoganglionozu, hiperganglionozu, odloženo sazrevanje ganglijskih ćelija i gliopatije. Intestinalne miopatije su izuzetno retka stanja, sa tipičnim morfološkim promenama kao što su atrofija mišićnog omotača creva, intracelularna vakuolizacija glatkih mišićnih ćelija i intersticijalna fibroza. Poremećaj u mreži i rasporedu IKĆ čini morfološku osnovu za konstipaciju sporog prolaza. Svaki od pomenutih poremećaja ima jedinstvene karakteristike i dijagnostičke izazove. Dijagnostikovanje ovih stanja često zahteva kombinaciju histoloških, histohemijskih, imunohistohemijskih i ponekad genetskih analiza. Integracija ovih metoda je od vitalnog značaja za tačnu dijagnozu i efikasno planiranje lečenja.

Ukratko, složenost poremećaja crevnog dismotiliteta zahteva detaljno razumevanje crevnog motiliteta i korišćenje naprednih dijagnostičkih metoda kako bi se pružile tačne dijagnoze i efikasni tretmani.

Ključne reči: Hiršprungova bolest, crevni dismotilitet, biopsija, imunohistohemijsko bojenje

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REVIEW ARTICLE

Pharmacological management of postoperative pain

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Summary

Postoperative pain is a widespread and underestimated problem both in Serbia and globally. Numerous studies conducted in countries with advanced healthcare systems have shown that even in the 21st century, postoperative pain is not adequately managed. More than 80% of patients undergoing surgical procedures experience acute postoperative pain, with 75% describing it as moderate, severe, or extreme. Postoperative recovery depends on patient characteristics and factors that facilitate postoperative recovery, including the presence or absence of postoperative complications. The pharmacology of postoperative pain targets pathophysiological mechanisms such as nociception, peripheral sensitization, ectopic activity, and central sensitization. Modern pharmacological management of postoperative pain involves balanced multimodal analgesia. The principle of multimodal analgesia is based on the multifactorial nature and complexity of pain transmission pathways and is defined as the use of various medications or techniques with different mechanisms of action on the peripheral or central nervous system, which can have additive or synergistic effects. Several drug groups are involved in the multimodal approach, each with a specific pathophysiological mechanism of action. The effectiveness of opioid analgesics in treating moderate to severe postoperative pain is achieved due to the lack of a ceiling effect. However, increasing dosage leads to increased side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors (COX-2), and systemic steroids reduce the inflammatory component of surgical pain. Systemic and local anesthetics reduce the release of inflammatory mediators, interleukin-(IL-6, IL-1β, and IL-1 receptor antagonist (-1RA)). Gabapentinoids bind to the α-2-δ-1 subunit of voltage-gated Ca^{2+} channels in the central nervous system (CNS), reducing the release of key excitatory neurotransmitters involved in nociception. α-2-agonists, such as clonidine and dexmedetomidine, modulate pain impulse transmission by activating the spinal cord's presynaptic and postsynaptic α2 receptors. Local anesthetics (e.g. lidocaine) block neural transmission by inhibiting voltage-gated Na^{+} channels, thus preventing the transmission of pain stimuli from the periphery to the central nervous system. N-methyl-D-aspartate receptor (NMDA receptor) antagonists, ketamine and magnesium, reduce central sensitization mechanisms.

Keywords: postoperative pain, pharmacological management, drugs

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INTRODUCTION

Pain, respiration, temperature, pulse, and blood pressure are the five essential vital signs. Pain is the most common symptom in clinical practice leading patients to seek medical attention. In patients suffering from prolonged intense pain, there is a reduced ability to function normally and a decrease in work capacity (1).

Postoperative pain remains a widespread and still underestimated problem both in Serbia and globally. Numerous studies conducted in countries with developed healthcare systems have shown that even in the 21st century, postoperative pain is not adequately managed despite advancements in pain therapy. After surgical intervention, a significant number of patients experience moderate to severe postoperative pain (2, 3). More than 80% of patients undergoing surgical procedures experience acute postoperative pain, with 75% of these patients describing the pain as moderate, severe, or extreme (4). Approximately 30-40% of patients experience inadequately managed postoperative pain. There are differences in pain perception among different populations due to varying genetics, social, and cultural factors.

Postoperative pain is a specific entity. Although inflammation and nerve tissue damage occur, the pathophysiology of postoperative pain is unique, and its consequences are specific. Both acute and inadequately managed postoperative pain are not only unpleasant experiences but also trigger a stress response, increasing the risk of complications alongside the surgical trauma (5). These processes initiate a cascade of endocrine, immune, and inflammatory responses, and the body experiences increased stress hormone levels, enhanced catabolism, tachycardia, increased myocardial consumption, increased cardiac volume, a tendency towards thromboembolism, vasoconstriction, and reduced gastrointestinal tract mobility. The result of these changes is increased morbidity and mortality (6). Uncontrolled pain can lead to postoperative cognitive dysfunction and may also result in the development of chronic pain. Adequate management of postoperative pain can lead to faster recovery, better outcomes, and shorter hospital stays (7).

PATHOPHYSIOLOGY OF POSTOPERATIVE PAIN

Postoperative recovery depends on patient characteristics and factors that facilitate recovery, including the presence or absence of complications after surgery. At the site of surgical intervention, there is significant tissue trauma, leading to the release of numerous inflammatory mediators: potassium, hydrogen ions, adenosine, prostanoids, bradykinin (BK), histamine (5-HT), nerve growth factors (NGF), cytokines, and chemokines. These inflammatory mediators affect the function of nociceptors (pain receptors) around the trauma (8). Nerves transmit impulses to the dorsal horns of the spinal cord, the first site where these stimuli are processed sensorily from the periphery. Information about the stimulus is then relayed to higher centers in the CNS, where pain acquires a "conscious" component.

Peripheral nerve damage leads to sensitization, characterized by spontaneous nerve activity, a lowered activation threshold for nociceptors, and increased response to stimuli. Nerve damage itself leads to an increased frequency of nociceptor impulse firing, and consequently, an increase in pain intensity (7, 8). Pain manifests at the peripheral level due to a reduced nociceptor threshold and at the central level by heightened excitation of spinal neurons responsible for transmitting pain signals (6-8).

Peripheral sensitization occurs due to nociceptor activation by various stimuli and is characterized by an amplification of signals in peripheral nociceptive neurons. There is a lowered threshold and heightened response of nociceptive neurons at the periphery. Clinically, peripheral sensitization manifests as hyperalgesia and allodynia. Hyperalgesia is a phenomenon characterized by increased sensitivity to pain. This condition occurs after injury and can become a chronic disorder. Allodynia is the experience of pain, usually on the skin, caused by a stimulus that would not normally provoke pain (9).

The increased influx of pain impulses from the periphery to the spinal cord dorsal horns leads to central neuron sensitization. This process amplifies signals in central nociceptive neurons within the spinal cord dorsal horns. The activation of NMDA receptors underlies the phenomenon of central sensitization. After surgical intervention, there is an increased response to normal mechanical stimuli (allodynia) and the development of a zone of secondary hyperalgesia in the tissue around the surgery site. In addition to contributing to acute pain (such as secondary hyperalgesia and wind-up phenomena), central sensitization in response to trauma or surgery can result in pathological chronic pain conditions (10). α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the spinal cord contribute to pain and hyperalgesia following surgery. Other molecules involved in central sensitization after surgery include extracellular signal-regulated kinases (ERK), brain-derived neurotrophic factor (BDNF), tumor necrosis factor-alpha (TNF-α), mitogen-activated protein kinases (MAPKs), monoamine oxidase B (MAO-B), toll-like receptors (TLR), and cyclooxygenase-2 (COX-2) (11). Spinal inhibitory mechanisms can prevent central sensitization after surgery of spinal α-adrenergic receptor, gamma-aminobutyric acid (GABA) receptor activity. Opioids modulate central sensitization in a complex manner (12).

Descending inhibitory pathways also play an important role at the level of the spinal cord, modulating the transmission of pain impulses. The principle of modulation refers to the mechanism by which pain suppression occurs at the dorsal horns of the spinal cord and at high-

er levels in the nervous system. Endogenous substances such as enkephalins (ENK), norepinephrine (NE), and GABA activate opioid, α-adrenergic, and other receptors that inhibit the release of glutamate from primary afferent nociceptors, blocking the postsynaptic response of second-order neurons. All these pathophysiological mechanisms can be targets for a multimodal approach to minimize the impact of biological processes associated with pain (13).

The pharmacology of postoperative pain is directed towards pathophysiological mechanisms such as nociception, peripheral sensitization, ectopic activity, central sensitization, reduced inhibition, and others.

MEASUREMENT OF POSTOPERATIVE PAIN

In clinical practice, for the simple assessment of acute pain intensity in conscious and verbally communicative patients, unidimensional scales and questionnaires are used. Commonly used scales for assessing postoperative pain are the numeric scale, the verbal scale, the visual-analog scale, and the facial expression scale, which is suitable for children and individuals with limited communication (Wong-Baker faces pain rating scale).

Unidimensional scales are based on self-assessment of pain. They are simple, effective, and minimally burdensome for the respondent (14), and are as follows:

- Numeric rating scale (NRS). This scale consists of ten intervals marked with Arabic numerals from 0 to 10: 0 means no pain; 1-3 indicates mild pain (slightly affects daily activities); 4-6 represents moderate pain (significantly affects daily activities); and 7-10 denotes severe pain (prevents daily activities) **(Figure 1a)**. The therapeutic goal is to achieve values between 0 and 4.
- Verbal rating scales (VRS). These scales allow the patient to describe the intensity of pain using visual and verbal descriptors. Commonly used categories include: no pain, mild pain, moderate pain, and severe pain **(Figure 1b)**.
- Visual analog scale (VAS).VAS is one of the most frequently used tools for measuring pain **(Figure 1c)**. It consists of a 10 cm line, one end labeled "no pain", and the other labeled "the worst possible pain" indicating maximum pain. The patient is asked to mark a point on the line that corresponds to their subjective pain intensity by drawing a vertical line.
- Facial expression scale (Wong-Baker faces pain rating scale). This scale is used for children and individuals with limited verbal communication abilities. It features a series of facial expressions arranged in a gradation of pain intensity. Each facial expression corresponds to a numerical value, allowing the patient to indicate their pain level by selecting the face that best represents their experience **(Figure 1d)** (16).

MULTIDIMENSIONAL PAIN ASSESSMENT

Multidimensional pain assessment involves using a variety of instruments to capture different aspects of pain as follows:

- Brief pain inventory. This questionnaire examines pain and the subjective impact of pain on daily life activities and functional ability (17).
- McGill pain questionnaire. This tool allows for the ranking of multiple dimensions of the subjective pain experience, including sensory, affective, and evaluative aspects (18).
- Neuropathic pain scale. This scale assesses eight qualities of neuropathic pain (sharp, dull, burning, cold,

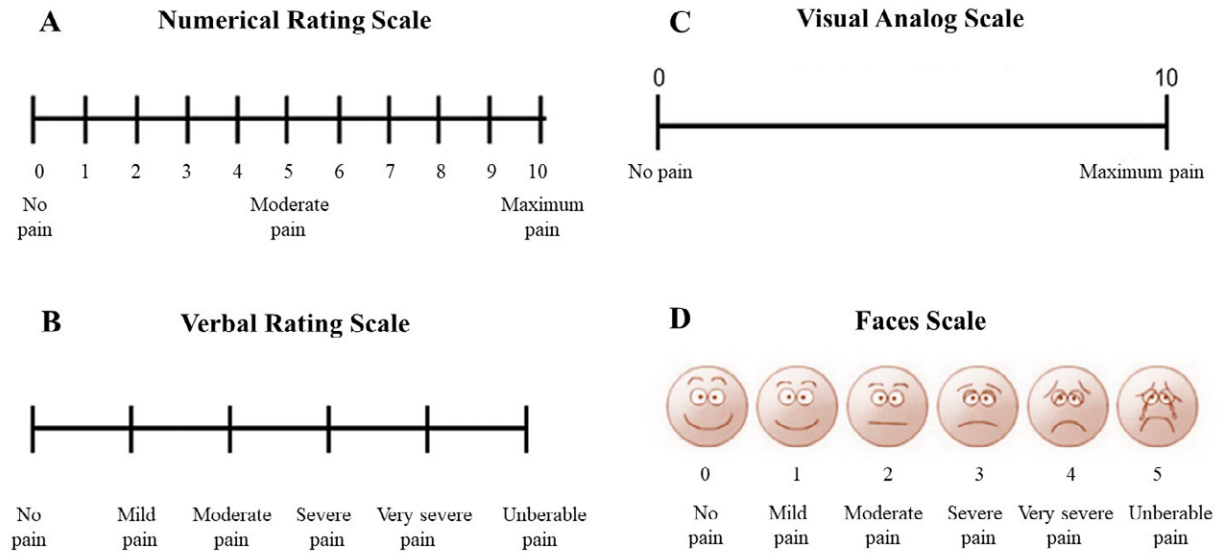

Figure 1. Unidimensional scales for measurement of postoperative pain

sensitive, itchy, deep, superficial) and grades each quality with values ranging from 0 to 10 (19, 20, 21, 22).

MULTIMODAL ANALGESIA

Postoperative analgesia aims to reduce pain intensity and improve functional activity. Modern pharmacological treatment of postoperative pain involves balanced multimodal analgesia. The principle of multimodal analgesia is based on the multifactorial nature and complexity of pain pathways. It is defined as the use of various medications or techniques with different mechanisms of action on the peripheral or central nervous system, which can have additive or synergistic effects (23). The goal of balanced analgesia is to optimize pain relief while minimizing side effects. The choice of analgesics should be tailored to the surgical procedure, as the effectiveness of different analgesics varies with different types of surgery. Multimodal analgesia encompasses both systemic drug administration and regional and neuroaxial techniques. Ideally, multimodal strategies should be initiated during the intraoperative period and continued postoperatively (23).

Opioid analgesics have long been used as a standard for treating postoperative pain (24). The efficacy of opioid analgesics for moderate to severe postoperative pain is due to the absence of a plateau effect. However, increasing the dose leads to increased side effects. Given the pathophysiology of postoperative pain, using only opioid analgesics is not justified. Systemic opioids block nociception through mu, delta, kappa receptors, and central and peripheral G receptors. They have side effects such as respiratory depression and postoperative ileus, which occur through mu-opioid receptors in the medulla oblongata and the gastrointestinal tract and can also cause nausea and vomiting through receptors in the chemoreceptor trigger zone. These side effects delay patient recovery by postponing gastrointestinal function recovery and early feeding (25). ERAS (enhanced recovery after surgery) protocols emphasize the key recommendation to avoid opioids and use a multimodal strategy (26). Multimodal analgesia also includes preventive analgesia, or administering medications to reduce pain before, during, and after surgery. Randomized studies have shown that multimodal analgesia is associated with better pain control and reduced opioid use compared to the use of a single drug (27, 28).

Several classes of medications are involved in the multimodal approach, each with a specific pathophysiological mechanism of action. Non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and systemic steroids reduce the inflammatory component of surgical pain. Systemic and local anesthetics reduce excessive release of inflammatory mediators (IL-6, IL-1β, and IL-1RA) by decreasing the upregulation of inflammatory cells. Gabapentinoids, by binding to the α-2-delta-1 subunit of voltage-gated Ca^{2+} channels in the CNS, reduce the release of key excitatory neurotransmitters involved in nociception and play a crucial role in neuropathic pain therapy. α-2 agonists, such as clonidine and dexmedetomidine, modulate pain impulse transmission in the spinal cord by activating presynaptic and postsynaptic α2 receptors. Local anesthetics (e.g., lidocaine) block neural transmission by inhibiting voltage-gated Na^{+} channels, thus preventing pain stimulus transmission from the periphery to the central nervous system. NMDA antagonists, such as ketamine and magnesium, reduce the mechanism of central sensitization (29-31).

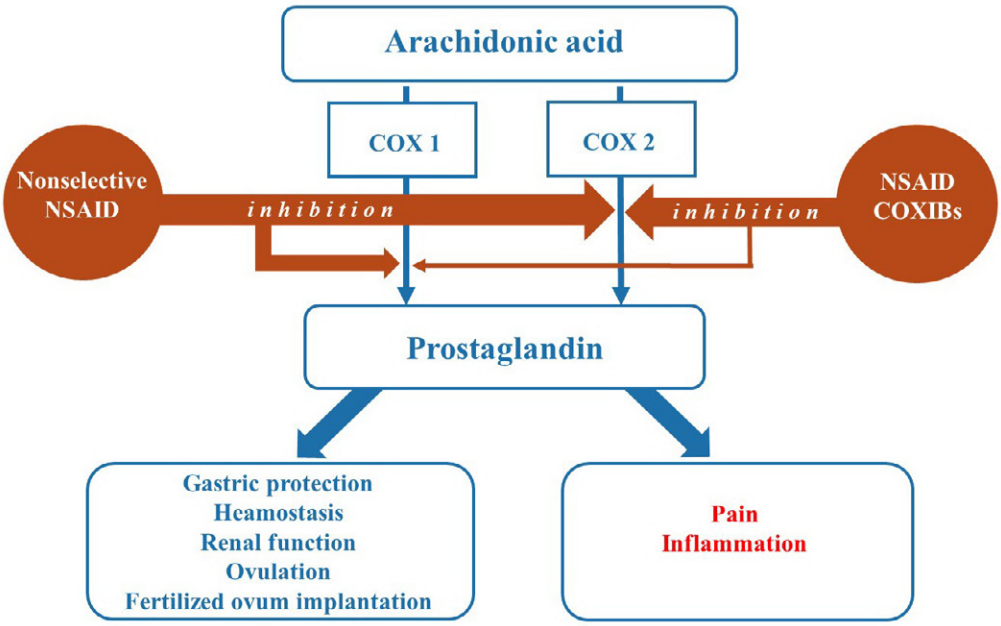

Figure 2. The mechanism of analgesic action of NSAIDs

NSAIDS

NSAIDs are medications used for the treatment of mild to moderate pain. They are not effective for the most severe pain. The mechanism of analgesic action of NSAIDs involves the inhibition of prostaglandin (PG) synthesis both peripherally and in the CNS (32) **(Figure 2)**. NSAIDs inhibit COX enzyme, which metabolizes arachidonic acid into PG and thromboxane (TXA2). There are two COX isozymes, COX-1 and COX-2 (33). NSAIDs can be non-selective inhibitors of both COX-1 and COX-2 or selective inhibitors of COX-2 (coxibs).

In addition to their primary mechanism of action through COX inhibition, non-opioid analgesics activate other mechanisms. They interact with endocannabinoids, NO, serotonergic, noradrenergic, and cholinergic systems (34). NSAIDs also affect ion channels (voltage-gated Na+ channels, voltage-gated L-type Ca2+ channels, voltage-gated and ligand-gated K+ channels, TRP ion channels, etc.), which can contribute to both their analgesic and adverse effects (35-37).

NSAIDs can have significant side effects on the gastrointestinal, cardiovascular systems, and kidneys. They may also prolong bleeding time and exacerbate bronchial asthma. Coxibs, a subset of NSAIDs, generally have fewer gastrointestinal side effects compared to non-selective COX inhibitors and do not inhibit platelet aggregation (32). Additionally, coxibs are considered safer for patients with aspirin-induced asthma. **Table 1** lists NSAIDs used orally for postoperative pain management.

Table 1. NSAIDs used orally for postoperative pain management.

Drug	Maximum dose	Dosing interval
Ibuprofen	2400 mg/24 h	4-6 h
Naproxen	1500 mg/24 h	6-8 h
Ketoprofen	300 mg/24 h	6-8 h
Indomethacin	200 mg/24 h	8-12h
Ketorolac	300 mg/24 h	6-8 h
Diclofenac	150 mg/24h	8-12h
Celecoxib	200 mg/24 h	24 h
Meloxicam	15 mg/24h	24h
Metamizole-sodium	4g/24h	6h

Legend: The most common NSAIDs with maximum doses and dosing interval used orally for postoperative pain management

PARACETAMOL

Paracetamol is an analgesic used for the treatment of mild to moderate pain. Its analgesic effect is primarily due to COX-1 and COX-2 inhibition both peripherally and centrally. Its analgesic effects are also mediated through activation of the descending pain modulation pathways, including serotonergic, endocannabinoid, and opioid systems (38). Central analgesic effects of paracetamol involve various mechanisms, particularly through the production of the bioactive metabolite AM404 in the central nervous system (CNS). AM404 significantly activates the TRPV1 receptor, which plays a crucial role in how neurons respond to pain within the brain and the dorsal horn. In the periaqueductal gray, AM404 triggers a signaling pathway that includes the TRPV1 channel, mGlu5 receptor, PLC, DAGL, and CB1 receptor (39). Paracetamol has weak anti-inflammatory properties.

Paracetamol does not cause serious adverse effects on the gastrointestinal tract or the cardiovascular system, it does not inhibit platelet aggregation and does not worsen bronchial asthma. The maximum recommended dose of paracetamol is 4 g per day for adults and 65 mg/kg daily for children. For elderly patients and individuals with existing liver function impairment, a daily dose exceeding 2 g is not recommended. Overdose of paracetamol can lead to severe liver damage. Toxic doses are 7.5-10 g per day for 1-2 days in adults, and 150 mg/kg in children (40). Antidotes for paracetamol poisoning include acetylcysteine and methionine. Prolonged use of high doses of paracetamol can also have toxic effects on the kidneys.

Paracetamol reduces the need for opioids after surgery. The use of morphine is decreased 24 h after surgery when opioids are used in combination with paracetamol. Randomized controlled trials (RCTs) have shown that 1 g of paracetamol is effective in managing postoperative pain when combined with 400 mg of ibuprofen, 60 mg of codeine, or 10 mg of oxycodone (41). When given prophylactically, intravenous paracetamol is associated with reduced postoperative nausea and vomiting (42). Paracetamol, when used in combination with other analgesics, can be part of a multimodal approach to postoperative pain management.

OPIOID ANALGESICS

Opioids are used for treating moderate to severe pain, both acute and chronic. When used appropriately for medical purposes, opioids are effective and safe medications. They are employed to manage acute severe pain, moderate to severe malignant pain, moderate to severe chronic organic pain, postoperative pain, and neuropathic pain. Opioids are used before, during, and after anesthesia and can be administered alone in high doses for cardiovascular surgeries. They work by inhibiting the excitation of nerve endings in the periphery, blocking pain transmission in the spinal cord's dorsal horn, and activating descending pain control pathways.

OPIOID MECHANISM OF ACTION

Opioids exert their analgesic effects by binding to specific receptors (mu, kappa, delta) in the CNS and peripheral tissues. Activation of opioid receptors inhibits presynaptic release and postsynaptic response to excitatory neurotransmitters like glutamate and substance P (32,

43). Additionally, opioids activate descending inhibitory pain pathways by inhibiting inhibitory (GABAergic) interneurons. In inflammatory pain, the activation of mu receptors inhibits the TRPV1 ion channel through G proteins and cAMP. Some opioids, such as fentanyl, tramadol, and buprenorphine, also block voltage-gated Na^+ channels (40). Opioids are highly effective as they act at multiple sites in the pain pathways (presynaptic and postsynaptic regions, various parts of the nervous system).

Opioids can be classified based on origin into natural, semisynthetic, and synthetic types. They are also categorized by potency into strong and weak opioids, and by action into agonists, partial agonists, and antagonists. Additionally, they can be classified based on action speed into fast and slow-acting opioids (44). Commonly used opioids are mu receptor agonists (μ). Morphine and fentanyl are the most well-known and potent analgesics. They have no upper limit of efficacy and can relieve even the most severe pain but are limited by side effects such as respiratory depression. Partial agonists and agonist-antagonists (nalbuphine, pentazocine, and butorphanol) have weaker analgesic effects compared to pure agonists but also cause fewer side effects such as sedation, psychomimetic effects, and dependency.

Tramadol has a unique mechanism of action. It has a weak affinity for μ receptors and inhibits serotonin and norepinephrine reuptake. It causes less respiratory depression and dependence compared to μ receptor agonists. Tapentadol is similar to tramadol but does not inhibit serotonin reuptake, reducing interactions with other serotonergic drugs. It has greater potency and fewer active metabolites compared to tramadol. Tapentadol is used for moderate to severe chronic pain and has 20 times less affinity for μ receptors than morphine but provides three times less analgesic effect.

Opioids have a broad range of side effects, including nausea, vomiting, constipation, dry mouth, bile duct and sphincter spasms, muscle rigidity, hypotension, respiratory depression, bradycardia, tachycardia, palpitations, postural hypotension, hallucinations, dizziness, euphoria, dysphoria, mood changes, dependence, confusion, drowsiness, sleep disorders, headaches, sexual dysfunction, urinary difficulties, ureteral spasms, miosis, vision disturbances, sweating, skin flushing, rash, urticaria, and itching (45, 46). Sudden discontinuation of opioid therapy can lead to signs of physical dependence, so the dosage should be reduced gradually, first by 50-75%, then by about 20% per day (40).

Recent technological innovations in opioid delivery include formulations that provide extended or rapid release of the active substance, infusion systems, and mini pumps for continuous intravenous and intraspinal administration. These technologies help individualization of the treatment and improve tolerability. Intravenous PCA (patient-controlled analgesia) and epidural analgesia, particularly PCEA (patient-controlled epidural analgesia), offer superior postoperative analgesia, reduce complications, and enhance patient recovery. However, there is a significant fear of misuse and "opiophobia" (47).

Table 2. Forms and doses of opioid analgesics in pain therapy

Drug	Dosage formulation/ route of administration	Dose for the pain therapy
Morphine	solution for injection /i.v. ili i.m.	20 mg/ml solution for injection
	oral drops oral solution syrup	20 mg/ml 10 or 30 mg/5ml 10 mg/5ml
Hydromorphone	extended-release tablet	8, 16 i 32 mg once daily
Oxicodone	capsule extended-release tablet oxicodone+naloxone - extended-release tablet	2, 10, 20 mg on 4-6 h 5, 10, 20, 40, 80 mg on 12 h 5+2,5; 10+5; 20+10; 40+20 on 12 h
Petidine/Meperidine	solution for injection 100 mg/2ml	Dose 0,5-1mg/kg (25-50 mg) •Max 600 mg, not longer than 48h
Fentanyl	spray fentanil patch – chronic pain	10-20 μg/kg for children i 400-800 mcg for adults 30 min before pain procedure or for breakthrough pain. 25, 50, 75, 100 μg/h 12, 25, 50, 75,100 μg/h
Buprenorphine	sublingual tablet	2 i 8 mg on 24 h
Codeine	tablet	30 mg na 6h do 60 mg on 4h
Tramadol	solution for injection • extended-release tablet	50, 100 mg 50, 100, 150 mg • Max 400-500 mg/day

Legend: The most common opioid analgesics (forms and doses) in pain therapy.

i.v. – intravenous; i.m. – intramuscular.

Table 3. Patient-Controlled Analgesia (PCA)

Drug	Initial – bolus dose	Rate of continuous infusion	Lockout interval (min)
Morphine	0.5-2.5 mg		
	1-2	5-10	
Fentanyl	10-20 μg		
	-	4-10	
Alfentanyl	0.1-0.2 μg	-	5-8
Sufentanyl	2.5 μg	-	4-10
Metadone	0.5-2.5 mg	-	8-20
Meperidine	5-25 mg	-	5-10
Pentazocine	5-30 mg	-	5-15
Nalbuphine	1-5 mg		5-15
Buprenorphine	0.03-0.1 mg	4-6	8-20

Table 2 shows different forms and doses of opioid analgesics for pain therapy, whereas **Table 3** shows the benefits and applications of infusion PCA and PCEA systems.

LOCAL ANESTHETICS

Local anesthetics (LAs) are adjunctive medications used in pain therapy. They have both analgesic and anti-inflammatory effects. The mechanisms of action for local anesthetics are diverse and include as follows:

- Blocking voltage-gated Na^+ channels. This prevents the propagation of nerve impulses.
- Blocking Ca^{2+} and Na^+ channels. This further inhibits nerve signal transmission.
- Blocking presynaptic muscarinic receptors. This interferes with neurotransmitter release.
- Blocking TRPV1 channels. These channels play a crucial role in developing hyperalgesia after injury and/or inflammation.
- Blocking NMDA receptors. This action helps modulate pain signaling (48).

Through these mechanisms, local anesthetics alleviate pain and hyperalgesia. They reduce inflammation and local sensitization by directly suppressing certain stages of the inflammatory response (e.g., neutrophil activation) and by blocking specific pathways in nerve cells activated during inflammation. Some local anesthetics, such as bupivacaine and tetracaine, block TRPV1 channels, while lidocaine activates them and causes a burning sensation after subcutaneous injection (49).

Local anesthetics can be used alone or as part of a multimodal analgesia approach. Routine use of peripheral nerve blocks and infiltration of wounds with long-acting local anesthetics, in addition to regional and general anesthesia, improves postoperative pain control across a wide range of surgical procedures. When used preoperatively, they reduce the need for analgesics and anesthetics during surgery. They also decrease the incidence of postoperative nausea and vomiting by reducing opioid use. These techniques are the most effective, with analgesia typically lasting only 6-8 h (50).

For epidural regional anesthesia, bupivacaine (0.1-0.2%, 1-2 mg/ml), levobupivacaine (0.1-0.2%, 1-2 mg/ml), and ropivacaine (0.2%, 2 mg/ml) are commonly used. Lidocaine is the most frequently used local anesthetic for infiltration anesthesia, central neuroaxial blocks, and peripheral nerve blocks. In the treatment of localized neuropathic pain (e.g., postherpetic neuralgia, diabetic neuropathy), 5% lidocaine is applied locally in the form of a patch (10 cm × 14 cm) (51). Pharmacokinetic studies have shown that only 3% of lidocaine reaches systemic circulation, making minimal systemic side effects, even lower than those seen with pregabalin use.

GABAPENTINOIDS

Gabapentinoids (gabapentin and pregabalin) are adjunctive medications used in the management of postoperative pain. These drugs are structural analogs of γ-aminobutyric acid (GABA) but do not act via GABA receptors. Instead, they bind to the α2δ1 subunit of presynaptic voltage-gated Ca^{2+} channels and inhibit them. By inhibiting these channels, gabapentinoids reduce the release of excitatory neurotransmitters, which helps block the development of hyperalgesia and central sensitization (52). Additionally, there is evidence suggesting that gabapentinoids exert antinociceptive effects through the activation of noradrenergic inhibitory pathways.

Gabapentinoids are used in the treatment of chronic neuropathic pain (e.g., postherpetic neuralgia, diabetic neuropathy, and spinal cord injury-induced pain), fibromyalgia, epilepsy, and anxiety (pregabalin only). They are increasingly utilized in acute conditions, such as acute neuropathic pain (e.g., burn injuries) and perioperative analgesia (53). In the management of postoperative pain, gabapentinoids are not typically used as monotherapy but are rather added to opioid therapy. This combination enhances opioid analgesia, reduces postoperative nausea and vomiting, and helps prevent opioid tolerance (54).

So far, the doses and duration of treatment for postoperative pain have not been standardized. Pregabalin has a more favorable pharmacological profile compared to gabapentin. Its absorption is dose-independent, it is 2 to 3 times more potent than gabapentin, and it has fewer side effects. However, pregabalin can still lead to confusion, drowsiness, potential respiratory depression when combined with remifentanil, changes in cognitive status, and dependency (55).

α-2 AGONISTS

These are adjunctive analgesics used in pain management. Clonidine and dexmedetomidine are examples of drugs belonging to this category. The mechanism of

action of α-2 agonists inhibits Ca^{2+} channel opening and suppresses neurotransmitter release (56). α-2 adrenergic receptor agonists, when administered intrathecally or epidurally, can be beneficial as adjunctive therapy for postoperative, neuropathic, and cancer pain, providing extended analgesia (57). When combined with local anesthetics, they lead to prolonged block duration.

Clonidine is more commonly used in the treatment of postoperative pain. Dosages for clonidine in epidural analgesia are as follows: premedication at 0.15-0.3 mg orally, intramuscularly, or intravenously can reduce morphine requirements by up to 50%; intrathecally, 0.075 mg is added; and epidurally, 1-2 μg/kg as a single dose or 3 μg/kg/24 h (58). Dexmedetomidine is used less frequently. Its drawbacks include the need for intravenous administration, high cost, and the requirement for cardiovascular monitoring due to its characteristic biphasic response. Specifically, blood pressure changes are dose-dependent due to the activation of presynaptic or postsynaptic α-2 receptors, leading to either vasoconstriction or vasodilation of blood vessels with reflex bradycardia (59). Adverse effects of α-2 agonists include hypotension, bradycardia, sedation, nausea, and vomiting.

NMDA ANTAGONISTS – KETAMINE AND MAGNESIUM

Ketamine

Ketamine is an anesthetic that functions as an analgesic when used in subanesthetic doses (60). Its mechanism of action primarily involves non-competitive antagonism of NMDA receptors. Ketamine exerts analgesic properties through opioid μ and δ receptors, AMPA and GABA receptors, and by blocking K^+, Ca^{2+}, and Na^+ channels. It also inhibits NO synthesis and activates descending inhibitory pathways at the level of the spinal cord by increasing the release of dopamine, serotonin (5-HT), and norepinephrine while inhibiting their reuptake (61).

When administered intraoperatively or postoperatively, either as a bolus or infusion, ketamine statistically significantly reduces postoperative pain scores and opioid consumption (62). Recommended doses include an intravenous bolus of ketamine ranging from 0.1 to 0.5 mg/kg, which can be followed by an infusion of 0.1 to 0.6 mg/kg/h. This infusion may be stopped at the end of the surgery or continued until the third postoperative day (63). Doses exceeding 0.35 mg/kg or infusions for acute pain greater than 1 mg/kg are not recommended without intensive monitoring. The American Pain Society suggests a preoperative bolus of 0.5 mg/kg ketamine, followed by an intraoperative infusion of 10 mcg/kg/min, with or without a postoperative lower dose infusion (64).

A single analgesic dose can quickly (within 5-10 min) and transiently (for 2-3 h) reduce pain and the symptoms of allodynia, hyperalgesia, and the wind-up phenomenon. However, the side effects of ketamine limit its clinical use. The most common side effects include psychotropic effects (such as dysphoria, hallucinations, vivid dreams, disorientation, and confusion), nausea, headaches, diplopia, drowsiness, and dizziness. These effects are dose-dependent, typically resolved quickly upon cessation of the drug, and their frequency decreases with lower doses and/or the addition of benzodiazepines (65). Chronic use of ketamine may lead to hepatotoxicity, uropathy (including cystitis, dysuria, hematuria, and incontinence), and cognitive impairments. Contraindications for ketamine use include poorly controlled cardiovascular diseases, pregnancy, psychosis, hepatic dysfunction, and elevated intraocular or intracranial pressure (66).

Magnesium (Mg)

Mg is the fourth most abundant ion in the human body and plays numerous roles in physiological functions (67). It exerts analgesic effects through several mechanisms, by blocking NMDA receptors, and Ca^{2+} channels, and modulating Na^+ and K^+ channels. After local application, Mg^{2+} ions on the periphery modulate the activity of transient receptor potential (TRP) channels, such as TRPV1, TRPV4, and TRPA1 (68). When combined with ketamine, Mg has antinociceptive effects, partly through the activation of serotonergic, noradrenergic, and GABA-ergic systems (65). Mg enhances the analgesic effects of opioids and prevents opioid-induced hyperalgesia. When used perioperatively, MgSO4 (magnesium sulfate) can reduce the need for general anesthetics and improve postoperative analgesia (69).

Typically, during anesthesia induction, MgSO4 is administered intravenously as a bolus dose of 30-50 mg/kg, followed by a continuous infusion of 6-25 mg/kg/h until the end of the surgery or for 4-24 h after the initial bolus. A bolus dose of Mg without infusion has also proven effective in postoperative analgesia (70). Mg has a high therapeutic index, few side effects, and a favorable cost-to-efficacy ratio. It is a safe medication with no adverse effects at doses up to 28 g administered over 24 h (71, 72).

Author Contributions

The conception or design of the work - KSV; preparing the draft of the manuscript – KSV; SV; BM; DS; AJ; interpretation of revised version of manuscript - KSV.

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MEDIKAMENTOZNA TERAPIJA POSTOPERATIVNOG BOLA

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Sažetak

Postoperativni bol je i dalje veoma rasprostranjen i još uvek potcenjen problem kako u našoj zemlji, tako i u svetu. Brojne studije koje su sprovedene u zemljama s razvijenim sistemom zdravstvene zaštite pokazale su da čak ni u 21. veku postoperativni bol nije adekvatno tretiran. Više od 80% pacijenata koji se podvrgavaju hirurškim procedurama iskuse akutni postoperativni bol, a 75% pacijenata opisuje akutni bol kao srednje težak, težak ili ekstreman. Postoperativni oporavak zavisi od karakteristika pacijenta, ali i od faktora koji omogućavaju postoperativni oporavak, odnosno od prisustva ili odsustva komplikacija posle operacije. Farmakologija postoperativnog bola je usmerena prema patofiziološkim mehanizmima kao što su: nocicepcija, periferna senzitizacija, ektopična aktivnost, centralna senzitizacija. Savremeno medikamentno lečenje postoperativnog bola podrazumeva balansiranu multimodalnu analgeziju. Princip multimodalne analgezije je baziran na multifaktorijalnoj prirodi i kompleksnosti puteva prenošenja bola, a definiše se kao upotreba različitih lekova ili tehnika sa različitim mehanizmom dejstva na periferni ili centralni nervni sistem, koji mogu imati aditivan ili sinergistički efekat. Nekoliko grupa lekova je uključeno u multimodalni princip, i svaki od njih ima specifičan patofiziološki mehanizam dejstva. Efikasnost opioidnih analgetika u terapiji umerenog do teškog postoperativnog bola ostvaruje se zbog nedostatka plato efekta. Međutim, povećanjem doze dolazi do povećanja neželjenih efekata. Nesteroidni anti-inflamatorni lekovi (NSAIL), ciklooksigenaza-2 inhibitori (COX-2) i sistemski steroidi smanjuju inflamatornu komponentu hirurškog bola. Sistemski i lokalni anestetici redukuju oslobađanje inflamatornih medijatora (IL-6, Il-1β, i IL-1RA). Gabapentinoidi, vezujući se za alfa-2-delta-1 subjedinicu voltažnih kalcijumskih kanala u centralnom nervnom sistemu, redukuju oslobađanje važnih ekscitatornih neurotransmitera uključenih u nocicepciju. Alfa-2-agonisti, kao što su klonidin i deksmedetomidin, aktiviranjem presinaptičkih i postsinaptičkih α2 receptora u kičmenoj moždini modulišu transmisiju bolnih impulsa. Lokalni anestetici (lidokain) blokiraju neuralnu transmisiju blokirajući natrijumske kanale, pa preveniraju transmisiju bolnih stimulusa sa periferije u centralni nervni sistem. NMDA antagonisti, ketamin i magnezijum, smanjuju mehanizam centralne senzitizacije.

Ključne reči: postoperativni bol, farmakološko lečenje, lekovi

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REVIEW ARTICLE

The 100-year legacy of the Institute of Medical Chemistry: a century of chemistry education at the Faculty of Medicine, University of Belgrade

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Summary

The Institute of Medical Chemistry one of the oldest institutes of the Faculty of Medicine University of Belgrade, was founded in 1923. Recognizing the role of chemistry in understanding medical sciences, the founders of the Faculty of Medicine engaged leading authorities of the time in the field of chemistry: Sima Lozanić, Milivoje Lozanić, and Petar Matavulj, establishing a solid foundation for the quality education of future doctors. Over more than a century, the teachers and associates of the Institute have successfully addressed specific challenges in medical education, adapting to contemporary trends in science and education.

Keywords: Institute of Medical Chemistry "Prof. Dr. Petar Matavulj", Faculty of Medicine University of Belgrade, 100-year legacy

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INTRODUCTION

Institute of Medical Chemistry "Prof. Dr. Petar Matavulj[th], 2023, marked the 100[th] anniversary of its establishment with a festive symposium, where lectures on the history of the institute were held (1, 2).

BRIEF HISTORY OF THE INSTITUTE

Faculty of Medicine, the University of Belgrade, established in 1920, did not initially have all its teaching bases; they were consecutively formed. Professors Đorđe Joannović and Richard Burian recognized the importance of understanding medicine at the molecular level and accordingly engaged chemistry professors to provide students with chemistry education. In 1922, Professor Petar Matavulj was invited to teach chemistry. At that time, he was an assistant at the Chemistry Institute in Lausanne. Until the establishment of the Institute of Chemistry of the Faculty of Medicine in 1923, lectures in chemistry were held by professor Sima Lozanić and his son Milivoje Lozanić at the Faculty of Philosophy, the Department of Chemistry. Sima Lozanić was a chemist, scientist, professor, president of the Academy of Sciences, rector of the Great School, and the first rector of the University of Belgrade. He graduated in law at the Belgrade High School and then spent four years in Zurich and Berlin studying chemistry with the famous scientists Wislicenus and Hoffmann (3).

The Institute of Chemistry was founded in 1923 in two rooms located in a wooden barrack at Guberevac, where the Internal Propaedeutic Clinic was also located. One of the rooms was used for student laboratory practice, and the other was the professor's laboratory. The course lasted for two semesters, with five (5) lectures and ten (10) hours of practical laboratory classes per week. The first generation that completed the entire chemistry course at the Faculty of Medicine under professor Petar Matavulj enrolled in 1925 (4).

In 1925, the Institute of Chemistry was relocated to the building of the Institute of Pathology. From 1925 to 1932, practical laboratory classes were conducted at today's Institute of Microbiology, and in 1932 they were relocated to the Institute of Chemistry, when the first proper chemical laboratory with 24 seats was equipped. In 1938, the Institute was relocated to the Institute of Histophysiology's building, situated on the left, above the Institute of Histology. When the Faculty of Medicine founded the Department of Pharmacy in 1939, the Institute expanded, and a larger number of laboratories were placed in the building's basement for the needs of the analytical chemistry of the Department of Pharmacy. The building of the Institute of Histophysiology was destroyed during the bombing on April 6[th], 1941, and together with it, the Institute of Chemistry was completely burned down. Part of the salvaged material, extracted from the ruins, was transferred to the Institute, which was relocated to the ground floor of the Institute of Pathology. During the occupation, classes were not held at the Institute. In 1947, the Institute of Chemistry moved to the Internal "B" Clinic. After the restoration of the Institute of Histophysiology in 1950, the Institute of Chemistry moved to the premises it occupies today (5).

From 1948 to 1994, the Institute of Chemistry provided education not only to medical students but also to dental students. In the first few years after the establishment of the Faculties of Medicine in Novi Sad (1960), Niš (1960), Priština (1969), and Kragujevac (1976), the staff of the Institute of Chemistry participated in organizing and conducting chemistry classes at these faculties.

The number of chemistry classes has changed since the establishment of the department. Until 1977, students studied chemistry for two semesters i.e., 30 weeks, and since 1977 to 2004 for one semester, i.e., 15 weeks. Until the academic year 2003/04, the chemistry teaching was conducted in the first semester during the first year of studies with a total of 135 hours **(Figure 1)** (6).

Following the revised curriculum from 2004/05, the chemistry is a part of the joint subject "Medical Biochemistry and Chemistry" for second-year students of the integrated academic medical studies (both in Serbian and English). The first 9 weeks are dedicated to chemistry (during the third semester), with a total of 72 classes (45 theoretical-lectures and seminars, and 27 practical laboratory classes). Professors and assistants of the Institute also teach 13 elective courses for students in the 1[st], 2[nd], 3[rd], 4[th], and 5[th] years of the integrated academic studies of medicine.

Within postgraduate studies, members of the Department of Chemistry in Medicine participate in the implementation of specialist studies in clinical biochemistry and laboratory medicine, and doctoral studies in biochemical and physiological sciences. Since 1995, our professors are engaged in the preparatory courses for the entrance exam in chemistry (60 classes), and in collaboration with chemistry professors from other medical faculties, the professors of the Institute prepare the entrance exam in chemistry.

SCIENCE AT THE INSTITUTE

From its foundation to the 1980s, the most important issues of scientific research included: examination of RNA and DNA content and nuclease activity in the blood of patients with various malignancies, determination of the guanase activity in the blood in various neuropsychiatric and renal diseases, examining the properties and structure of nucleohistones during aging, the influence of insulin on the metabolism of proteins, lipids and carbohydrates, examination of the properties of sunflower oil

PLAN NASTAVE MEDICINSKE HEMIJE

Nedelja	PREDAVANJA	Broj časova	KONSULTACIJE	VEŽBE
I	Struktura i hemijske veze Oksido-redukcije i redoks sistemi Osnovi elektrohemije	3 2 5	Upoznavanje; uzimanje podataka; karton Zakoni hemijskog sjedinjavanja; periodni sistem elemenata; tipovi jedinjenja; stehiometrijski zadaci	
II	Uvod u organsku hemiju Struktura i klasifikacija organskih jedinjenja Tipovi neorganskih jedinjenja Voda i vodeni rastvori	3 2 5	Stehiometrijski zadaci	Hemijske reakcije jona: Ag^{+}, Pb^{2+}, Hg^{2+}, Cl^{-}, NO_3^{-}
III	Koncentracije rastvora, koligativne osobine Energetika hemijskih reakcija	3 2 5	Hemijske veze; stehiometrijski zadaci Test I	Hemijske reakcije jona: Zn^{2+}, Fe^{3+}, Ca^{2+}, Ba^{2+}, NH_4^{+}, J^{-}, SO_4^{2-}, CO_3^{2-}
IV	Hemijska kinetika Ugljovodonici: alkani, alkeni, dieni; izomerije	3 2 5	Diskusija testa I Koncentracije rastvora	Pravljenje rastvora određene koncentracije
V	Aromatični ugljovodonici Halogenski derivati Hidroksilni derivati Hemijska ravnoteža	3 2 5	Koligativne osobine rastvora Test II (koncentracije)	mol/l HCl
VI	Teorije kiselina i baza Konstanta disocijacije Suzbijanje disocijacije, amfoternost	3 2 5	Oksidoredukcije Diskusija testa II	mol/l J_2
VII	Alkoholi, fenoli, tio derivati ugljovodonika Proizvod rastvorljivosti, hidroliza	3 2 5	Hemijska kinetika Teorije kiselina i baza, neutralizacija, hidroliza Test III (koligativne osobine rastvora, oksidoredukcije)	mol/l NaCl
VIII	Glicidi, monosaharidi Derivati monosaharida	6	Stehiometrijski zadaci	Pregled predjenog gradiva
IX	Holozidi, oligo i polisaharidi	6	Puferi, acido-bazna ravnoteža Test IV (hidroliza, puferi, oksidoredukcije	Pravljenje rastvora pufera odredjene pH vrednosti
X	Amini, karboksilni derivati ugljovodonika Derivati kiselina Derivati ugljene kiseline	5	Hemijske reakcije u organskoj hemiji Diskusija testa IV	Reakcije alkohola i fenola, aldehida i ketona
XI	Supstituisane kiseline, halogenske, hidroksi, aldehidne i ketonske. Amino kiseline	5	Test I (organska hemija)	Reakcije ugljenih hidrata
XII			N a d o k n a d e v e ž b i	
XIII	Medicinski značajni elementi i njihova jedinjenja	6	Karbonske kiseline; derivati kiselina; lipidi Test II (organska hemija)	Reakcije organskih kiselina i lipida
XIV	Heterociklusi Proteini Nukleinske kiseline	6	Supstituisane kiseline i belančevine	Reakcije amino kiselina i belančevina

Figure 1.The syllabus of Medical Chemistry from 1986

modified by temperature and aging, comparison of methods of electrophoretic separation of serum proteins on various gels and application in solving clinical problems.

As part of the professional work at the Institute, various chemical analyses of clinical samples were performed (at that time current analyses in blood: urea, glucose, amino acids, creatinine, cholesterol, etc.). Also, chemical analyses of mineral water were performed. Chemical analyses of drugs were carried out for the Commission for Drugs under the Ministry of Health.

Since the 1980s, scientific research work has included the isolation, purification and characterization of biomolecules from different sources: human, animal, microbial, and plant. The research is based on preparative biochemistry, fundamental enzymology, structural and functional protein tests, identification and analysis of metabolites, using spectrophotometry, electrophoretic and related techniques and methods.

Nowadays, an important turn of scientific research has been made towards new methods and techniques in the study of genomes, proteomes, and metabolomes. Scientific

Figure 2. Prof. Dr. Petar Matavulj

research is conducted at the Institute in five research laboratories: the Laboratory for Protein Biochemistry, the Laboratory for Protein Mass Spectrometry, the Laboratory for Biomolecule Analytics, the Laboratory for Fundamental Enzymology and *In Vitro* Toxicology, and the Laboratory for Bioinorganic and Bioorganic Chemistry in Medicine. The research includes areas such as protein biochemistry, toxicology, microbial and human enzymology, biomolecule analytics, and bioinorganic chemistry. This research is carried out through national research projects as well as international research projects and collaborations.

DISTINGUISHED PROFESSORS

Prof. P. Matavulj, founder of the Institute, the Dean of the Faculty of Pharmacy and Acting Dean of the Faculty of Medicine **(Figure 2)**, was born in 1892 in Šibenik, in a merchant family. He studied six grades of high school in Zadar and matriculated in Zagreb in 1908. He graduated from the Faculty of Medicine in Vienna in 1914. In 1915 he was an assistant at the Department of Chemistry at the Technical Faculty of Aachen, and from late 1915 to 1923 he was an assistant at the Institute of Chemistry and Physics at the

Figure 3. Prof. Dr. Pavle Trpinac with his colleagues and medical chemistry demonstrators in front of the Institute

University of Lausanne. At that time, he graduated from the Faculty of Philosophy and passed the doctoral exam in physical chemistry. Professor Matavulj was the founder of the Institute of Chemistry at the Faculty of Medicine in Belgrade in 1923 and its first director from its founding to 1948 when he passed away. Until 1930, he was a part-time chemistry teacher when he was elected as an associate professor and in 1940 as a full professor at the Faculty of Medicine (7).

Prof. P. Trpinac **(Figure 3.)**, Director and Head of the Department in 1948-1975, was born in 1905 in Novi Sad. He graduated from the Faculty of Medicine in 1934. During his studies, from 1927 to 1934, he worked as a student assistant at the Institute of Chemistry of the Faculty of Medicine. In 1934, he was elected to the position of a teaching assistant. He studied chemistry from 1935 to 1938. He finished the first four semesters at the Technological Department of the Technical Faculty in Belgrade and a two-year training in Paris (1937-1938), in physical chemistry and radioactivity with Professor Irene Joliot-Curie. In 1939, he was elected to the position of assistant professor for medical chemistry at the Faculty of Medicine in Belgrade. More than forty generations of medical students listened to the chemistry lessons of this outstanding lecturer. He trained medical chemistry demonstrators to conduct practical laboratory classes (8).

Prof. Dr. Božica Rotović **(Figure 4.)**, was elected the dean of the Faculty of Medicine in 1973. She served as a dean for two terms. She graduated in Chemistry at the Faculty of Philosophy in Belgrade in 1938. She completed her doctoral dissertation in 1955, in Strasbourg (9).

Figure 4. Prof. Dr. Božica Rotović

Prof. Dr. Miloš Mladenović was a member of the Serbian Academy of Sciences and Arts. Miloš Mladenović completed three years at the Seminary in Sremski Karlovci, after which he attended the group of natural sciences - chemistry group at the Faculty of Philosophy in Belgrade. Finally, in 1921, he went to Graz to study chemistry (9).

DIRECTORS OF THE INSTITUTE SINCE ITS ESTABLISHMENT TO THE PRESENT DAY (10):

- 1923-1948 Prof. Petar Matavulj, Ph.D.
- 1948-1975 Prof. Pavle Trpinac, Ph.D.
- 1975-1980 Prof. Olga Bugarski, Ph.D.
- 1980-1984 Prof. Ružica Vlajnić, Ph.D.
- 1984-1989 Prof. Nevena Dimitrijevic, Ph.D.
- 1989-1995 Prof. Anka Dražić, Ph.D.
- 1995-2000 Prof. Zorana Vujovic, Ph.D.
- 2000-2004 Assist. Prof. Kristina Gopčević, Ph.D.
- 2004-2009 Assoc. Prof. Vesna Vujić, Ph.D.
- 2009-2015 Assoc. Prof. Danijela Krstić, Ph.D.
- 2015-2021 Prof. Kristina Gopčević, Ph.D.
- 2021- Assoc. Professor Lidija Izrael Živković, Ph.D.

HEADS OF THE DEPARTMENT FROM ITS ESTABLISHMENT TO THE PRESENT DAY (10):

- 1923-1948 Prof. Petar Matavulj, Ph.D.
- 1948-1975 Prof. Pavle Trpinac, Ph.D.
- 1975-1981 Prof. Milanka Čorbić, Ph.D.
- 1981-1985 Prof. Olga Bugarski, Ph.D.
- 1985-1989 Prof. Ružica Vlajnić, Ph.D.
- 1989-2000 Prof. Nevena Dimitrijević, Ph.D.
- 2000-2002 Prof. Ivanka Karadžic, Ph.D.
- 2002-2004 Prof. Anka Dražić, Ph.D.
- 2004-2012 Prof. Zorana Vujović, Ph.D.
- 2012-2015 Prof. Ivanka Karadžić, Ph.D.
- 2015-2021 Prof. Vesna Vujić, Ph.D.
- 2021- Prof. Danijela Krstić, Ph.D.

PUBLISHED BOOKS

The first textbook used by medical students:

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100 GODINA INSTITUTA ZA HEMIJU U MEDICINI MEDICINSKOG FAKULTETA UNIVERZITETA U BEOGRADU

Kristina Gopčević[1], Vesna Vujić[1], Nataša Avramović[1], Lidija Izrael Živković[1], Ana Medić[1], Teodora Đukić[1], Zorana Lopandić[1], Danijela Krstić[1]

Sažetak

Institut za hemiju u medicini, jedan od najstarijih instituta Medicinskog fakulteta Univerziteta u Beogradu, osnovan je 1923. godine. Sagledavajući ulogu hemije u razumevanju medicinskih nauka, osnivači Medicinskog fakulteta angažovali su vodeće autoritete toga doba u oblasti hemije: Simu Lozanića, Milivoja Lozanića i Petra Matavulja, postavivši čvrste temelje za kvalitetnu edukaciju budućih lekara. Tokom više od jednog veka, nastavnici i saradnici instituta uspešno odgovaraju na specifične izazove u medicinskoj edukaciji, prilagođavajući se savremenim trendovima u nauci i obrazovanju.

Ključne reči: Institut za hemiju u medicini "Prof. dr Petar Matavulj", Medicinski fakultet Univerziteta u Beograu, istorijat

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CASE REPORT

Primary leiomyosarcoma of the inferior vena cava – radical resection and vascular reconstruction

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Summary

Introduction: Sarcomas are rare tumors that account for less than 1% of malignant tumors in adults. Primary leiomyosarcoma (LMS) of the inferior vena cava (VCI) is a very rare tumor with an incidence of <1/100,000 of all malignant diseases in adults. This paper presents the case of a woman with LMS of the VCI who underwent radical tumor resection with vascular reconstruction.

Case report: A 71-year-old woman went to the doctor because of painless hematuria. As part of the diagnostic evaluation, in addition to US and CT examination of the abdomen, CT angiography with 3D reconstruction was performed. The conclusion of the radiologist was that the described tumor mass first corresponds to a primary LMS of the VCI VCI that propagated laterally into the lumen of the left renal vein, while the right renal artery was infiltrated by the tumor. The patient was presented to the multidisciplinary team at the Institute for Oncology and Radiology of Serbia (IORS), which decided for operative treatment. The tumor was completely removed en bloc with the right kidney, right suprarenal gland and the confluence of the left renal vein into the VCI. The VCI was reconstructed with a graft with end-end anastomosis, while the left renal vein was implanted in the graft with end-side anastomosis.

Conclusion: LMS of the VCI is an extremely rare tumor. Surgical resection of the tumor and the involved blood vessel with negative resection margins is the only therapeutic option that improves survival. Very often, in addition to complicated vascular reconstructions, surgery also includes multivisceral resections, in order to achieve the best possible therapeutic effect

Key words: leiomyosarcoma, vena cava inferior, sarcomas, surgery

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INTRODUCTION

Primary LMS of the VCI is a very rare tumor. Early diagnosis is usually difficult and the prognosis is poor, due to very often advanced stage. We present a case of a woman with primary LMS who underwent radical resection of the tumor, along with vascular reconstruction.

CASE REPORT

A 71 year- old female presented with painless haematuria.

Ultrasonography of the abdomen was performed and showed a thick wall cystic mass in the right kidney, as well as avascular mass outside of the kidney, 60x40mm in size. The renal vein was thrombosed, and proximally the VCI was filled with a tumor mass, with partial patency. What was described distally was stasis or thrombosis of the VCI – differential diagnosis was RCC of the right kidney.

Subsequently, CT of the abdomen and the pelvis was performed. It showed a tumor mass in the area of the VCI that extended from L2 to porta hepatis and which dislocated and compressed the VCI forward, with unclear demarcation of the posterior wall of the vein – differential diagnosis - a conglomerate of lymph nodes para-aortic on the right, 64x41mm in size. The suprahepatic portion of the VCI was dilated.

The patient was then presented to a multidisciplinary team at IORS, which made a decision for CT angiography of the VCI, in order to discuss surgery resection.

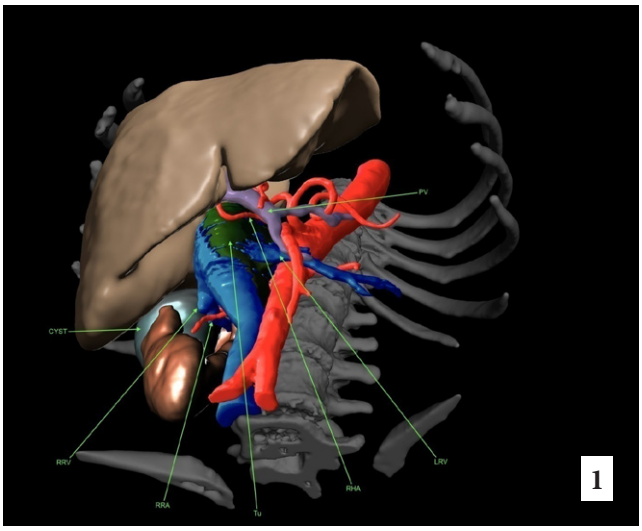
CT angiography was performed and showed a lobular, infiltrative, heterodense retroperitoneal mass 74x69x51mm, dominantly at the posteromedial wall of the VCI, irregularly narrowing the lumen. In the upper part it was reaching a caudal part of intrahepatic segment of the VCI, 4cm from the hepatic veins confluence. With the lower part, the mass was 85mm above common iliac veins. Lateral aspect of the tumor mass propagated into the lumen of the left renal vein. With its anterolateral aspect, it was very close to the right hepatic artery which was in this case originating from the upper mesenteric artery. The tumor made a compression on the main trunk of the portal vein, as well as suppression on the right renal vein, without any visible signs of intraluminal propagation. The right adrenal gland, and the right renal artery were infiltrated with the tumor.

According to the CT conclusion, described mass was in the first place LMS of the VCI **(Fig. 1-8)**.

There were no distant metastases at the moment of diagnosis.

The patient was once again presented to the multidisciplinary team, which decided on a surgical procedure. She was admitted to hospital on 21st January 2021, and the surgery was performed four days later. Preoperative urea and creatinine values were 9,7 mmol/L and 120 μmol/L.

We entered the abdomen through a bilateral subcostal laparotomy. Exploration confirmed the retrohepatic tumor, around 8x7cm in diameter. It was located about 3cm below the hepatic veins confluence, reaching the level of renal veins **(Fig. 9)**.



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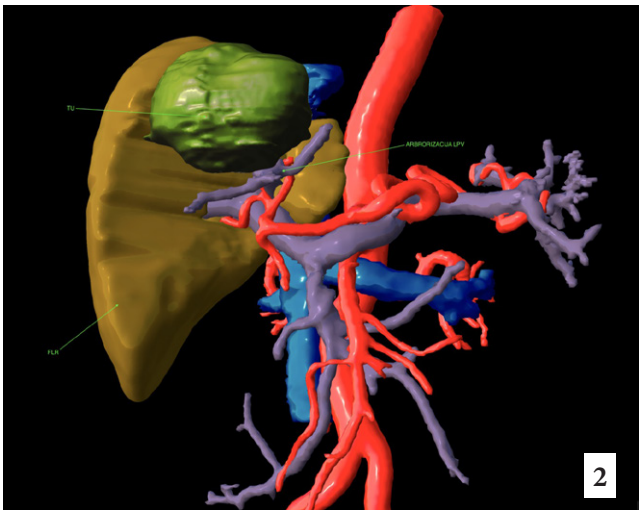

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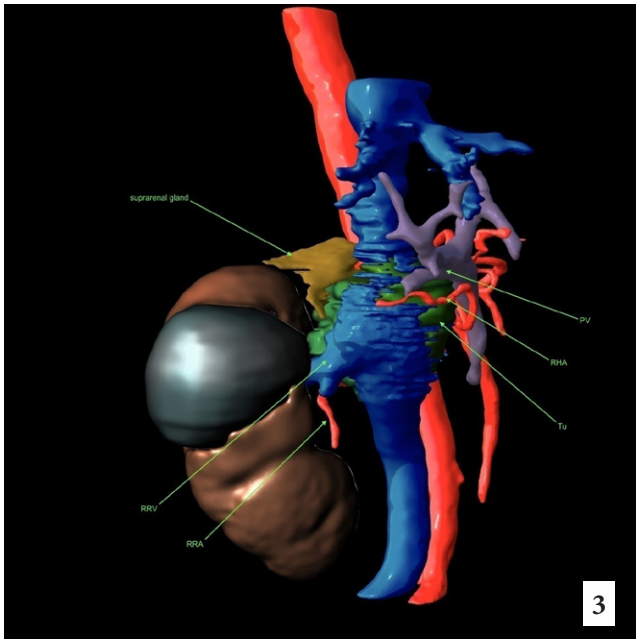

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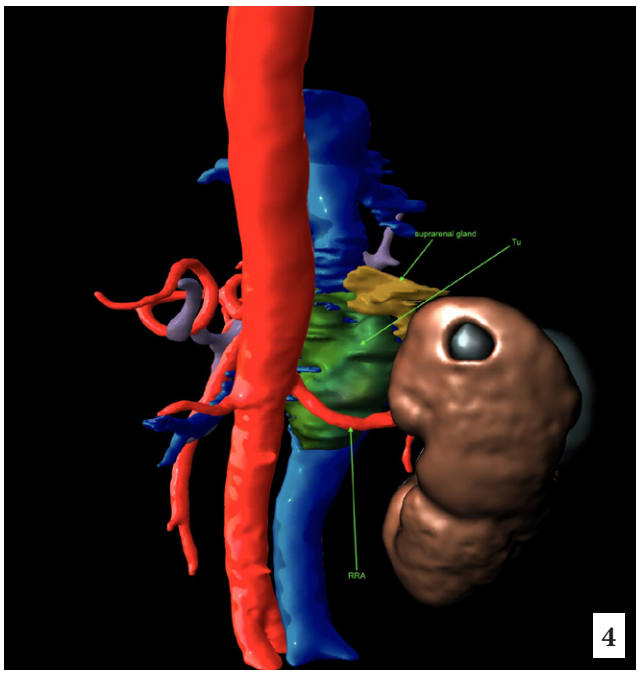

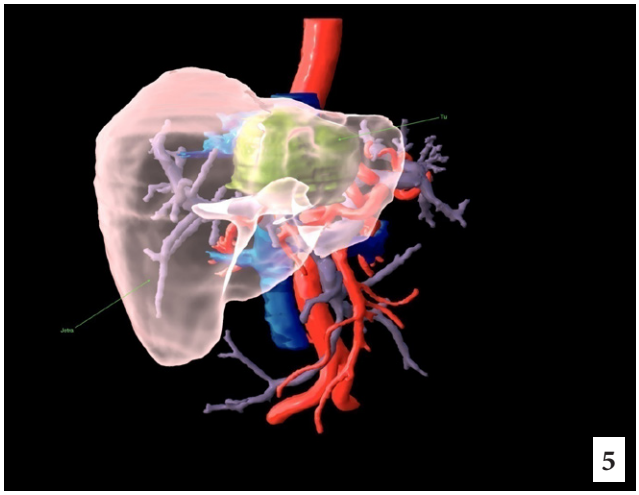

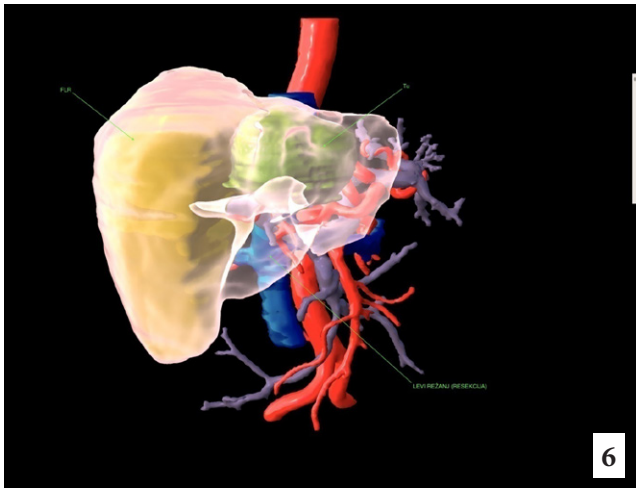

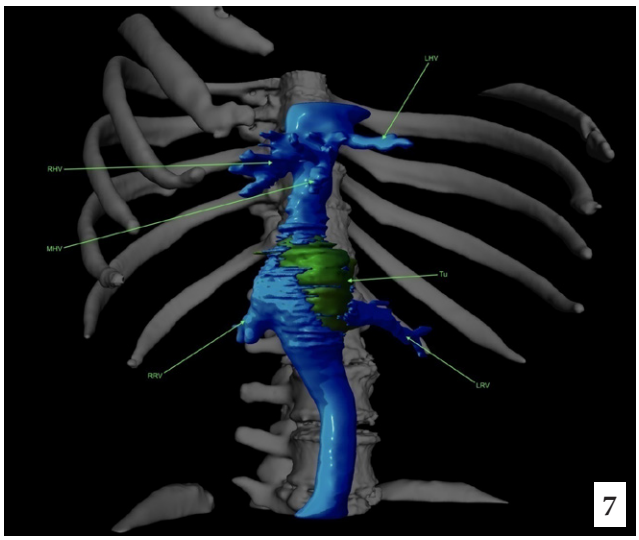

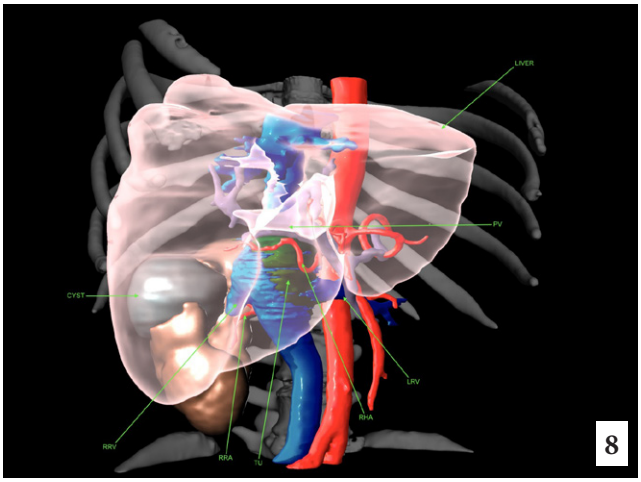

Fig. 1-8. CT angiography presenting the VCI tumor (green) and surrounding structures (PV – portal vein; LRV – left renal vein; RHA – right hepatic artery; RRA – right renal artery; RRV – right renal vein; LRV – left renal vein; LHV – left hepatic vein; MHV – middle hepatic vein; RHV – right hepatic vein).

There was an obvious thrombus identified in almost entire right renal vein as well as in the small portion of the left renal vein. The tumor had completely dislocated the renal vein confluences. The right kidney was enlarged and cystic. No other tumor changes were verified in the abdomen and pelvis by careful exploration. The right colon, duodenum and the head of the pancreas were mobilized and the access was made to the retroperitoneum and the VCI. After that we mobilized the liver, accessed also the retrohepatic portion of the VCI and made a proximal control. Several lumbar veins were ligated to free the VCI. We also made the distal control of the VCI, as well as the control of the left renal vein. The tumor with the involved right kidney, right suprarenal gland, and the left renal vein confluence was removed **(Fig. 10)**.

We used polyester (Dacron) graft for the reconstruction of the VCI, in end-to-end fashion. An end-to-side anastomosis was created with the left renal vein **(Fig. 11)**.

The overall operative time was three and a half hours. The patient was discharged on postoperative day eight, with postoperative urea and creatinine values of 8 mmol/L and 164 μmol/L.

Histopathological examination showed vascular leiomyosarcoma, G2, 75x75x60mm in size and R0 resection **(Fig. 12)**.

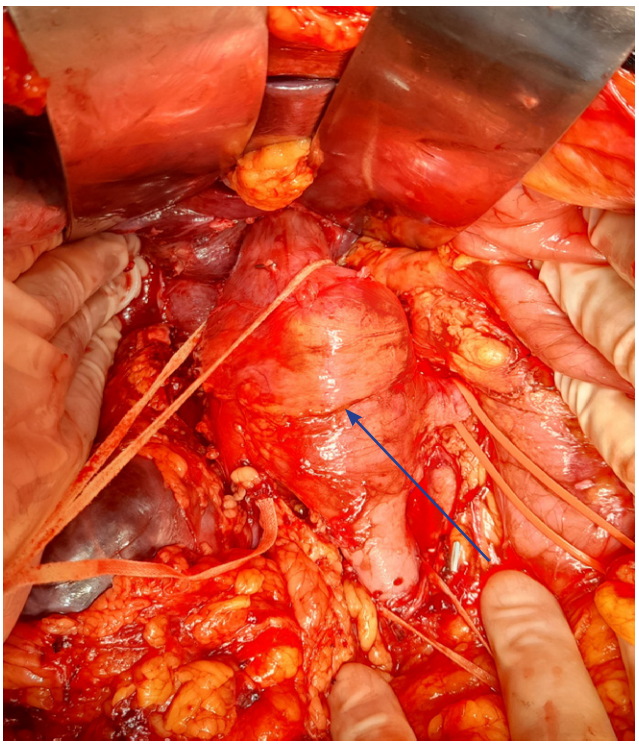

Fig. 9. Intraoperative finding of the VCI tumor (blue arrow).

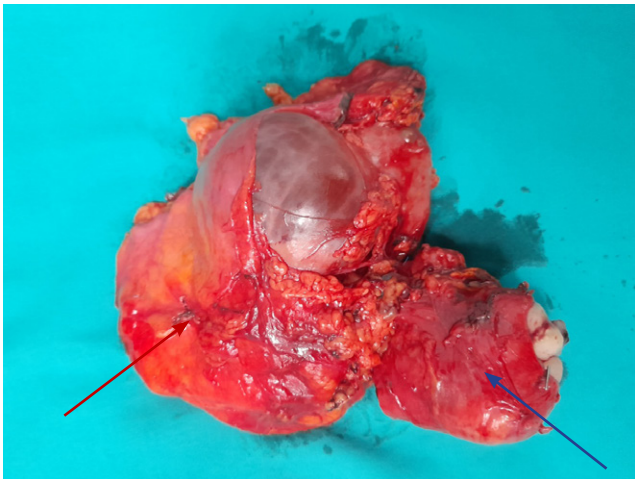

Fig. 10. VCI tumor (blue arrow) and the right kidney (red arrow) after removal

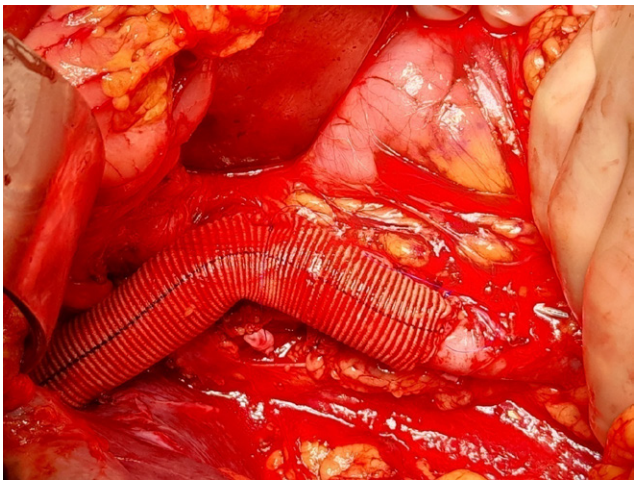

Fig. 11. Intraoperative photo after the reconstruction of the VCI with a graft

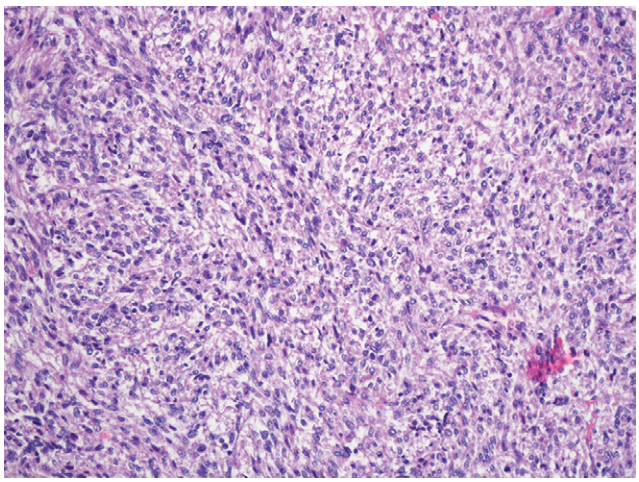

Fig. 12. Microscopic pathological finding.

Adjuvant therapy was not administered.

It has been three and a half years since the operation and the patient is still undergoing regular monthly check-ups.

DISCUSSION

Sarcomas are rare tumors accounting for less than 1% of cancer in adults and represent 15% of cancers in children. Majority of sarcomas are soft tissue tumors, including primary LMS which account for 0.5 to 1% of all malignant tumors. Most sarcomas are of unknown cause, but there are some known risk factors, such as radiation exposure, occupational chemical exposure, trauma, and chronic lymphedema (1).

VCI is the most common site of vascular LMS. Primary LMS of the VCI is a rare tumor accounting for around 0.5% of soft tissue sarcomas in adults. The incidence is <1/100 000 of all malignant diseases in adults. The prognosis is poor. Patients have intra- or extra-luminal tumor growth, very often with invasion of neighboring structures (2). In 1871, Perl et al. were the first to describe this tumor at an autopsy. It was a case of LMS of the VCI originating from the smooth muscles of a blood vessel. Melchior was the first to report a case of this tumor in 1928, which was treated surgically, by resection of the distal third of the VCI (3).

According to a recent pooled data analysis, fewer than 400 cases of LMS of the VCI have been reported, with most studies limited to single case reports (4). Patients are predominantly women (80%), mean age of 54 (3, 5).

The clinical behavior of most soft tissue sarcomas is determined by anatomic location, hystological subtype, grade and size. Presentation depends on the involved segment of the VCI. In relation to the localization of the malignant process, VCI is according to Kulaylat et al. divided into three segments:

1. Segment I or infrarenal segment (lower segment), involved in 36% of cases.

2. Segment II or inter- and supra- renal segment, from the hepatic veins to the renal veins (middle segment), affected in 44%.
3. Segment III or suprahepatic segment, from the right atrium to the hepatic veins, with potential intracardiac propagation (upper segment) (12).

The most common segment affected by the tumor is the segment between the renal and hepatic veins, which is also associated with the best prognosis, while the involvement of the upper segment of the VCI, intraluminal growth as well as potential obstruction of VCI are associated with poor prognosis (13).

The diagnosis is often made late, due to a long asymptomatic period, non-specific abdominal symptoms caused by tumor compression on surrounding structures. Very often patients present with abdominal pain and discomfort, as well as a palpable mass in the abdomen. In case of middle segment involvement, nephrotic syndrome or renal hypertension can occur. Almost a third of patients have lower extremity edema, due to obstruction of the VCI. Often there are also non-specific symptoms and signs such as nausea, vomiting or fever. Thrombotic mass can cause pulmonary embolism, tricuspid valve insufficiency, cardiac arrhythmias, as well as failure of the liver and kidneys due to "outflow" obstruction (10, 14, 15, 16). There can also exist symptoms due to metastatic disease.

Diagnostic imaging includes ultrasonography, CT and MRI. Chest CT should be performed at presentation and before any radical treatment, to evaluate for lung metastasis, knowing that distant metastases occur most often in the lungs, which 80% of the time occur within 2 to 3 years of the initial diagnosis (1). Other sites include the liver, bones and brain (17). Lymph node metastases in sarcomas are rare (less than 5%), but the incidence is higher in some subtypes, including angiosarcomas (1, 6).

Surgical resection of the tumor and affected vessel with negative margins is the only treatment shown to improve survival (7, 8, 9,10). Very often, along with complicated vascular reconstructions, surgery involves multivisceral resections, in order to achieve best therapeutical effect (11). Surgery is considered for patients without metastatic disease and with resectable primary tumor. Pre-operatively, high quality imaging is reviewed to determine the likely extent of resection, specifically including the need for potential en-bloc resection of adjacent organs. In cases where up-front surgical approach would expose the patient to excessive morbidity (such as bilateral nephrectomy, multi-visceral resection, or prohibitively high risk of positive margins), neoadjuvant chemotherapy and/or chemoradiotherapy is considered (18).

Overall 5-year survival rate for patients with all stages of soft tissue sarcoma is 50% to 60%. There is no much difference in LMS of the VCI, with the 5-year survival rate between 31% and 67% with R0 resection (1, 2).

CONCLUSION

LMS of the VCI is an extremely rare tumor entity. Surgical resection of the tumor and affected vessel with negative margins is the only treatment shown to improve survival. Very often, along with complicated vascular reconstructions, surgery involves multivisceral resections, in order to achieve the best therapeutical effect. Also, patients with LMS of the VCI should be treated in experienced centers by experienced surgeons.

Statements and Declarations

The patient's consent to the publication of the paper has been obtained.

The paper has never been published or concurrently submitted for publication to any other journal.

All authors who have met the authorship criteria have read and approved the manuscript.

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PRIMARNI LEJOMIOSARKOM DONJE ŠUPLJE VENE - RADIKALNA RESEKCIJA I VASKULARNA REKONSTRUKCIJA

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Uvod: Sarkomi su retki tumori koji čine manje od 1% malignih tumora kod odraslih. Primarni lejomiosarkom donje šuplje vene je veoma redak tumor čija je incidencija <1/100 000 svih malignih bolesti kod odraslih. U ovom radu predstavljen je slučaj žene sa lejomiosarkomom donje šuplje vene kojoj je urađena radikalna resekcija tumora uz vaskularnu rekonstrukciju.

Prikaz bolesnika: Žena stara 71 godinu, javila se lekaru zbog bezbolne hematurije. U sklopu dijagnostičke evaluacije pored UZ i CT pregleda abdomena učinjena je i CT angiografija sa 3D rekonstrukcijom. Zaključak radiologa je bio da opisana tumorska masa najpre odgovara primarnom lejomiosarkomu donje šuplje vene koji se lateralno levo propagirao u lumen leve bubrežne vene, dok je desna bubrežna arterija bila infiltrisana tumorom. Pacijentkinja je prikazana konzilijumu na Institutu za onkologiju i radiologiju Srbije koji je doneo odluku o operativnom lečenju. Tumor je u celosti odstranjen u bloku sa desnim bubregom, desnom nadbubrežnom žlezdom i ušćem leve bubrežne vene u donju šuplju venu. Donja šuplja vena je rekonstruisana uz pomoć grafta termino-terminalnom anastomozom, dok je leva bubrežna vena implantirana u graft termino-lateralnom anastomozom.

Zaključak: Lejomiosarkom donje šuplje vene je ekstremno redak tumor. Hirurška resekcija tumora i zahvaćenog krvnog suda sa negativnim ivicama resekcije je jedina terapijska opcija koja poboljšava preživljavanje. Vrlo često uz komplikovane vaskularne rekonstrukcije, hirurgija uključuje i multivisceralne resekcije, kako bi se postigao najbolji mogući terapijski efekat.

Ključne reči: lejomiosarkom, donja šuplja vena, sarkomi, hirurgija

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Simpozijum „Stremljenja i novine u medicini“ Medicinskog fakulteta u Beogradu

Appendix sa apstraktima

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Tradicionalni simpozijum „Stremljenja i novine u medicini“ Medicinskog fakulteta u Beogradu, održava se svake godine u nedelji svečanosti koja se organizuje povodom Dana fakulteta 9. decembra.

Specijalni broj časopisa “Medicinska istraživanja“ prati simpozijum u obliku Knjige sažetaka.

Ovogodišnji simpozijum “Stremljenja i novine u medicini“ održava se od 2. do 6. decembra 2024. godine.

Članovi Organizacionog odbora simpozijuma„Stremljenja i novine u medicini“

Prof. dr Ivana Novaković, predsednik
Prof. dr Dragana Šobić Šaranović
Prof. dr Vera Pravica
Prof. dr Jasna Jančić
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Prof. dr Katarina Paunović
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Dr sc. Viktorija Popović

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Sadržaj

MINI SIMPOZIJUM
BOLESTI ADRENALNOG KORTEKSA - GENETIČKI I KLINIČKI ASPEKTI

Medicinski fakultet Univerziteta u Beogradu, Klinika za endokrinologiju, dijabetes i bolesti metabolizma Univerzitetskog kliničkog centra Srbije

GENETIČKI ASPEKTI BOLESTI NADBUBREGA

Jadranka Antić

Tokom poslednjih 25 godina genetička pozadina bolesti nadbubrega transformisana je identifikacijom velikog broja kandidat gena koji se dovode u vezu sa različitim tipovima tumora nadbubrega. Feohromocitomi i paragangliomi, aldosteron produkujući adenomi (APA), kongenitalna adrenalna hiperplazija, primarna makronodularna adrenalna hiperplazija, primarna pigmentirana nodularna adrenokortikalna bolest i adrenokortikalni karcinom (ACC) mogu biti uzrokovani prisustvom germinativne mutacije u određenom genu, bez obzira na prisustvo/odsustvo porodične istorije ili sindromske bolesti pri početnoj dijagnozi. Oko 40% feohromocitoma i paraganglioma može biti posledica prisustva germinativne mutacije u genima *SDHA, SDHB, SDHC, SDHD, VHL, RET, MAX, TMEM127, NF1, FH, EPAS1, SLC25A11, GOT2, MDH2, PHD2, KIF-1Bβ, MERTK, MET* i *H3F3A*. Kod najvećeg broja APA se prema najnovijim podacima može detektovati prisustvo somatskih mutacija u genima *KCNJ5, CACNA1D, CACNA1H, ATP1A1, ATP2B3, CLCN2* i himernom genu *CYP11B1-CYP11B2*. Kongenitalna adrenalna hiperplazija prouzrokovana je prisustvom germinativnih mutacija u genima *CYP21A2, CYP11B1, CYP17A1, 3BHSD2* i *StAR*. Primarna makronodularna adrenalna hiperplazija može se genetički determinisati, pre svega kod pacijenata sa bilateralnim uvećanjem nadbubrega i onih sa porodičnom istorijom Cushing-ovog sindroma, drugih endokrinih tumora i endokrinih sindroma, familijarne adenomatozne polipoze (FAP), hereditarnog leiomiomatosa sindroma i McCune-Albright sindroma. Prisustvo mutacija detektovano je u genima *ARMC5, MEN1*, APC, *MCR2, GNAS1* i *FH*. U slučaju mikronodularne adrenalne hiperplazije i pigmentne mikronodularne adrenalne bolesti najčešće je reč o prisustvu inaktivirajuće germinativne mutacije u genu *PRKAR1A*. ACC može biti komponenta Li-Fraumeni sindroma usled prisustva germinativne mutacije u genu *TP53* (detektuju se kod 50% pacijenata sa ACC). Prisustvo ACC je opisano i kod pacijenata sa Lynch, MEN1 i Beckwith-Wiedemann sindromima, FAP i neurofibromatozom tip 1. Zahvaljujući najnovijim otkrićima na polju genetike adrenalnih tumora i razvoja metode sekvenciranja nove generacije koje postaje rutinska praksa u genetičkim laboratorijama, genetičko testiranje trebalo bi da postane deo redovne dijagnostike pacijenata sa adrenalnim tumorima, pošto rezultati genetičkog testiranja mogu imati presudan značaj za njihovo dalje lečenje.

Ključne reči: Tumori nadbubrega, genetičko testiranje, sekvenciranje nove generacije, kandidat geni, germinativne mutacije.

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KONGENITALNA ADRENALNA HIPERPLAZIJA - NEKLASIČAN OBLIK

Đuro Macut

Kongenitalna adrenalna hiperplazija (KAH) je najčešći genetički poremećaj u endokrinologiji. Prevalencija neklasičnog oblika KAH (NK-KAH) kod hiperandrogenih žena iznosi do 10%. KAH je uzrokovan nedostatkom 21-hidroksilaze (inaktivirajuće mutacije u genu CIP21A2) i nasleđuje se autozomno recesivno. Mutacije koje dovode do NK-KAH se smatraju blažim i uzrokuju samo povećanje androgena. U diferencijalnoj dijagnozi hiperandrogenih simptoma, a pre svega hirzutizma, neophodno je razmotriti postojanje sindroma policističnih jajnika (PCOS) kao najčešćeg reproduktivnog poremećaja kod žena. Ukupan testosteron može biti povišen kod NK-KAH i PCOS, dok povišen DHEAS može usmeriti dalje ispitivanje prema NK-KAH. Povećana učestalost gojaznosti i insulinske rezistencije kod pacijenata sa NK-KAH koja započinje u mladosti može dovesti do povećanja stope metaboličkih posledica i kardiovaskularnih bolesti tokom odraslog doba kod oba pola. Poremećaj rasta, kao i smanjena mineralna gustina kostiju i osteoporoza, nisu stalni nalazi kod pacijenata sa NK-KAH i mogu zavisiti od pola i vrste ili doze primenjenih kortikosteroida. U retkim situacijama, odraslim osobama sa NK-KAH nakon stimulacije sa 250 μg ACTH i odgovorom kortizola <500–550 nmol/l treba savetovati lečenje glukokortikoidima tokom bolesti, traume ili hirurške intervencije. Optimalni tretman glukokortikoidima je postignut kada nivoi 17-hidroksiprogesterona u serumu variraju između malo povišenih i do tri puta iznad gornje granice referentnog opsega, dok se androstenedion održava unutar referentnog opsega. Kardiometabolički poremećaji se mogu lečiti statinima, insulinskim senzitaizerima i lekovima protiv gojaznosti. Oralni kontraceptivi (OCP) i antiandrogeni (AA) predstavljaju terapiju prve linije za simptome hiperandrogenizma, dok se glukokortikoidi mogu koristiti kod žena koje ne prihvataju ili ne tolerišu OCP ili AA. Progestageni se mogu koristiti kada je OCP kontraindikovana. U lečenju infertiliteta kod žena, mogu se koristiti kortikosteroidi kao monoterapija ili u kombinaciji sa klomifen citratom ili gonadotropinima.

Ključne reči: kongenitalna adrenalna hiperplazija, hiperandrogenizam, kortikosteroidi, oralni kontraceptivi, antiandrogeni

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KUŠINGOV SINDROM - IZAZOVI U DIJAGNOSTICI I LEČENJU

Valentina Elezović Kovačević

Endogeni Kušingov sindrom (CS) je retka bolest koju karakteriše stanje dugotrajne hiperkortizolemije, te je pravovremena dijagnoza od izuzetne važnosti kako bi se omogućilo brzo lečenje i prevencija morbiditeta i mortaliteta. Svaki od biohemijskih dijagnostičkih modaliteta ima ograničenja sa senzitivnošću i specifičnosti koje značajno variraju. Biohemijski evaluacija je posebno zahtevna kod pacijenata kod kojih hiperkortizolemija fluktuira svakodnevno, što često zahteva ponavljanje ili kombinaciju više testova, posebno kada je potrebno razdvojiti CS od fizioloških, neneoplastičnih stanja hiperkortizolizma tkz. pseudokušingovog sindroma. Na kraju, konvencionalni MR hipofize može biti negativan u do 60% slučajeva pacijenata sa ACTH zavisnim Kušingovim sindromom i tumorom hipofize tj. Kušingovom bolesti (CD), dok lažno pozitivni nalazi mogu postojati kod pacijenata sa ektopičnom sekrecijom ACTH. Novija, 3T-MR visoke rezolucije je superiornija metoda koja omogućava otkrivanje adenoma veličine i do 2 mm. Razlikovanje CD od ektopične sekrecije ACTH može zahtevati čak i invazivne procedure kao što je bilateralno uzorkovanje donjih petroznih sinusa. Novije metode mogu olakšati dijagnostičke nesigurnosti, pružajući precizniju dijagnozu pre podvrgavanja pacijenta dodatnim snimanjima ili pak invazivnim procedurama. Određivanje vrednosti kortizola i kortizona u kosi glave može da ukaže i na dužinu trajanja bolesti i od posebnog je značaja u slučajevima cikličnog CS. Slično, funkcionalna snimanja (oktreosken, 68 Ga PET-CT/MR, 1C-Metionin (MET) PET-CT/MRI i 18F-Fluoroetil-L-tirozin (FET) PET-CT/MR) donekle olakšavaju diferencijalnu dijagnozu i lokalizaciju tumora.

Nakon postavljanja dijagnoze neophodno je efikasno lečenje koje podrazumeva normalizaciju nivoa kortizola kao i lečenje komorbiditeta. Hirurška resekcija je generalno prva terapijska linija kada god je moguće. Izbor tretmana druge linije, uključujući lekove, bilateralnu adrenalektomiju i terapiju zračenjem (npr za kortikotropne tumore), mora biti individualizovano za svakog pojedinačnog pacijenta.

Ključne reči: Kušingov sindrom, hiperkorticizam, semplovanje petroznih sinusa, ispitivanje hipotalamo-hipofizne-adrenalne osovine, inhibitori adrenalne steroidogeneze

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PRIMARNI ALDOSTERONIZAM - NOVINE U ETIOPATOGENEZI I DIJAGNOSTICI

Bojana Popović, Dušan Ilić

Primarni aldosteronizam (PA) je najčešći sekundarni uzrok hipertenzije koji doprinosi kardiovaskularnom, metaboličkom i nefrološkom morbiditetu nezavisno od godina starosti pacijenta i vrednosti krvnog pritiska. Razumevanje PA je poslednjih godina doživelo revolucionarne promene, prvenstveno zahvaljujući razvoju imunohistohemijskih metoda patohistološke obrade i metoda molekularne dijagnostike. Razvoj specifičnih antitela protiv enzima CYP11B2 (aldosteron-sintaza) omogućio je definisanje izvora produkcije aldosterona u hirurški resekovanom adrenalnom tkivu. Pokazano je da se broj aldosteron-produkujućih klastera ćelija u zoni glomerulozi kore nadbubrega uvećava sa starenjem, što je dovelo i do novog razumevanja patofiziologije PA kao starosno-zavisne bolesti sa kontinuuom izraženosti renin-nezavisne produkcije aldosterona od blage, do klinički potpuno ispoljene. Genetička metoda sekvenciranja nove generacije (*next generation sequencing*) doprinela je razumevanju da je ovakav patofiziološki tok posledica akumulacije somatskih mutacija u tkivu zone glomeruloze nadbubrega. Zahvaćeni geni kodiraju jonske kanaliće, i to kalijumske (*KCNJ5*), kalcijumske (*CACNA1D* i *CACNA1H*) i hloridne (*CLCN2*), kao i ATP-azu (*ATP1A1* i *ATP2B3*). U retkim slučajevima mutacije u navedenim genima mogu biti i germinativne, dovodeći do naslednih formi PA. Ostvaren je i napredak u razumevanju povremene udruženosti blage autonomne produkcije kortizola kod osoba sa PA, a kao posledica somatskih mutacija u *KCNJ5* (koekspresija CYP11B2 i CYP11B1), *PRKACA* i *GNAS*. Podizanje svesti o mogućoj kosekreciji kortizola otvorilo je i pitanje modifikacije protokola za proceduru semplovanja adrenalnih vena, prvenstevno segmenta koji se odnosi na procenu uspešnosti kateterizacije. Iako nijedan od alternativnih postupaka nije standardizovan, ispituju se metode korišćenja metanefrina i drugih steroida (11-deoksikortizol, androstenedion, 11β-hidroskiandrostenedion). Konačno, kao alternativa invazivnoj venskoj kateterizaciji ispituju se metode funkcionalne dijagnostike, prvenstveno pozitron-emisiona tomografija (PET) sa ^{11}C-metomidatom, ali su podaci još uvek oskudni. Uprkos svim novim saznanjima, PA se i dalje nedovoljno dobro prepoznaje i potrebno je raditi na podizanju svesti o prevalenci i kriterijumima dijagnostike ovog poremećaja, čijim pravilnim i blagovremenim lečenjem bi se značajno smanjio morbiditet i mortalitet pogođenih pacijenata.

Ključne reči: Primarni aldosteronizam, Konov sindrom, Konšingov sindrom, sekundarna hipertenzija, hipokalemija

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ADRENOKORTIKALNI KARCINOM - MOLEKULARNA BIOLOGIJA I LEČENJE

Sanja Ognjanović

Karcinom kore nadbubrega (ACC) je veoma redak agresivan karcinom koji čini 0.02% svih malignih tumora. Incidencija ACC iznosi 0.5-2.0/1.000000. Ukupno 5-godišnje preživljavanje iznosi 38-46%, a u IV stadijumu bolesti manje od 20%. Definisano je nekoliko molekularnih i genetskih alteracija u tumorigenezi sporadičnih i naslednih tumora. Nađene su somatske mutacije u genima koji su uključeni u signalne puteve kao što su povećana ekspresija IGF2 gena, aktivacija Wnt/beta-catenin puta, potom gena uključenih u regulaciju ćelijskog ciklusa i inhibiciju apoptoze. Germinativne mutacije u ovim genima su povezane sa naslednim sy u kojima je komponenta ACC, kao što su Li-Fraumeni sy, Lynch sy, MEN1 sy, famlijarna adenomatozna polipoza, Beckwith-Wiedemann sy, Carney kompleks i neurofibromatoza tip1. Klinička slika je heterogena, zavisi od vrste hormona koji tumor produkuje i može se ispoljiti Kušingovim sy, virilizacijom, feminizacijom i mineralokortikoidnim ekscesom. U slučaju nefunkcijskih tumora simptomi su nespecifični i posledica su kompresije i infiltracije susednih organa. Hormonska evaluacija se sprovodi pre i postoperativno radi adekvatne preoperativne pripreme, i radi detekcije rekurentne bolesti. Terapija ACC je vrlo kompleksna i usmerena je na kontrolu tumorskog rasta i kontrolu hormonske hipersekrecije. Radikalna hirurška resekcija jedina dovodi do izlečenja. Iako je ona moguća kod pacijenata u I, II i III stadijumu bolesti, prisustvo okultnih mikrometastaza je uzrok lokalnog recidiva i udaljenih metastaza. Glavni prognostički faktori koji ujedno opredeljuju i terapijski pristup su stadijum tumorske bolesti, resekcioni status, patohistološki gradus (Ki67 indeks, mitotski indeks) i prisustvo Kušingovog sy. Nakon hirurške resekcije, u slučaju neresektabilnih tumora i rekurentne bolesti primenjuju se različiti terapijski modaliteti kao što su medikamentna terapija koja obuhvata lečenje adrenolitičkim lekom mitotanom, citotoksične i lekove u kontroli hormonskog ekscesa, i potencijalno radoterapiju. Većina aktuelnih terapijskih protokola je neadekvatna u kontroli bolesti, sa značajnim neželjenim efektima i neophodno je bolje razumevanje molekularnih mehanizama tumorigeneze koje bi dovelo do razvoja novih efikasnijih lekova.

Ključne reči: Karcinom kore nadbubrega, adrenokortikalni karcinom, mitotan, hiperkorticizam, hiperandrogenizam.

MINI SIMPOZIJUM
100 GODINA INSTITUTA ZA FARMAKOLOGIJU, KLINIČKU FARMAKOLOGIJU I TOKSIKOLOGIJU MEDICINSKOG FAKULTETA UNIVERZITETA U BEOGRADU

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ISTORIJAT INSTITUTA ZA FARMAKOLOGIJU I TOKSIKOLOGIJU I KLINIČKU FARMAKOLOGIJU: 20.VEK

Ljiljana Gojković Bukarica

Ove godine slavimo 100 godina od kako je osnovana farmakologija u Srbiji, što Srbiju potvrđuje kao savremenu evropsku državu. Farmakološki insitut Medicinskog fakulteta u Beogradu je osnovan 1924.godine. Osnovao ga je profesor iz Jene, Arnold Holste (završio Medicinski fakultet u Getingenu), učenik „oca" moderne farmakologije, Oswalda Scmiedeberga i prvi upravnik Instituta. Kao nastavnik on je bio veoma popularan među studentima, a brzo je naučio srpski jezik i prvi udžbenik napisao ćiriličnim pismom. Njegov prvi asistent je dr Radivoje Pavlović (diplomirao na Medicinskom fakultetu Tekelijanum). Prof. Pavlović je osnivač Kliničkih farmakoterapijskih seminara što je temelj kliničke farmakologije u Srbiji i časopisa Medicinski pregled (1926). Kada je prof. Pavlović postao redovni profesor na upražnjeno mesto je došao dr Ilija Dimitrijević, diplomirani student medicine iz Ženeve, sa specijalizacijom iz hemije iz Berlina i mikrobiologije iz Pariza. Pre II sv. rata, na institutu su pored gore navedenih profesora radili i doc. Siniša Bogdanović, i ukazni asistent dr Dimitrije Atanacković (kasnije osnivač Instituta za farmakologiju u Rijeci i Skoplju). Posle II sv. rata na institutu su radili prof. Bogdanovic i dr Milenko Milošević i dr Vladislav Varagić, koji su se kasnije svrstali u najuglednije profesore Medicinskog fakulteta. Tokom 20. i početkom 21. veka na Institutu su radili ugledni profesori: Borislav Radmanović, Dušan Beleslin, Milovan Krstić (osnivač Stremljenja i novina u medicini), Tomislav Kažić, Bogosav Vasić, Milorad Terzić, Draginja Andjelković, Leposava Grbović, Ranka Samardzić, Milica Prostran, Slobodan Milovanović, Danica Jovanović-Mićić, i asistenti Ivana Matić, Zvonko Katušić i Vlada Maletić. Nastavnici koji su radili na našem Institutu osnovali su Institute farmakologije u Skoplju, Rijeci, Nišu, Novom Sadu i Kragujevcu, takođe i Jugoslovensko i Srpsko društvo farmakologa, sekciju za Farmakoterapiju SLD i sekciju Kliničke farmakologiju SFD, časopise, Medicinski pregled i Acta physiologica&pharmacologica Jugoslavica i objavili brojne udžbenike za studente i poslediplomce.

Ključne reči: Farmakologija sa toksikologijom, 100-godišnjica, 20. vek, profesori i asistenti

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VEK NASTAVE IZ FARMAKOLOGIJE NA MEDICINSKOM FAKULTETU U BEOGRADU

Zoran Todorović

Nastava iz Farmakologije sa toksikologijom ne samo na Medicinskom fakultetu u Beogradu, već i u našoj zemlji uopšte, izvodi se od 1924/25. godine. Godinu dana ranije, na istom fakultetu za redovnog profesora je izabran Nemac Arnold Holste, prethodno vanredni profesor Medicinskog fakulteta u Jeni. Od samog početka, Holsteu u nastavi pomaže lekar, interista, dr Radivoje Pavlović. Prve generacije studenata našeg fakulteta farmakologiju su učili iz nemačkog udžbenika Meyer & Gottlieb. Na Holsteovu inicijativu, prof. Radivoje Pavlović je 1928. napisao prvu Recepturu, a naredne godine, sa prof. Ilijom Dimitrijevićem, prvi udžbenik Materia Medica. Pavlović je započeo 1929. godine i prvu nastavu iz farmakoterapije u vidu seminara za lekare. Posle II svetskog rata, izdavani su udžbenici iz Farmakologije i toksikologije profesora Bogdanovića i Varagića, kao i Kliničke farmakologije (dva izdanja), uz brojne priručnike i prevod britanskog udžbenika Rang & Dale (dva izdanja).

Naša katedra je započela nastavu iz Farmakologije sa toksikologijom i na drugim fakultetima u zemlji (recimo, Medicina - Kragujevac i Farmacija i Veterina - Beograd), kao i nastavu iz Kliničke farmakologije. Danas, Katedra izvodi nastavu svih stepena, od studija sestrinstva, preko integrisanih akademskih studija medicine, do specijalističkih akademskih studija (ranije - magisterijuma), master akademskih studija, specijalizacija i užih specijalizacija do doktorskih studija, kako na srpskom, tako i na engleskom jeziku. U praktičnoj nastavi se koriste snimljene vežbe, softveri, kao i učenje kroz rešavanje problema i rešavanje slučajeva, a u planu je i osnivanje nastavnih baza na klinikama Medicinskog fakulteta. Vredi spomenuti i učešće u evropskom projektu Epharnet, kao i u nacionalnom timu za reformu visokog obrazovanja. Budućnost naše farmakologije su brojni saradnici koji su angažovani u svim oblicima nastave i izabrali su farmakologiju kao svoj životni poziv.

Ključne reči: farmakologija, klinička farmakologija, stogodišnjica

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SUR2A: MOJ OMILJENI ZAŠTITNIK SRCA

Aleksandar Jovanović

SUR2A je atipični ABC protein koji služi kao regulatorna podjedinica ATP-senzitivnih K+ (KATP) kanala. Na eksperimentalnim životinjama utvrđeno je da povećanje nivoa ovog proteina u miokardu štiti srce od različitih vrsta metaboličkih stresova, uključujući ishemiju. Povećanje SUR2A dovodi do povećanja broja potpuno formiranih KATP kanala, što je povezano sa njihovom ranijom aktivacijom u toku ishemije, kao i povećanom produkcijom ATP-a pomoću enzima koji su fizički povezani sa podjedinicama kanala. Aktivacija KATP kanala skraćuje akcioni membranski potencijal i sprečava ulaz kalcijuma u ćelije, dok proizvodnja ATP-a povećava subsarkolemalni nivo ATP-a osiguravajući energiju za vitalne procese koji zahtevaju energiju na ovoj lokaciji. Najnovija otkrića su da SUR2A takođe može regulisati ekspresiju gena koji su važni u kardioprotekciji. Razmotreno je kako povećati ekspresiju SUR2A na efikasan i bezbedan način. Utvrđeno je da postoje dva moguća obećavajuća pristupa. Jedan je pristup genskoj terapiji sa virusom koji sadrži SUR2A koji je bio uspešan na nivou srčanih ćelija, a drugi je bio oralni nikotinamid, oblik vitamina B3, koji je bio efikasan u *ex vivo* uslovima. Na bazi svih ovih otkrića, verujemo da strategije protiv ishemije srca koje se baziraju na SUR2A zaslužuju da se ozbiljno istražuju i razmatraju u budućnosti. Terapija ishemijske bolesti srca koja koristi endogene kardioprotektivne faktore, uključujući SUR2A, bila bi odličan dodatak trenutnim terapijskim strategijama ishemijske bolesti srca i drugih kardiovaskularnih bolesti kod kojih bi povećanje otpornosti srca na stres bilo korisno.

Ključne reči: SUR2A, KATP kanali, kardioprotekcija

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TDM I INDIVIDUALNO DOZIRANJE LEKOVA: PRAVA DOZA ZA PRAVOG PACIJENTA

Gordana Dragović, Božana Dimitrijević

Terapijski monitoring leka (*Therapeutic drug monitoring*, TDM) je efikasan metod za individualizaciju antimikrobne terapije, kako kod kritično bolesnih bolesnika, tako i kod pacijenata sa oboljenjima/infekcijama koje su doživotno prisutne, poput HIV infekcije. Naime, TDM omogućava individualizovani pristup lečenja u cilju optimizacije doze određenih antimikrobnih lekova, ali i drugih grupa lekova poput antiepileptika, antiaritmika, kardiotonika, ali i lekova koji se koriste u terapiji autoimunih, gljivičnih i virusnih oboljenja. Kako je cilj svakog lečenja primena odgovarajuće, precizno definisane doze propisanog leka, koja daje najveću verovatnoću za lečenje/izlečenje uz prisustvo minimalnog broja neželjenjih i toksičnih efekata, do danas se upotreba antimikrobnog TDM-a pokazala veoma važnom u cilju postizanja terapijskih koncentracija lekova. Upravo se primena TDM-a kod kritično bolesnih pacijenata, preporučuje se u konsenzusnim smernicama jer značajno utiče na ishod lečenja.

Prepoznat je značaj primene TDM-a u kliničkoj praksi, ali i prepreke prilikom implementacije TDM u lečenju kritično obolelih pacijenata. Tako su individualne karakteristike samog pacijenta prepoznate kao izuzetno važne prilikom odabira pravog leka u pravoj dozi, za individualnog pacijenta. Međutim, individualne varijacije u genima koji kodiraju jonske transportne polipeptide (*Organic-anion-transporting-polypeptides*, OATP), porodice membanskih transportnih proteina koja vrši influx brojnih endogenih i ksenobiotskih supstanci u **ćeliju**, takođe su važne. Možda su još više važni nivoi ekspresije OATP-a, posebno ekspresije OATP1B1 i OATP1B3, glavnih transportera lekova u hepatocitima. Pored navedenog, na farmakokinetiku antimikrobnih lekova takođe utiču i pregnanski X receptor (*pregnane X receptor,* PXR) i konstitutivni androstanski receptor (*constitutive androstane receptor,* CAR), koji regulišu transkripciju velikog broja gena čiji produkti, enzimi, učestvuju u metabolizmu značajnog broj antmikrobnih lekova. Imajući u vidu kompleksne interakcije pomenutih proteina, kao i interindividualne, ali i intraindividualne varijacije koje utiču na farmakokinetiku antimikorbnih lekova, nedvosmisleno se može zaključiti da je u određenim situacijama primena terapijskog monitoringa leka neophodna u odabiru prave doze za pravog pacijenta.

Ključne reči: terapijski monitoring leka, prilagođavanje doze, individizacija lečenja.

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NOVA SAZNANJA U ISTRAŽIVANJU BOLA: OD LABORATORIJE DO KLINIČKE PRAKSE

Katarina Savić Vujović

Danas se bol uz disanje, temperaturu, puls i pritisak smatra petim vitalnim znakom. Bol je najučestaliji simptom u kliničkoj praksi zbog koga se pacijenti javljaju lekaru. Kod bolesnika koji pate od dugotrajnog osećaja intenzivnog bola smanjena je mogućnost normalnog funkcionisanja kao i radna sposobnost Bol je i dalje veoma rasprostranjen i još uvek potcenjen problem kako u našoj zemlji, tako i u svetu.

Mehanizam nastanka bola je kompleksan proces. Bol se prema trajanju deli na akutni i hronični, a prema mehanizmu nastanka na: nociceptivni (somatski i visceralni), nenociceptivni (neuropatski) i mešoviti. Procena bola je preduslov efikasnog otklanjanja bola. Kako je bol subjektivan fenomen, samoprocena bola je zlatni standard. Za procenu bola koriste se merni instrumenti: jednodimenzionalne i višedimenzionalne skale bola. Jednodimenzionalne skale su vizelno-analogna, numerička i verbalna.

Pristup u otklanjanju bola može biti: farmakoterapijski i nefarmakoterapijski (fizikalna tetrapija, psihotera-

pija, akupunktura, periferne i centralne nervne blokade, hirurške metode). Farmakoterapija bola podrazumeva upotrebu analgetika. Najjednostavnija podela analgetika je na neopioidne, opioidne i adjuvantne analgetike. Novija podela anlgetika podrazumeva podelu na osnovu mehanizma dejstva leka. Multidisciplinarnost se ogleda u radu tima stručnjaka, koji zajedno učestvuju u evaluaciji, lečenju i praćenju pacijenta sa bolom.

Savremeno medikamentno lečenje bola podrazumeva balansiranu multimodalnu analgeziju. Multimodalna analgezija, u farmakoterapijskom smislu, podrazumeva lečenje u kojem se koristi više lekova, koji deluju različitim mehanizmima. Princip multimodalne analgezije je baziran na multifaktorijalnoj prirodi i kompleksnosti puteva prenošenja bola, a definiše se kao upotreba različitih lekova ili tehnika sa različitim mehanizmom dejstva na perifernom ili centralnom nervnom sistemu, koje mogu imati aditivan ili sinergistički efekat. Potrebne su manje doze leka, a povećana je efikasnost analgezije i smanjena učestalost neželjenih dejstava.

Efikasna i pravovremena analegezija poboljšava kvalitet života pacijenta, skraćuje vreme lečenja i oporavka, povećava zadovoljstvo pacijenta i olakšava rad medicinskog osoblja.

Ključne reči: bol, analgetici, terapija, multimodalna analgezija, savremeni pristup

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PRIMENA BIOMARKERA U FARMAKOLOŠKIM I TOKSIKOLOŠKIM STUDIJAMA

Marko Stojanović

Biomarkeri predstavljaju ključne alate u savremenim farmakološkim i toksikološkim studijama, omogućavajući precizniju procenu efekata lekova i drugih supstanci na organizam. Korišćenje biomarkera omogućava identifikaciju ranih znakova toksičnosti, što je od suštinskog značaja za razvoj sigurnijih terapija i bolje razumevanje mehanizama toksičnih efekata. U farmakološkim studijama, biomarkeri se koriste za procenu farmakokinetike i farmakodinamike, omogućavajući optimizaciju doziranja i minimizaciju neželjenih efekata. U toksikološkim studijama, biomarkeri igraju ključnu ulogu u proceni biološke distribucije i dugoročnih efekata supstanci, uključujući nanomaterijale i druge inovativne agense. Posebna pažnja u skorijim istraživanjima posvećena je polooksometalatima, koji su proučavani kao potencijalni kontrastni agensi za kompjuterizovanu tomografiju. Ispitivanja *in vivo* toksičnosti ovih materijala ukazuju na njihovu obećavajuću primenu, ali istovremeno zahtevaju oprez zbog potencijalne toksičnosti i složenosti njihove biološke distribucije. Upotreba biomarkera u ovim studijama omogućava detaljnu procenu sigurnosti i efikasnosti ovih novih agensa, pružajući dragocene informacije za budući razvoj i kliničku primenu. Na ovaj način, biomarkeri doprinose ne samo boljoj evaluaciji postojećih supstanci, već i ubrzanju razvoja novih terapija i dijagnostičkih alata, čime se značajno unapređuje kvalitet i sigurnost zdravstvene zaštite.

Ključne reči: biomarkeri, farmakologija, toksikologija, polooksometalati, *in vivo* ispitivanja

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IN VITRO INTERAKCIJE JONA BAKRA SA LEKOVIMA

Bojana Božić Cvijan[1], Milica Bajčetić[1,2]

Bakar (Cu^{2+}) je esencijalni mikro element i redoks aktivni metal koji lako donira i prima elektrone. Njegova koncentracija u telesnim tečnostima je striktno regulisana zbog učešća u radu brojnih enzima, ali i zbog mogućih patoloških stanja i toksičnih efekata koji mogu nastati prilikom promena u njegovoj koncentraciji. Povišena koncentracija jona bakra je opisana kod neonatalne hiperbilirubinemije kod preterminskih i terminskih neonatusa, infekcije, inflamacije, dijabetesa, oboljenja jetre, Vilsonove bolesti. S druge strane, smanjena koncentracija jona bakra je povezana sa pojedinim patološkim stanjima poput Menkeovog sindroma, limfosarkoma i osteoporoze.

Poznato je da joni bakra mogu uticati na aktivnost lekova na dva načina: stupajući u redoks ili koordinativne reakcije ili gradeći komplekse sa lekovima. U *in vitro* uslovima u prisustvu jona bakra opisana je degradacija ili smanjenje antimikrobne aktivnosti amoksicilina, ampicilina, meropenema, cefaleksina i neomicina. Takođe, u *in vitro* uslovima u neutralnoj pH sredini opisana je i degradacija hidralazina u prisustvu jona bakra. Ovi rezultati upućuju na oprez prilikom upotrebe pomenutih lekova u stanjima sa povišenom koncentracijom jona bakra, kao i prilikom istovremene primene suplemenata koji sadrže bakar ili konzumiranja hrane koja je bogata bakrom. S druge strane, pojedine studije su opisale postojanje takozvanih bakar-zavisnih jedinjenja, poput disulfirama, za čiju efikasnost je neophodno prisustvo jona bakra. Bakar-zavisna jedinjenja sa antimikrobnim dejstvom samostalno ili u kombinaciji sa antibioticima efikasni su u lečenju infekcija izazvanih multirezistentnim sojevima bakterija (npr. *S. aureus, M. tuberculosis, E. coli* itd).

Imajući u vidu da bakar-lek interakacije mogu dovesti do izmenjene efikasnosti i/ili bezbednosti terapije, buduća istraživanja o potencijalu jona bakra da stupa u interakcije sa lekovima u fiziološkim uslovima mogu značajno unaprediti efikasnost i bezbednost farmakoterapije.

Ključne reči: bakar, antibiotici, *in vitro*, interakcije.

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MODEL DOKSORUBICINSKE KARDIOMIOPATIJE KOD PACOVA

Vladislav Pajović, Marija Kosić, Nina Japundžić-Žigon

Doksorubicin je antraciklinski antibiotik, jedan od najefikasnijih antitumorskih lekova koji se koristi u terapiji brojnih maligniteta. Međutim, njegovu upotrebu i efikasnost ograničava pojava odložene kardiotoksičnosti koja je rezistentna na terapiju. Najčešće korišćen model za izučavanje doksorubicinske kardiomiopatije je pacov. Cilj naših istraživanja je bio da definišemo fenotip kardiomiopatije. Eksperimenti su rađeni na mužjacima Wistar soja pacova sa ugrađenim radiotelemetrijskim transmiterom za registrovanje hemodinamskih parametara. Jedinke su nasumično raspoređene u eksperimentalnu (5 mg/0,5 mL/kg, I.V. doksorubicin; n=18) i kontrolnu grupu (0,5 mL/kg I.V. fiziološki rastvor; n=6). Pre i nakon intravenske aplikacije doksorubicina pacovi su podvrgnuti ehokardiografiji, proceni autonomnih spektralnih markera i funkcije barorefleksa. Na kraju eksperimenta sakupljena je krv, srce, bubreg i jetra. Ehokardiografski, biohemijski i autonomni parametri su korišćeni za identifikovanje fenotipova nezavisnom metodom mašinskog učenja. Pokazali smo da postoje dva fenotipa doksorubicinske kardiomiopatije kod pacova. Fenotip 1 karakteriše pad ejekcione frakcije leve komore, dilatacija leve komore, stanjenje zida leve komore, pad srčane frekvence, povećanje senzitivnosti barorefleksa i NT-proBNP-a. Fenotip 2 karakteriše očuvana ejekciona frakcija leve komore, hipetrofija i povećanje mase leve komore, očuvane vrednosti srčane frekvence, povećanje senzitivnosti barorefleksa i umereno povećanje NT-proBNP-a. Oba fenotipa su opisana kod čoveka, što ovaj eksperimentalni model kod pacova čini pouzdanim za ispitivanje doskorubicinske kardiomiopatije. Primena nove tehnologije nanočestica je smanjila, ali nije iskorenila pojavu kardiotoksičnosti. Mi smo takođe pokazali da se kardiotoksičnost može značajno smanjiti primenom antidepresiva, paroksetina.

Ključne reči: doksorubicin, kardiomiopatija, fenotip, paroksetin, pacov.

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TRANSLACIONA FARMAKOLOGIJA

Milica Bajčetić[1,2], Bojana Božić[1]

Translaciona farmakologija (TF) predstavlja interdisciplinarnu primenu biomedicinskih istraživanja koja dvosmerno povezuju laboratoriju (bazična istraživanja) i „bolesnički krevet“ (kliničku praksu). Pametni lekovi, ciljane terapije i inovativne formulacije su najilustrativniji primeri. Zahvaljujući translaciji podataka iz predkliničkih istraživanja neonatalna populacija u relativno kratkom periodu dobila je adekvatnu formulaciju za terapiju srčane insuficijencije uzrokovane dilatacionim kardiomiopatijama i urođenim srčanim manama - oralnu disperzibilnu mini tabletu enalaprila. Ova prva inovativna formulacija za neonatuse razvijena je u okviru projekta Lena (*Labeling of Enalapril from Neonates up to Adolescents*) koji je finansiran iz sredstava Evropske unije (*Seventh Framework Program (FP7/2007-2013) under the grant agreement no. 602295*) i odnedavno se nalazi na tržištu pod nazivom Aqumeldi©. Translaciona istraživanja mogu značajno doprinositi bezbednosti terapije. Npr., N-acetil cistein (NAC), antidot kod trovanja acetaminofenom prevenirao je nefrotoksičnost uzrokovanu ifosfamidom (IFO) na LLCPK-1ćelijama i modelu pacova. Rezultati farmakokinetičke analize NAC I IFO na modelu pacova translirani su u cilju lečenja 10 godišnje devojčice sa primarnim neuroektodermalim tumorom i akutnom renalnom insuficijencijom. NAC je u potpunosti prevenirao nefrotoksičnost kod pacijentkinje nakon terapije IFO i očuvao bubrežnu funkciju tokom 12 godina praćenja. S druge strane, Kohranova baza podataka pokazala je da suporativna terapija vitaminima C i E smanjuje efikasnost terapije neonatalne sepse. Molekularno istraživanje *redox* ravnoteže u eritrocitima pokazalo je da vitamin E uklanja vodonik peroksid iz krvi što smanjuje odbrambeni kapacitet organizma. TF omogućava takođe da se primećeni efekti terapije u svakodnevnom radu “vrate u laboratoriju” kako bi se objasnili mehanizmi kojim se ostvaruje to dejstvo. Npr., metilprednizolon dovodi do brze modulacije TOPS-a i obnavlja aktivnost endogene antioksidativne zaštite u eritocitima što rezutira kliničkim i ehokardiografskim poboljšanjem kod dece sa multisistemskim inflamatornim sindromom udruženim sa COVID-19. TF značajno skraćuje vreme i troškove istraživanja i predstavlja odličnu alatku za unapređenje bezbednosti i efikasnosti postojećih i novih terapija.

Ključne reči: translaciona farmakologija, inovativne formulacije lekova, ODMT, MIS-C, oksidativni stres.

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ULOGA KLINIČKOG FARMAKOLOGA U ETIČKOM ODBORU

Nevena Divac

U naučno-istraživačkom radu, kako bazičnom, tako i kliničkom, neophodno je poštovanje jasno definisanih standarda, metoda i etičkih principa, kako bi se zaštitila dobrobit subjekata, osigurala naučna vrednost rezultata i sprečila zloupotreba. Etički odbori, formirani u cilju obezbeđivanja dobrobiti laboratorijskih životinja, kao i etički odbor koji obezbeđuje poštovanje etičnosti u kliničkim ispitivanjima lekova i medicinskih sredstava, ključna su tela u tom procesu. U radu ovih odbora, klinički farmakolozi imaju značajnu ulogu i često veoma kompleksne zadatke.

U skladu sa dostupnošću novih naučnih saznanja o faktorima koji utiču na dobrobit životinja, kao i sposobnosti životinja da osete i izraze bol, patnju, stres i trajno oštećenje, etički odbori (komisije) procenjuju opravdanost predloženih eksperimenata, i predlažu i kontrolišu sprovođenje mera za unapređenje njihove dobrobiti. Članovi našeg Instituta učestvuju u radu etičkih komisija za rad sa eksperimentalnim životinjama primenjujući svoja znanja, a i edukacija budućih istraživača iz oblasti dobre laboratorijske prakse sprovodi se na Institutu.

Etičnost u kliničkim ispitivanjima lekova u Srbiji od 2019. godine je u nadležnosti Etičkog odbora Srbije. Etički odbor odobrava i prati sprovođenje kliničkih ispitivanja lekova u zdravstvenim ustanovama na teritoriji Republike Srbije, obezbeđuje usklađenost sa međunarodnim načelima i smernicama profesionalne etike, odlučuje i daje mišljenja o spornim pitanjima. Poznavanje bazične farmakologije, kliničke medicine i edukacija iz oblasti bioetike čine kliničke farmakologe značajnim članovima ovog tela, koji često rešavaju kompleksna pitanja, pogotovo ona koja se odnose na ispitivanja ranih faza, ispitivanja koja uključuju vulnerabilne ispitanike ili retke bolesti. Od osnivanja ovog tela, aktivni smo članovi i svojim učešćem doprinosimo poboljšanju kvaliteta rada ovog tela.

Ključne reči: etičnost, eksperimentalne životinje, klinička ispitivanja, klinički farmakolog

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KLINIČKI FARMAKOLOG NA ČELU TIMA ZA FRAGILNI X U SRBIJI: BAZIČNA ISTRAŽIVANJA U CILJU RAZVOJA KLINIČKE PRAKSE

Dragana Protić

Fragilni X sindrom (FXS) je najčešći monogenetski uzrok intelektualne zaostalosti i jedan od vodećih uzroka poremećaja iz spektra autizma nastalog mutacijom pojedinačnog gena. Uzrok ovog sindroma je puna mutacija (>200 CGG tripleta) u FMR1 genu koji se nalazi na X hromozomu. Važno je napomenuti da se pored pune mutacije, u istoj porodici detektuje i nepotpuna mutacija (55-200 CGG) FMR1 gena koja može da bude uzrok neuroloških, psihijatrijskih i ginekoloških poremećaja kod odraslih. Stoga, kod fragilnog X, neophodno je posmatrati porodicu kao celinu, a ne pojedinačnog pacijenta. Usled intenzivnog razvoja ove naučne i zdrastvene oblasti u Srbiji tokom poslednje decenije, sve veći broj porodica sa Fragilnim X zahteva evaluaciju specijalizovanog tima za dijagnostiku, terapiju i podršku. Klinički farmakolog ima ključnu ulogu u razvoju i vođenju multidisciplinarnog tima za Fragilni X u Srbiji, s obzirom na specifičnost farmakoterapije i izazove u implementaciji personalizovane medicine kod ovih pacijenata.

Neprocenjiv je značaj intenzivnih bazičnih i kliničkih istraživanja u polju Fragilnog X sa težnjom razvoja ciljane farmakoterapije. U tome, ključnu ulogu u procesu prevođenja rezultata istraživanja u kliničku praksu i optimizaciji doziranja i smanjenju neželjenih dejstava lekova kod pacijenata sa Fragilnim X imaju farmakolozi.

Iskustvo u ovoj oblasti u Srbiji ukazuje na potrebu za specifičnim prilagođavanjima u terapiji zbog različitih faktora kao što su zakonske regulative, dostupnost lekova i socioekonomski uslovi. Klinički farmakolog, kao lider tima, koordinira saradnju između istraživača, kliničara i pacijenata, što rezultira integrisanim pristupom koji vodi ka razvoju novih terapijskih protokola.

Zaključuje se da su bazična istraživanja od suštinskog značaja za unapređenje kliničke prakse u lečenju poremećaja povezanih sa Fragilnim X, a da je uloga kliničkog farmakologa u timu za Fragilni X u Srbiji centralna, jer omogućava primenu najnovijih naučnih saznanja iz farmakologije u svakodnevnoj praksi, uz poboljšanje kvaliteta života pacijenata i njihovih porodica.

Ključne reči: fragilni X sindrom, FMR1 gen, farmakoterapija, klinički farmakolog

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NEUROPSIHOFARMAKOLOGIJA - OD BAZIČNIH ISTRAŽIVANJA DO KLINIČKE PRAKSE

Janko Samardžić, Milica Branković, Dragan Obradović

Neuropsihofarmakologija predstavlja naučnu oblast u okviru farmakologije koja se bavi proučavanjem mehanizma delovanja psihofarmaka, njihovih farmakoloških efekata, kao i farmakokinetičkih i farmakogenetičkih karakteristika, i klinički značajnih interakcija. Nueropsihofarmakologija omogućava razumevanje neurobioloških osnova psihijatrijskih poremećaja, sa fokusom na ulogu odgovarajućih neurotransmiterskih sistema i receptora u centralnom nervnom sistemu, od značaja za savremenu farmakoterapiju. U laboratoriji za neuropsihofarmakologiju Medicinskog fakulteta Univerziteta u Beogradu, koja je usmerena na bihejvioralna istraživanja, primenjuju se različiti eksperimentalni modeli i testovi, poput reakcija izbegavanja averzivne draži i uzdignutog plus lavirinta (EPM) za testiranje anksiolitičkih efekata supstanci, zatim forsiranog plivanja (FST) za ispitivanje potencijalnih antidepresivnih svojstava, kao i čitave baterije testova za procenu uticaja supstanci na procese učenja i pamćenja kod eksperimentalnih životinja. Rezultati, proistekli iz rada laboratorije, publikovani su u brojnim referentnim naučnim časopisima i doprineli su jasnijem sagledavanju značaja benzodiazepinskog mesta vezivanja GABA-A receptora i njihove uloge u utvrđivanju kompleksne povezanosti faktora koji su uključeni u nastanak i razvoj poremećaja raspoloženja i kognicije. Aktuelna istraživanja usmerena su na farmakološku karakterizaciju selektivnih liganada za benzodiazepinsko mesto vezivanja, poput Z-lekova (zaleplon, zolpidem, eszopiklon), sa povoljni-

jim spektrom terapijskih i neželjenih efekata. Pored toga, posebna pažnja posvećena je farmakogenetičkim ispitivanjima, s obzirom da je farmakogenetika jedan od temelja personalizovane medicine i individualizacije farmakoterapije u neuropsihofarmakologiji. U kliničkom smislu, rezultati bazičnih istraživanja otvorili su novo polje proučavanja u oblasti neurobiologije anksioznosti, depresije i kognitivnih poremećaja i sugerisali drugačiji pristup u terapiji poremećaja raspoloženja i sa njima povezanih kognitivnih poremećaja. Angažovanje kliničkih farmakologa u zdravstvenim ustanovama, doprinelo je većoj sinergiji znanja bazične i kliničke neuropsihofarmakologije, te značajno unapredilo farmakoterapijski pristup neuropsihijatrijskim bolestima.

Ključne reči: neuropsihofarmakologija, bihejvioralna istraživanja, benzodiazepini, farmakogenetika, individualizacija terapije.

MINI SIMPOZIJUM
100 GODINA KLINIKE ZA OTORINOLARINGOLOGIJU I MAKSILOFACIJALNU HIRURGIJU UNIVERZITETSKOG KLINIČKOG CENTRA SRBIJE I 70 GODINA KATEDRE ZA OTORINOLARINGOLOGIJU I MAKSILOFACIJALNU HIRURGIJU MEDICINSKOG FAKULTETA UNIVERZITETA U BEOGRADU

Medicinski fakultet Univerziteta u Beogradu

Klinika za otorinolaringologiju i maksilofacijalnu hirurgiju Univerzitetskog kliničkog centra Srbije

PRVI VEK POSTOJANJA, PROŠLOST I BUDUĆNOST KLINIKE ZA ORL I MFH UKCS

Nenad Arsović

Klinika za bolesti uva, nosa i grla je osnovana 1924. godine u Opštoj državnoj bolnici u Beogradu, u zgradi gde je danas smešteno Srpsko lekarsko društvo. Prvi upravnik Klinike bio je profesor Ljubiša Vulović. Godine 1984. Klinika se seli u zgradu dotadašnje Vojne bolnice iz 1921. godine u Pasterovoj ulici, gde se i danas nalazi i deo je Univerzitetskog kliničkog centra Srbije. Prvi vek postojanja obeležavamo sa predavanjima o istorijatu klinike, negujući kulturu sećanja i pijeteta prema našim učiteljima, sa pogledom u budućnost i dobrim planiranjem razvoja i implementacije savremenih vidova dijagnostike i lečenja bolesti uha, grla i nosa i maksilofacijalne regije. Statutom Medicinskog fakulteta u Beogradu iz 1954. godine formirana je Katedra za otorinolaringologiju čiji je osnivač i rukovodilac bio profesor Srećko Podvinec, a kojoj se 1978. godine dodaje i maksilofacijalna hirurgija. Katedra za otorinolaringologiju i maksilofacijalnu hirurgiju Medicinskog fakulteta danas broji 18 članova koji su angažovani u nastavi na integrisanim akademskim studijama medicine na srpskom i engleskom jeziku i svim vidovima poslediplomske nastave.

Ključne reči: Klinika za ORL i MFH, istorijat, medicinski fakultet

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PRIMENA SAVREMENIH MEDICINSKIH TEHNOLOGIJA U LEČENJU KARCINOMA LARINKSA- TLM, TORS, BIOLOŠKA TERAPIJA

Vladimir Đorđević

Kratak pregled savremnih metoda koje su se, prema našem iskustvu, pokazale kao korisne i nezamenljive u svakodnevnoj kliničkoj praksi.

Laringomikroskopija se primenjuje u dijagnostici karcinoma larinksa dugi niz godina, a sve više zauzima mesto i u terpiji maligniteta u larinksu.

Transoralna robotska hururgija, kao najsavremenija tehnologija, značajno poboljšava mogućnosti koje je dosegla laringomikroskopija.

Biološka i naročito imunoterapija, poslednjih godina se sve više primenjuju u nehirurškom lečenju karcinoma ove lokalizacije, preliminarni rezultati su obećavajući, a pravo mesto i uloga ovih modaliteta lečenja biće procenjeni u godinama koje dolaze.

Ključne reči: karcinom larinksa, laringomikroskopija, robotska hirurgija. biološka i imuno terapija.

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ŽIVOTNO UGROŽAVAJUĆE KOMPLIKACIJE GNOJNOG OTITISA SU I DALJE TEMA U 21. VEKU

Ljiljana Čvorović

Napredak u radiološkoj dijagnostici, potentni antibiotici i savremene mikrohirurške tehnike su značajno smanjili morbiditet i mortalitet od intrakranijalnih otogenih komplikacija u zapadnoj hemisferi. Međutim, ove komplikacije se i dalje javljaju, sa stopom mortaliteta od približno 10%.

Prikazaćemo svoja iskustva sa 28 pacijenata koji su lečeni od intrakranijalnih otogenih komplikacija u proteklih pet godina. Razmatraćemo trenutne dijagnostičke procedure, efikasne hirurške tehnike i antibiotske tretmane. Međutim, od ključne važnosti je razmotriti i druge moguće faktore koji doprinose pojavi ovih komplikacija, uključujući porast bakterijske rezistencije na antibiotike, individualne karakteristike pacijenata i pojavu medicinskih grešaka.

Otogene intrakranijalne komplikacije potencijalno su opasne po život. Rana dijagnoza je presudna za efikasno antimikrobno i hirurško lečenje. Bliska saradnja otorinolaringologa, pedijatara, infektologa, mikrobiologa, radiologa i neurohirurga je imperativ. Standardizovanje procedura kroz promociju smernica za upotrebu antibiotika, korišćenje tehnologije za razvoj nacionalnih elektronskih zdravstvenih kartona, poboljšanje dostupnosti

mikroskopije za pregled ušiju radi adekvatne dijagnoze i pružanje kontinuirane edukacije o ovim retkim stanjima su ključni koraci u smanjenju njihovog pojavljivanja.

Ključne reči: otogene komplikacije, gnojni otitis

Medicinski fakultet Univerziteta u Beogradu
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RINOPLASTIKA - NAJSTARIJA ESTETSKA PROCEDURA

Bojan Pavlović

Nosna piramida položena je u centralnim partijama lica i svojom veličinom i oblikom daje doprinos izgledu i simetriji lica. Brojni uzroci mogu dovesti do poremećaja funkcije i izgleda nosa, zato ne čudi činjenica da se operacije nosa danas rade često, širom sveta.

Rinoplastika je naziv za veliki broj operativnih zahvata koji imaju za cilj promenu izgleda nosne piramide. Iako se čini da je estetska operacija nosa savremeni trend, rinoplastika ima dugu istoriju.

Tehnike rekonstrukcije nosa datiraju iz drevnih vremena, kada je amputacija nosa predstavljala metodu kažnjavanja. U svojim spisima 600g.p.n.e. Sushruta je opisao metodu korišćenja lista za pravljenje modela rane i formiranje flapa sa obraza.

Tokom postojanja Rimskog carstva, Celsus je u delu De Medicina opisao operativne tehnike nosa, ušiju i usana.

U petnaestom veku italijanski autori opisali su korišćenje peteljkastog flapa sa ruke za rekonstrukciju, dok je u devetnaestom veku započeto korišćenje čeonog flapa.

Opisi prve zatvorene tehnike rinoplastike opisao je 1887.godine John Orlando Roe. Prvi opisi hirurških tehnika koje su dovele do razvoja otvorene rinoplastike pojavili su se 1921.godine.

Danas se koriste minimalno invazivne tehnike, koje su preuzele najboljeg od otvorene i zatvorene (endonazalne) metode. One imaju za cilj da uz minimalnu traumu i sa skrivenim rezovima reše anatomski problem, omogućei stabilnu strukturu nosne piramide uz očuvanje ili unapređenje funkcije nosa.

Ključne reči: rinoplastika, estetska hirurgija

Medicinski fakultet Univerziteta u Beogradu
Klinika za otorinolaringologiju i maksilofacijalnu hirurgiju Univerzitetskog kliničkog centra Srbije

ALERGENSKA IMUNOTERAPIJA - PRIMENA U OTORINOLARINGOLOGIJI

Miljan Folić

Alergijski rinitis (AR) je veoma često hronično oboljenje koje ostvaruje značajan morbiditet i negativan uticaj na kvalitet života pacijenata. Nastaje nakon izlaganja sezonskim i/ili celogodišnjim alergenima, a u zavisnosti od izazivača i obrasca izlaganja alergenima, simpotomi mogu biti intermitentni i perzistentni.

Alergenska imunoterapija (AIT) poznata kao i desenzibilizacija ima za cilj da izazove ili ponovno uspostavi toleranciju na alergen redukujući sklonost organizma da stvara IgE antitela.

AIT je indikovana kod AR pacijenata sa nedovoljno ostvarenim benefitom nakon standardne antialergijske terapije. Što se tiče ostalih ORL manifestacija u čijoj patogenezi alergija može imati ulogu, poput rinosinuzitisa, adenoidne hiperplazije i sekretornog otitisa, ne postoje sistematski pregledi i meta analize kojima bi se utvrdila efikasnost AIT.

AR je često udružen sa astmom i deca sa AR imaju više od 3 puta veći rizik da razviju astmu kasnije u životu u odnosu na decu koja ne boluju od AR. U ovoj prezentaciji diskutuje se o mogućem preventivnom efektu AIT, o mogućnosti da primena AIT kod zdravih osoba spreči nastanak alergijske bolesti ili da kod osoba sa alergijskim manifestacijama spreči nastanak drugih alergijskih stanja (npr. da li primena AIT kod osoba sa AR može da spreči nastanak astme). Takođe, istražuje se mogućnost AIT kod senzibilisanih osoba da osujeti razvoj dodatne senzibilizacije. Konačno diskutuje se o efikasnosti i bezbednosti dva modaliteta AIT - sublingvalne i subkutane imunoterapije kod pacijenata sa AR.

Ključne reči: alergenska imunoterapija, alergijski rinitis, senzibilizacija

Medicinski fakultet Univerziteta u Beogradu
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MAKSILOFACIJALNA HIRURGIJA KAO REKONSTRUKTIVNA HIRURGIJA

Goran Stojković

Maksilofacijalna hirurgija kao specijalnost koja obuhvata lečenje patoloških stanja širokog spektra, regije glave i vrata, uzrokovanih tumorima, traumatologijom, infekcijama ili urođenim anomalijama, morala je zbog specifičnosti regije koju tretira, da u sebe impregnira još jednu izuzetno zahtevnu hiruršku granu, a to je rekonstruktivna hirurgija.

Davno postavljeni hirurški postulati, da svakoj hirurški tretiranoj regiji, mora biti vraćena njena funkcionalnost, dopunjena je ultimativnim zahtevom, da se moraju uzeti u obzir i svi estetski aspekti s obzirom da je regija glave i vrata konstatno vidljiva, da se ne prekriva i da ima ozbiljan uticaj na kvalitet života pacijenata u postoperativnom periodu.

U rekonstruktivnoj hirurgiji glave i vrata, glavno mesto zauzimaju režnjevi, i to, lokalni režnjevi kada koristimo okolno tkivo da bi nadomestili uklonjeno, peteljkasti režnjevi, koji nam daju značajno veće mogućnosti i uzimaju se iz susednih regiona sa svojom postojećom vaskularizacijom i na kraju, slobodni režnjevi koji se uzimaju iz udaljenih donorskih regija i kada se čini potpuna transplantacija tkiva sa mikrovaskularnim anastomozama u recipijentoj regiji.

Ključne reči: maksilofacijalna hirurgija, rekonstrukcija, režnjevi

MINI SIMPOZIJUM
60 GODINA INSTITUTA ZA MEDICINSKU I KLINIČKU BIOHEMIJU MEDICINSKOG FAKULTETA UNIVERZITETA U BEOGRADU

Institut za medicinsku i kliničku biohemiju, Medicinski fakultet Univerziteta u Beogradu

ISTORIJAT INSTITUTA ZA MEDICINSKU I KLINIČKU BIOHEMIJU

Nataša Petronijević

Institut za biohemiju je osnovan 1. januara 1959. godine kao deo Instituta za fiziologiju. U oktobru 1964. godine Katedra biohemije se formalno razdvaja od Katedre fiziologije kada se i Institut za biohemiju izdvaja kao potpuno samostalna ustanova u okviru Medicinskog fakulteta. Prof. dr Ljubiša Rakić postaje prvi upravnik samostalnog Instituta za biohemiju. Nastavnici i saradnici Instituta su i osnivači Katedri za biohemiju na medicinskim fakultetima u Nišu, Novom Sadu, Kragujevcu, Prištini i Podgorici. Od 2000. godine Institut za biohemiju menja naziv u Institut za medicinsku i kliničku biohemiju.

Tri nastavnika Instituta, akademici prof. dr Ljubiša Rakić (1980-1982 i 1982-1984), prof. dr Bogdan Đuričić (2004-2006 i 2006-2008) i prof. dr Tatjana Simić (2024-) su bili Dekani Medicinskog fakulteta Univerziteta u Beogradu, dok su funkciju prodekana obavljali prof. dr Ljubiša Rakić (1969-1971), prof. dr Vesna Cvejić (2001-2003) i prof. dr Tatjana Simić (2009-2018).

Naučna istraživanja na Institutu uvek su bila raznovrsna, intenzivna i kvalitetna. Istraživanja CNS-a koja su pokrenuli akademik prof. dr Ljubiša Rakić i prof. dr Bogomir Mršulja, istraživanja oksidativnih oštećenja čije je osnove postavila prof. dr Jasmina Mimić-Oka, kao i ispitivanje molekularnih mehanizama ćelijske smrti koje je uveo akademik prof. dr Bogdan Đuričić, su nastavljena do danas. Zahvaljujući značajnim ostvarenim naučnim rezultatima na Institutu je 2023. godine oformljen Centar izuzetnih vrednosti za redoks medicinu, čiji je osnivač i rukovodilac prof. dr Tatjana Simić, i u koji su uključeni svi nastavnici i saradnici Instituta.

Tokom svog postojanja, Institut i članovi Katedre su ostvarivali plodonosnu saradnju sa brojnim institucijama u zemlji i inostranstvu. Danas je Institu za medicinsku i kliničku biohemiju savremena ustanova čija naučna delatnost obuhvata oblasti eksperimentalne, molekularne i translacione medicine. Intenzivnu istraživačku aktivnost na Institutu ilustruje činjenica da su u poslednjih 10 godina istraživači Instituta objavili više od 200 naučnih publikacija u časopisima indeksiranim u JCR listi.

Ključne reči: Institut za medicinsku i kliničku biohemiju, istraživanja CNS, oksidativni stres, molekulski mehanizmi ćelijske smrti, Centar izuzetnih vrednosti za redoks medicinu

Institut za medicinsku i kliničku biohemiju, Medicinski fakultet Univerziteta u Beogradu

NASTAVNA DELATNOST INSTITUTA ZA MEDICINSKU I KLINIČKU BIOHEMIJU

Aleksandra Isaković, Ana Savić Radojević

Nastavna delatnost Instituta za medicinsku i kliničku biohemiju obuhvata organizaciju većeg broja nastavnih programa dodiplomske, poslediplomske, kao i specijalističke nastave.

U okviru dodiplomske nastave, biohemija se od 1959. godine izdvojila iz nastave fiziologije kao samostalni predmet. Na drugoj godini integrisanih akademskih studija (IAS) medicine se organizuje dvosemetralna nastava iz predmeta medicinska biohemija kroz praktičnu i teorijsku nastavu na srpskom i engleskom jeziku. Od akademske 2005/06. godine, prvih devet nedelja pripada nastavi hemije u sklopu zajedničkog predmeta medicinska biohemija i hemija. Pored toga, katedra uspešno organizuje i deset modula izborne nastave: programirana ćelijska smrt, osnovi eksperimentalne medicine, osnovi laboratorijskih tehnika u izučavanju proteina, in vitro modeli u medicinskim istraživanjima, biohemijske osobenosti pojedinih tkiva, osnovi neurohemije, signalni putevi, laboratorijska dijagnostika, biohemijski aspekt fizičke aktivnosti i urođene bolesti metabolizma. Za studente četvrte godine IAS medicine organizuje se nastava iz predmeta klinička biohemija (na srpskom i engleskom jeziku). U okviru osnovnih akademskih studija sestrinstva (OAS) održava se nastava iz predmeta medicinska biohemija.

Poslediplomska nastava se organizuje od 1966. godine u vidu magistarskih i specijalističkih akademskih studija, a danas su nastavnici Katedre osnivači i rukovodioci tri modula doktorskih akademskih studija: molekularna medicina (od 2006. god), neuronauke (od 2011. god) i biologija tumora i oksidativna oboljenja (od 2016. god). Specijalistička nastava na Institutu obuhvata realizaciju programa dve specijalizacije: Klinička biohemija (od 1989. god) i Laboratorijska medicina (od 2011. god), kao i pet programa užih specijalizacija: Laboratorijske tehnike za izučavanje proteina, Molekularno biološka i imunohemijska dijagnostika, Kliničko-biohemijska reumatologija, Laboratorijska dijagnostika u onkologiji i Laboratorijska endokrinologija. Do danas je diplomu specijaliste Kliničke biohemije je steklo više od 200 doktora medicine, a diplomu specijaliste Laboratorijske medicine petnaest doktora medicine, koji uspešno rade i rukovode biohemijskim laboratorijama.

Ključne reči: Medicinska biohemija, Klinička biohemija, Laboratorijska medicina, Molekularna medicina, Neuronauke, Biologija tumora i oksidativna oboljenja

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[2]*Srpska akademija nauka i umetnosti*

ŽIVOT I DELO PROF. DR BOGOMIRA MRŠULJE, DOPISNOG ČLANA SANU

Tatjana Simić[1,2], Nataša Petronijević[1]

Prof. dr Bogomir Mršulja, dopisni član SANU, je rođen 1940. godine u Lendavi u Sloveniji. Gimnaziju i studije medicine završio je u Beogradu. Po diplomiranju zaposlio se kao asistent na Institutu za biohemiju Medicinskog fakulteta u Beogradu i nastavio istraživački rad započet još u studentskim danima. U zvanje docenta izabran je 1970, vanrednog profesora 1978, a u zvanje redovnog profesora biohemije 1984. godine. Bio je upravnik Instituta za biohemiju, šef Katedre za biohemiju i šef Katedre za poslediplomsku i specijalističku nastavu iz Kliničke biohemije Medicinskog fakulteta u Beogradu. Na Institutu je organizovao i rukovodio Laboratorijom za neurohemiju, kroz koju su prošli mnogi istraživači i nastavnici medicinskih fakulteta u Beogradu i drugih institucija širom zemlje.

Usavršavao se u National Institute of Health u Betezdi (SAD) kao visiting scientist u Laboratoriji za neuropatologiju i neuroanatomske nauke (1973—75) i kao specijalni ekspert y Laboratoriji za neurohemiju (1983-84).

Za dopisnog člana SANU izabran je 1994. godine. Iste godine je dobio Oktobarsku nagradu grada Beograda.

Profesor Mršulja je bio međunarodni lider u oblasti istraživanja patofizioloških procesa pokrenutih ishemijom mozga. Njegov rad je, prevashodno, bio usmeren na ispitivanje promena u metabolizmu ugljenih hidrata, nukleotida, biogenih amina, i pokazateljima oksidativnog stresa u ishemiji i reperfuziji. Prvi je razvio metodu izolovanja kapilara mozga i ukazao na značaj njihove biohemijske organizacije za očuvanje krvno-moždane barijere. Rezultati njegovog istraživanja su, između ostalog, omogućili definisanje fenomena maturacije ishemične lezije, fenomena tolerancije moždanog tkiva na ishemiju nakon prethodne ishemije, sagledavanje štetnosti postishemične hiperglikemije za oporavak nervnog tkiva i rasvetljavanje kaskade reakcija koje dovode do ishemičnog oštećenja. Citirani su i u klasičnim udžbenicima neurohemije i uticali su na promenu terapijskog pristupa u lečenju ishemije mozga.

Pored značajnih naučnih dostignuća, širokih interesovanja i lucidnog vizionarstva, profesora Mršulju je veoma posebnim činila velika požrtvovanost i posvećenost učenicima i otvorenost prema novim idejama.

Ključne reči: Bogomir Mršulja, neurohemija, ishemija i reperfuzija mozga

Institut za medicinsku i kliničku biohemiju, Medicinski fakultet Univerziteta u Beogradu

60 GODINA ISPITIVANJA INTEGRATIVNE FUNKCIJE NERVNOG SISTEMA - PROF. DR LJUBIŠA RAKIĆ, SANU

Ivanka Marković

Prof. dr Ljubiša Rakić (1931-2022) je svoju akademsku karijeru na Medicinskom fakultetu započeo 1959. godine, a za upravnika samostalnog Instituta za biohemiju je postavljen 1964.godine U periodu 1980-1984. bio je dekan Medicinskog fakulteta u Beogradu. Za dopisnog člana SANU izabran 1974., a za redovnog člana 1983. godine. Bio je predsednik međuodeljenjskog Odbora za biomedicinska istraživanja, kao i potpredsednik SANU za prirodne nauke (2008–2015). Šezdesetih godina, osnovao je Laboratoriju za neurofiziologiju (danas Odeljenje za neurobiologiju) u Institutu za biološka istraživanja «Dr Siniša Stanković» Beogradskog univerziteta i Međunarodnu laboratoriju za istraživanje mozga u Kotoru pod pokroviteljstvom UNESCO-a i Nacionalnog instituta za zdravlje američke vlade (NIH), u kojima je tokom skoro četiri decenije radilo više desetina naučnika iz velikog broja zemalja. Od kraja šezdesetih godina do početka osamdesetih više puta je bio stalni gostujući profesor Univerziteta u Kaliforniji u Los Anđelesu, a tokom osamdesetih, na Baylor koledžu za medicinu u Hjustonu. Istraživanja profesora Rakića obuhvataju oblast centalnog nervnog sistema i, najšire gledano, odnose se na izučavanje neurološke osnove ponašanja. Postavljajući u centar istraživanja izučavanja osnovnih nervnih procesa, razdraženje i inhibiciju, razmatrao ih je sa aspekta parametara više naučnih disciplina - neurofizioloških, biohemijskih, imunoloških i evolucionih. Globalno uzevši, rezultati istraživanja doktora Rakića se mogu svrstati u nekoliko grupa: (1) regulacioni mehanizmi razdraženja i inhibicije u centralnom nervnom sistemu; (2) biohemijska organizacija centralnog nervnog sistema; (3) biološki ritmovi u mozgu; (4) istraživanje neuroimunologije i plastičnosti mozga; (5) evoluciona biohemija i fiziologija mozga sa posebnim naglaskom na regulacionu ulogu medijatora nervnog sistema u procesima rane embriogeneze; (6) krvno-moždana barijera; (7) centralni nervni sistem i rak i genska terapija tumora. Objavio je preko 500 radova u integralnom obliku 9 monografija, koji su obilato citirani u kompetentnoj naučnoj literaturi, kao i 5 udžbenika. Dobitnik je Sedmojulske nagrade (1968) i nagrade AVNOJ-a (1977 godine) za naučni rad.

Ključne reči: Ljubiša Rakić, evoluciona biohemija i fiziologija mozga, krvno-moždana barijera, biohemijska organizacija CNS

Srpska akademija nauka i umetnosti

RAZNOVRSNOST I KOMPLEKSNOST ĆELIJSKE SMRTI – ISTRAŽIVANJA PROF. DR BOGDANA ĐURIČIĆA, SANU

Vladimir Bumbaširević

Akademik Bogdan Đuričić bio je izuzetna ličnost, visokih moralnih standarda, velike intelektualne radoznalosti i neumorne stvaralačke energije. Celokupno njegovo naučno delo je vezano za izučavanja u oblasti biohemije i molekularne i ćelijske biologije. Ovim istraživanjima se bavio ne samo u našoj sredini, već i u čuvenim svetskim laboratorijama u SAD, Nemačkoj i Japanu. Profesor Đuričić je, pored svog izuzetnog doprinosa u nauci, uspešno obavljao i čitav niz značajnih funkcija u akademskom okruženju, čime je bitno doprineo afirmaciji i razvoju Medicinskog fakulteta i Univerziteta u Beogradu u celini.

Imao sam veliku čast i zadovoljstvo da još davne 1986. godine počeo da sarađujem sa prof. Đuričićem na istraživanjima apoptoze. Bilo je to u vreme kada je započeo veći interes za izučavanje ćelijske smrti, otkrićem gena uključenih u regulaciju ovog procesa, ukazujući na mogućnost njegove modulacije, te iznalaženja specifičnih terapiskih modaliteta u različitim bolestima.

Istraživanja ćelijske smrti u okviru zajedničkih projekata u kojima su učestvovale koleginice i kolege sa histologije, biohemije, imunologije, hematologije i neurologije, obuhvatala su ispitivanja mehanizama uključenih u regulaciju ovog procesa in vivo i in vitro uslovima, njegovu ulogu u razvoju različitih oboljenja, značaj za prognozu, kao i mehanizme uključene u razvoj rezistencije na terapijska sredstva. Svim ovim istraživanjima, profesor Đuričić doprinosio je svojim kreativnošću i obiljem nestandardnih ideja.

Pored publikacija i saopštenja na mnogim međunarodnim kongresima, magistarskih radova i doktorskih disertacija, navedena saradnja doprinela je i popularizaciji ovog naučnog problema u našoj sredini. U tom smislu smo 1995. godine organizovali i dva simpozijuma, jedan na Medicinskom fakultetu u Beogradu 1995. godine, a drugi u Akademiji medicinskih nauka SLD 1997. iz čega je proistekla i jedna monografija. I na kraju bih pomenuo i da je ova saradnja doprinela organizaciji kvalitetnih doktorskih studija iz molekularne medicine na našem fakultetu.

Ključne reči: Bogdan Đuričić, apoptoza, ćelijska smrt

MINI SIMPOZIJUM
JAVNO-ZDRAVSTVENI ASPEKTI BIHEJVIORALNIH ZAVISNOSTI: STARI NEPRIJATELJ U NOVOM RUHU

Institut za socijalnu medicinu, Medicinski fakultet Univerziteta u Beogradu

JAVNO-ZDRAVSTVENI ZNAČAJ BIHEJVIORALNIH ZAVISNOSTI- NOVI, NEDOVOLJNO PREPOZNATI IZAZOVI

Zorica Terzić Šupić

Poslednjih nekoliko decenija sve više su prepoznate zavisnosti od određenog ponašanja, koje imaju simptome karakteristične za zavisnosti od supstanci (žudnja, tolerancija, apstinencijalni sindrom), sličan prirodni tok bolesti, sličnog su komorbiditeta, genetskih karakteristika i neurobiološkog mehanizma. Ove oblike zavisnosti nazivamo bihejvioralnim zavisnostima (patološko kockanje, zavisnost od video igara, zavisnost od interneta/društvenih mreža, zavisnost od mobilnih telefona, kompulzivna kupovina, zavisnost od seksa, hrane, vežbanja, ljubavi, posla, solarijuma ili kompulzivno diranje kože i kose). Neke od njih, (kao što su problematično kockanje i poremećaj igranja video-igara) su deo međunarodnih klasifikacija bolesti (MKB-10, DSM-4, MKB-11 i DSM-5), sa već jasno definisanim kriterijumima za postavljanje dijagnoze. Značajno je naglasiti razlike između bihejvioralnih zavisnosti i preteranog učešća u nekoj aktivnosti, koje čak iako je udruženo sa štetnim posledicama nema sve karakteristike zavisnosti. Preterana konzumacija čokolade, čak i ukoliko je praćena dobijanjem u telesnoj masi, nije bihejvioralna zavisnost. Iako druga bihejvioralne zavisnostiza sada nisu prepoznate kao deo međunarodnih klasifikacija bolesti, to ne znači da ne predstavljaju psihijatrijske poremećaje. Do danas nisu uključeni u klasifikacije zbog nedostatka dovoljno dokaza o načinima procene, kliničkom toku i terapiji. Opisan je veliki broj poremećaja koji bi mogli da predstavljaju oblike bihejvioralnih zavisnosti, međutim njihova učestalost nije tačno poznata zbog malog broja istraživanja na reprezentativnim uzorcima. Prevalencija patološkog kockanja je najčešće ispitivana u opšoj populaciji i kreće se od 0,15% do 3,5%. U Srbiji iznosi 0,5%. Populacija adolescenata je najčešće ispitivana populacija u oblasti zavisnost od video igara (Holandija 5,4%), vežbanja (8,5% - 27%), interneta/društvenih mreža (20% u Istočnoj i Jugoistočnoj Aziji) i solarijuma (7,02% u Sjedinjenim Američkim Državama). U opštoj populaciji dominira zavisnost od posla 8,0% - 17,5%. U mnogim zemljama, u toku je saradnja između istraživača, kliničara i donosioca odluka kako bi se razvile preventivne i interventne strategije za poboljšanje ishoda oporavka i sprečavanje recidiva usled bihejvioralnih zavisnosti.

Ključne reči: bihejvioralne zavisnosti; klasifikacije bolesti; MKB-11; DSM-V

Institut za medicinsku fiziologiju, Medicinski fakultet Univerziteta u Beogradu

FIZIOLOŠKE OSNOVE ZAVISNOSTI

Dejan Nešić

Zavisnost je prinudni poriv koji samog sebe podstiče, odnosno, imanje jake fizičke ili psihološke potrebe da se nešto uradi ili upotrebi. Zavisnost je stanje u kojem osoba nije u stanju da prestane da koristi ili uzima neku psihoaktivnu supstancu odnosno kada osoba nije u stanju da prestane da ima zavisnost od određenog ponašanja. Psihoaktivne supstance ostvaruju svoje efekte delujući na promenu aktivnosti neurotransmitera u CNS-u na nivou sinaptičke pukotine. Psihoaktivne supstance mogu menjati aktivnost sledećih neurotransmitera: dopamina, serotonina, noradrenalina, acetilholina, gama aminobuterne kiseline, glutamata. Promena nivoa neurotransmitera u postsinaptičkoj pukotini je važan faktor koji determiniše uticaj psihoaktivnih supstanci na ponašanje i raspoloženje, delujući na *reuptake* (ponovno preuzimanje neurotransmitera), takođe, psihoaktivne supstance mogu ispoljiti agonističko ili antagonističko delovanje. Agonistički efekti pojačavaju transmisiju ili povećavaju produkciju neurotransmitera, pojačavajući oslobađanje neurotransmitera ili aktivirajući receptorska mesta koja normalno stimuliše specifičan neurotransmiter. Antagonistički efekti ometa oslobađanje neurotransmitera, blokirajući receptorska mesta za koja bi se vezao neurotransmiter, ili izazivaju „curenje“ neurotransmitera iz sinaptičkih vezikula. Za doživljaj nagrade, zadovoljstva, osećaja prijatnosti odgovorne su sledeće strukture CNS: mezokortikolimbički dopaminski sistem, odnosno ventralna tegmentalna area sa svojim projekcijama ka, amigdalnim jedrima i prefrontalnom korteksu, u subkortikalnim i kortikalnim strukturama CNS, strukturama limbičkog sistema, nucleus accumbensu, dopamin aktivira „puteve zadovoljstva” prilikom uzimanja psihoaktivnih supstanci, tako što prekomerno raste i brzo pada nivo dopamina, a ukoliko se ove epizode ponavljaju u kraćim vremenskim intervalima ne dolazi do normalne restitucije u dopaminskim depoima. Posle izvesnog vremena dolazi do trošenja rezervi dopamina u presinaptičkoj membrani, dolazi do dugotrajnog poremećaja balansa u količini dopamina u pomenutim strukturama. Kao rezultat učestalog egzogenog unosa psihoaktivnih supstanci i neadekvatnog oslobađanja prekomerne količine dopamina, kao i njegovog ubrzanog trošenja, dolazi do neuroadaptacije sinaptičkih membrana, one se prilagođavaju i „nauče” kako da funkcionišu u ovoj novonastaloj situaciji, pogotovo ukoliko se ovakva situacija ponavlja i traje. Neke od psihoaktivnih supstanci koje se zloupotrebljavaju, nakon administriran-a, izazivaju jačanje nagona

da se supstanca koristi. Ovaj fenomen - fenomen početka - označen je kao *„prajming“* (priming).

Ključ**ne reči:** zavisnost, psihoaktivne supstance, neurotransmiteri, dopamin, tolerancija, fenomen početka

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ZAGONETKA ZAVISNOSTI SA STANOVIŠTA SAVREMENE PSIHIJATRIJE

Olivera Vuković

Danas se zavisnost pretežno shvata kao hronično stanje, najčešće neurobiološkog porekla, koje zahteva dugotrajno lečenje. Istovremeno se ističe da je zavisnost individualni problem, sa fokusom na biomedicinsku paradigmu. Iako ovi modeli nude značajan uvid u mehanizme zavisnosti, postavlja se pitanje da li su dovoljno sveobuhvatni da obuhvate sve aspekte te pojave.

Dublje rasprave vode se kroz analizu istraživanja prirodnog toka bolesti i spontanih remisija. Neka istraživanja pokazuju da postoje ljudi koji uspevaju da prevaziđu svoju zavisnost bez ikakve intervencije i stručne pomoći, što dovodi u pitanje stabilnost dijagnoze i efikasnost različitih tretmana. Ovi nalazi ukazuju na potrebu za otvorenijim pristupom koji bi uzeo u obzir heterogenost zavisnosti i individualne razlike u njenom razvoju i ishodima.

Sociokulturni faktori takođe igraju značajnu ulogu. Zanimljiva perspektiva je da se zavisnost može posmatrati kao prilagođavanje dislokaciji u modernom, fragmentovanom društvu. U ovom kontekstu, zavisnost se posmatra kao način na koji savremeni čovek pokušava da ispuni osećaj praznine i smanji stres. U svetu koji postaje sve konkurentniji i potrošački, supstance i zavisnička ponašanja pružaju privremeni osećaj pripadnosti i identiteta, ali na duge staze dovode do još veće izolacije i pogoršanja zavisnosti.

Očigledno je da je zavisnost složena pojava koja se ne može svesti na jednostavne definicije ili tretmane. Potrebno je sveobuhvatno razumevanje koje će obuhvatiti i individualne biološke predispozicije i šire društvene i kulturne kontekste u kojima nastaje i funkcioniše. Samo takvim pristupom moguće je adekvatno odgovoriti na izazove koje zavisnost postavlja pred individuu i savremeno društvo.

Ključne reči: prirodni tok bolesti; socio-kulturalni faktori; faktori

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KOCKANJE SA ŽIVOTOM- PROBLEMATIČNO I PATOLOŠKO KOCKANJE, JAVNO-ZDRAVSTVENI ASPEKTI

Todorović Jovana, Vidojević Jovana

Patološko kockanje, odnosno poremećaj kockanja definišemo kao ,,trajni i rekurentni oblik kockanja koji dovodi do klinički značajnog oštećenja ili distresa (peto izdanje dijagnostičko-statističkog priručnika za mentalne bolesti, DSM-V)''. U petom izdanju dijagnostičko-statističkog priručnika za mentalne bolesti, poremećaj kockanja je jedini entitet u novoj kategoriji nazvanoj bihejvioralne adikcije. Često se može sresti i termin problematično kockanje koje nije na isti način svuda definisano i nije još uvek uključeno u dijagnostičke priručnike. Negativne posledice patološkog kockanja u vezi su sa finansijskim problemima, problemima u porodici, nasiljem u porodici, zloupotrebom psihoaktivnih supstanci, razvojem mentalnih poremećaja, čak i samoubistvom. Prevalencija patološkog kockanja u opštoj populaciji nije poznata i pretpostavlja se da varira između 0,15% i 3,5%, dok je kod adolescenata učestalost između 0,4% i 26%. U DSM-V se navodi devet kriterijuma za postavljanje dijagnoze patološkog kockanja: 1) potreba da se svaki put uloži više novca kada se kocka; 2) pojava apstinencijalnih simptoma kao što su iritabilnost, nervosa prilikom pokušaja da se umanji kockanje; 3) ponavljani neuspešni pokušaji da se kontroliše kockanje; 4) preterno razmišljanje o kockanju (preokupacija); 5) kockanje u cilju izbegavanja problema ili lošeg raspoloženja; 6) pokušaji da se nadoknade prethodni gubici; 7) laganje o učešću u kockanju i prikrivanje vremena provedenog u kockanju; 8) gubitak socijalnih kontakata, posla ili prilika za školovanje zbog kockanja; 9) oslanjanje na druge ne bi li se pokrili gubici. Faktori rizika su muški pol, starost ispod 30 godina, niži obrazovni status, nezaposlenost, izbeglištvo. Često se patološko kockanje javlja udruženo sa drugim psihijatrijskim poremećajima kao što su anksiozni poremećaji, zloupotreba supstanci, ali i hroničnim somatskim bolestima. Anksiozni poremećaji prisutni su kod 37,5% patoloških kockara, a zloupotreba psihoaktivnih supstanci kod oko 57,4%.U prevenciju pojave patološkog kockanja uključene su i Svetska asocijacija organizatora igara na sreću i Nacionalne lutrije evropskih zemalja, i tako je razvijen program odgovornog kockanja.

Ključne reči: poremećaj kockanja; prevalencija; faktori

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JAVNOZDRAVSTVENA KONCEPTUALIZACIJA PROBLEMATIČNE UPOTREBE INTERNETA

Milena Šantrić Milićević, Aleksandar Stevanović

Koncept zavisnosti od Interneta se još uvek razvija, i do sada se najčešće umesto o zavisnosti govori problematičnoj upotrebi Interneta. Početak razvoja ovog koncepta karakterišu razlike u stavovima o tome da li ono predstavlja izdvojen dijagnostički entitet ili je posledica drugih poremećaja, kao što je anksioznost. Jong i Grifit su prvi definisali zavisnost od Interneta kao jedinstveni entitet bolesti kod osoba zavisnih od određene Internet aplikacije, koja pokreće patološko ponašanje. Šo i Blek su istakli

da diskurs ove zavisnosti razvija sa porastom upotrebe računara i pristupa Internetu. Fenomenološki, podvrste zavisnosti od Interneta imaju svoje posebne karakteristike: neobuzdano korišćenje socijalnih mreža online kupovina i e-trgovanje, prekomerno online kockanje i igre na sreću, sajber-seksualne aktivnosti, patološka potreba za e-mail komunikacijom preko pretraživanih baza podataka i druženjem na Internetu, ili pregledanje – tzv."surfovanje" društvenim mrežama (npr. Facebook, Tik-Tok, Instagram).

Nasuprot njima, postoji struja istraživača koja sugeriše da je problematična upotreba Interneta verovatnije simptom drugog osnovnog poremećaja, odnosno da je Internet samo mehanizam isporuke, te da se usled drugog patološkog stanja poseže za prekomernom upotrebom Interneta. Oni najčešće pominju mentalne poremećaje koji se mogu pojaviti pre razvoja zavisnosti, ali mogu i proizaći iz zavisnosti od Interneta; ti poremećaji su depresija, socijalna fobija i neprijateljstvo, somatizacija, paranoična ideja, i fobična anksioznost. Takvo mišljenje je suprotno stavu da zavisnost od Interneta treba smatrati zasebnim poremećajem.

S obzirom da se u javnozdravstvenim istraživanjima prati incidencija i prevalencija prekomerne/problematične upotrebe, odnosno zavisnosti od Interneta, vrlo je jasno da je ovaj fenomen prepoznat kao problem javnog zdravlja od lokalnog do globalnog nivoa.

Da bi se konceptualne neusaglašenosti razrešile, potreban je konsenzus u pogledu izbora instrumenata i kriterijuma za merenje zavisnosti od Interneta i u tom smeru se očekuje razvoj ovog koncepta u budućnosti.

Ključne reči: problematična upotreba internet; zavisnost od interneta; mentalno zdravlje

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POVEZANOST PROBLEMATIČNE UPOTREBE INTERNETA SA RIZICIMA PO MENTALNO I FIZIČKO ZDRAVLJE

Janko Janković

Problematična upotreba interneta ili zavisnost od interneta je psihički poremećaj koji se manifestuje kao opsesivna želja da se provodi vreme na internetu. Podrazumeva sledeće četiri karakteristike: prekomernu upotrebu interneta; apstinencijalnu krizu - osećaj besa, napetosti i/ili depresije kada je kompjuter nepristupačan; toleranciju; i negativne posledice, kao što su svađe, laganje, loša postignuća, socijalna izolacija i umor. Problematična upotreba interneta je povezana sa različitim psihijatrijskim poremećajima i simptomima kao što su: poremećaj hiperaktivnosti i deficita pažnje, depresija, anksioznost, neprijateljski stav ili agresija, poremećaji ličnosti, poremećaj kontrole ponašanja, strah od druženja, somatski bol, opsesivno-kompulzivni poremećaj i nesanica.

Studija sprovedena u Nemačkoj je pokazala da su kod ispitanika koji su naveli da je igranje igrica bila njihova glavna aktivnost na internetu otkriveni pridruženi psihijatrijski poremećaji kao što su: konzumiranje droga, poremećaji raspoloženja, anksiozni poremećaji, i različiti poremećali ličnosti. Približno 43% devojčica i 13% dečaka sa poremećajem igranja igrica na internetu ima česte misli o samoubistvu naspram svega 4% devojčica i 2% dečaka bez navedenog poremećaja. Istraživanje iz Južne Koreje je pokazalo da srednjoškolci koji su zavisni od interneta imaju u 37,7% prekomernu dnevnu pospanost, u poređenju sa 7,4% onih koji nisu zavisni. Prevalencija nesanice, hrkanje, apneja, škrgotanje zubima i noćne more su takođe izraženije kod zavisnika od interneta u poređenju sa onima koji nisu zavisni. Kako je internet sveprisutan u našim životima u kućnom ambijentu, školi i na poslu, tako može stvoriti bračne, akademske i poslovne probleme.

Kao mera prevencije preporučuje se direktan razgovor sa osobama koje preterano ili problematično igraju igrice na internetu. Psihološke (kognitivna bihejvioralna terapija, bračna i porodična terapija) i farmakološke intervencije (metilfenidat, escitalopram i bupropion) pokazale su se veoma efikasnim za smanjenje vremena koje zavisnici od interneta provedu na mreži, kao i simptoma depresije i anksioznosti. Mnoge zemlje jugoistočne Azije su osnovale ustanove za lečenje zavisnosti od interneta.

Ključne reči: problematična upotreba interneta, zavisnost od interneta, psihički poremećaji, fizičko zdravlje

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BIHEJVIORALNE ZAVISNOSTI KOD ADOLESCENATA – IZAZOVI I MODELI PREVAZILAŽENJA

Roberto Grujičić, Ilija Božić

Adolescencija predstavlja tranzitorni period koji se odlikuje burnim emocionalnim i ponašajnim promenama mladih osoba. Ovaj period je praćen značajnim promenama, kako u biološkom smislu (npr. hormonalne, telesne i neurobiološke promene), tako i u psihološko-emotivnom i socio-kulturološkom domenu, a impulsivnost i emocionalna nestabilnost koje karakterišu ovaj period često dovode do pojave rizičnih ponašanja. Iako se ponašanja koja vode ka bihejvioralnoj zavisnosti mogu pojaviti u bilo kom periodu života, mogućnost razvijanja adikcije je u najvećoj meri prisutna u adolescenciji, kada se obično i pojavljuju prvi znaci mentalnih bolesti. U grupu ponašajnih zavisnosti svrstavaju se zavisnost od interneta i društvenih mreža, zavisnost od mobilnih telefona, kupovine, pornografije, fizičke aktivnosti, hrane, a zavisnost od kockanja i igranja video igara su u okviru MKB-11 dobili svoje dijagnostičke šifre, što ukazuje na njihov značaj. Tretman adolescenata sa bihejvioralnim zavisnostima nosi specifične izazove zbog niza faktora koji su povezani

sa biološkim, psihološkim i socijalnim karakteristikama osoba u ovom dobu. Njihova percepcija problema otežava prepoznavanje potrebe za tretmanom, a činjenica da adolescenti ne vide neposredne negativne posledice svog ponašanja smanjuje njihovu motivaciju za promenom ovog ponašanja. Razvoj autonomije mladih osoba koji je praćen nedostatkom poverenja u porodicu i zdravstvene radnike, smanjuje komplajansu prema lečenju. Bihejvioralne zavisnosti često nisu izolovane, već su povezane sa drugim oblicima zavisnosti ili sa mentalnim problemima kao što su depresija, anksioznost ili poremećaji u ishrani. Primećeno je da oko 60% adolescenata sa poremećajem zavisnosti ispunjava kriterijume i za neku drugu mentalnu bolest. Prisustvo komorbiditeta komplikuje dijagnostiku i zahteva da se u tretman uključi i lečenje identifikovanih pridruženih stanja. Prema tome, efikasan tretman zahteva holistički pristup koji uzima u obzir sve navedene izazove i pruža podršku kroz individualizovane terapijske strategije, edukaciju porodice i podršku iz šireg socijalnog okruženja, a pre svega uspostavljanje adekvatnog terapijskog saveza sa pacijentom.

Ključne reči: adolescencija, zavisnosti, ponašanje, impulsivnost, tretman

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ZAVISNOST OD PAMETNIH TELEFONA – EPIDEMIOLOŠKI ASPEKTI

Aleksandra Nikolić

Poslednjih godina zavisnost od pametnih telefona postaje sve prisutnija, naročito među mladima i studentima, što ima značajne posledice po njihovo mentalno zdravlje, socijalne odnose i akademski uspeh. Naše istraživanje, sprovedeno među studentima Medicinskog fakulteta Univerziteta u Beogradu (MFUB) i Univerziteta u Nišu (MFUN), pružilo je uvid u prevalenciju zavisnosti od pametnih telefona u ovoj populaciji. Rezultati su pokazali da je prevalencija zavisnosti kod svih studenata iznosila 20,8%, s nešto većom prevalencijom kod muškaraca (22,3%) u poređenju sa ženama (20,2%). Kod studenata MFUB, prevalencija zavisnosti bila je 19,7%, dok su muškarci imali 21%, a žene 19,1%. S druge strane, studenti MFUN pokazali su veću prevalenciju zavisnosti od pametnih telefona, koja je iznosila 24,1% i to 26% kod muškaraca i 23,2% kod žena. Statistički značajna razlika između studenata MFUN i MFUB ukazuje na to da studenti MFUN imaju značajno veću sklonost ka zavisnosti od pametnih telefona u poređenju sa studentima MFUB. Upoređujući ove podatke sa istraživanjima iz drugih zemalja, primetno je da se prevalencija zavisnosti od pametnih telefona na globalnom nivou razlikuje. Upotrebom iste skale procenjeno je da je 16,9% studenata u Švajcarskoj zavisno od pametnih telefona, u Kini 29,8%, u Brazilu 33,1%. Najveća prevalencija zavisnosti kod studenata nađena je u Saudijskoj Arabiji, čak 71,9%, Indiji i u Iraku 78,3%. Razlike u prevalenciji zavisnosti od pametnih telefona među studentima u različitim zemljama mogu biti posledica različitog društvenog i kulturnog okruženja, kao i razvijenosti i dostupnosti informaciono-komunikacionih tehnologija. Ovi nalazi ukazuju na potrebu za specifičnim intervencijama i strategijama prevencije koje uzimaju u obzir lokalne kulturne i socijalne faktore. Razumevanje varijacija u prevalenciji zavisnosti od pametnih telefona na globalnom nivou može pomoći u razvijanju efikasnijih metoda za smanjenje ove sveprisutne zavisnosti i pružanje odgovarajuće podrške studentima širom sveta.

Ključne reči: zavisnost, pametni telefoni, studenti

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MOBILNI TELEFONI U PREVENCIJI ZAVISNOSTI

Dejana Vuković

Sa povećanjem upotrebe mobilnih telefona posebno onih sa mogućnošću instaliranja aplikacija ("pametni telefoni"), zdravstveni radnici su postali zainteresovani za mogućnosti njihovog korišćenja u praćenju hroničnih stanja kao što su HIV, dijabetes, hipertenzija i astma. Mobilni telefoni pružaju zdravstvenim radnicima kontinuirane podatake o pacijentima u vezi sa ponašanjem, simptomima i fiziologijom. Mobilni telefoni omogućavaju lekarima i drugim zdravstvenim radnicima povezivanje sa teško dostupnim populacijama koje inače ne bi imale pristup zdravstvenim uslugama.

Uprkos tome što je zavisnost teško stanje, procenjuje se da ukupno manje od 20% ljudi sa poremećajem zavisnosti ima pristup adekvatnom lečenju i to važi za sve zemlje. Mobilno zdravlje (mHealth) može pomoći da se smanji ovaj „jaz u lečenju" poboljšanjem rane dijagnoze i pristupa lečenju. Svetska zdravstvena organizacija definisala je mobilno zdravlje kao svaku medicinsku intervenciju zasnovanu na mobilnim uređajima. Stoga, mobilni telefoni mogu igrati značajnu ulogu u prevenciji zavisnosti tako što omogućavaju lak pristup resursima, mrežama podrške i obrazovnim alatima. Zdravstvene aplikacije mogu ponuditi svakodnevne podsetnike, pratiti navike i pružiti strategije suočavanja za sprečavanje zloupotrebe supstanci ili drugih oblika zavisnosti. Mobilni telefoni takođe omogućavaju brzu komunikaciju sa savetnicima ili grupama za podršku vršnjacima. Pored toga, mogu se koristiti za pristup sadržaju koji promoviše zdrav život i svest o rizicima povezanim sa zavisnošću, što ih čini vrednim alatom u proaktivnim naporima u prevenciji zavisnosti. U kliničkoj praksi, zdravstvene aplikacije mogu ponuditi komplementaran pristup uobičajenom pristupu lečenja i poboljšati efikasnost terapije, konsolidovati i održati promenu ponašanja na dugoročnoj osnovi.

Iako trenutno postoji više od 300.000 zdravstvenih aplikacija samo mali broj je prošao ispitivanje delotvornosti. Neke aplikacije čak podstiču upotrebu supstanci,

implicitno ili eksplicitno. Rezultati publikovanih studija se najviše odnose na aplikacije koje pomažu u odvikavanju od pušenja, zloupotrebe alkohola i droga, a samo malobrojne drugim zavisnostima kao što su kockanje i prejedanje. Studije sugerišu da neke mobilne aplikacije mogu pozitivno uticati na zdravstveno ponašanje, smanjenje upotrebe cigareta i alkohola. Studije koje su rađene su pratile pacijente u kratkom vremenskom periodu, pa nije jasno koliki su efekti u srednjem odnosno dužem periodu.

Potrebno je više randomizovanih kontrolisanih ispitivanja tokom dovoljno dugog perioda, najmanje 12 meseci, i u većem obimu da bi se mogli predvideti održivi rezultati. Uticaj ovih intervencija se mora meriti u različitim kontekstima (sa ili bez lečenja, na različitu težinu zavisnosti, u različitim sociodemografskim kontekstima) da bi se bolje razumela njihova ograničenja i profil pacijenata koji bi mogli biti prijemčiviji za ovu vrstu intervencije.

Ključne reči: mobile phone, smartphone app, substance use disorder

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JAVNO-ZDRAVSTVENI IZAZOVI KOMPULZIVNE KUPOVINE:„TAJNI SVET SNOVA JEDNE KUPOHOLIČARKE”

Vesna Bjegović-Mikanović, Ivana Sotirović

Kompulzivnu kupovinu, oniomaniju, karakteriše neodoljiva i nekontrolisana želja za kupovinom, često bez obzira na potrebu ili finansijske mogućnosti, uz delovanje emocionalnih ili psiholoških faktora. Pojedinci sa ovim poremećajem mogu da dožive osećaj euforije ili olakšanja tokom kupovine, ali to često prate osećaj krivice, stida ili finansijski problemi. Premda je kompulzivna kupovina, kao fenomen, u nauci poznata još od početka dvadesetog veka, tek poslednjih godina zaokuplja pažnju naučne i opšte javnosti, pa je i predmet brojnih eksperimentalnih i javnozdravstvenih studija. Ovaj naratavni pregled ima za cilj da rasvetli javnozdravstvene izazove kompulzivne kupovine čija se prevalencija, u zavisnosti od zemlje, kreće od 4% do 8,9%.

Inspirisan nedavnom popularnom publikacijom „Tajni svet snova jedne kupoholičarke”, ovaj pregled pruža rezime dokaza, identifikujući zajedničke teme, trendove, nedostatke i razilaženja u naučnoj literaturi. U strategiji pretraživanja obim je ograničen na javnozdravstvene aspekte kompulzivne kupovine. Posebna pažnja posvećena je faktorima koji se povezuju sa ovim poremećajem ponašanja i inicijativama koje integrišu preventivne pristupe u rešavanju izazova kompulzivne kupovine.

Teorijski i istraživački pristupi kompulzivnoj kupovini često se oslanjaju na postojeće modele koji objašnjavaju poremećaje ponašanja. Nekoliko istraživačkih instrumenata je razvijeno i validirano za procenu kompulzivnog poremećaja kupovine (*Compulsive Buying Scale, Richmond Compulsive Buying Scale, Yale-Brown Obsessive-Compulsive Scale—Shopping Version, Bergen Shopping Addiction Scale Pathological Buying Screener, Edwards Compulsive Buying Scale* i mnoge druge). Ovi alati su dizajnirani da procene ozbiljnost kompulzivnog ponašanja pri kupovini, psihološke aspekte i uticaj poremećaja na život pojedinca i zajednice. Preliminarni dokazi iz eksperimentalnih neuropsiholoških studija ukazuju na to da je kompulzivna kupovina povezana sa traženjem nagrade, žudnjom za kupovinom i donošenjem nepovoljnih odluka pod nejasnim uslovima rizika koji se mogu pripisati poremećenoj emocionalnoj povratnoj informaciji. Poremećaj nije povezan sa deficitima u opštem funkcionisanju – istraživanja su pokazala da osobe sa ovim kompulzivnim poremećajem ne pokazuju značajne razlike u opštim kognitivnim zadacima, kao što su pažnja i koncentracija, u poređenju sa zdravim kontrolama. Međutim, studije ukazuju na pristrasnost pažnje prema signalima vezanim za kupovinu, posebno kod onih sa velikom ozbiljnošću simptoma, što sugeriše da stimulansi za kupovinu mogu pokrenuti pojačano kognitivno angažovanje kod pogođenih pojedinaca. Druga linija studija je istraživala odnos između stresa i kompulzivne kupovine, naglašavajući da je stres značajan faktor u razvoju i održavanju kompulzivnog ponašanja pri kupovini. Psihofarmakološke studije sa selektivnim inhibitorima ponovnog preuzimanja serotonina ili opioidnim antagonistima su preliminarne sa malim uzorcima. Malo je istraživanja koja ispituju da li je ovaj poremećaj nasledan. Sve studije naglašavaju nekoliko izazova javnog zdravlja u prevenciji kompulzivne kupovine. Pored ekonomskog uticaja i gubitka produktivnosti, izazovi se odnose i na udruženost kompulzivne kupovine sa drugim poremećajima mentalnog zdravlja (depresija, anksioznost, zloupotreba supstanci), kao i sa stigmom i izolacijom. Kompulzivna kupovina pogoršava mentalno zdravlje i stvara prepreke za traženje pomoći. S druge strane, kompulzivna kupovina opterećuje zdravstveni sistem i povećava zahteve za zdravstvenim uslugama.

Javnozdravstvene studije pokazuju da postoji potreba za inicijativama javnog zdravlja koje se fokusiraju na prevenciju i ranu intervenciju, posebno u populacijama visokog rizika, kao što su one sa porodičnom istorijom poremećaja kontrole impulsa ili one koje doživljavaju značajne životne stresove. Rešavanje javnozdravstvenih izazova zahteva sveobuhvatan pristup koji uključuje obrazovanje, prevenciju, lečenje i promene politike kako bi se ublažio uticaj kompulzivnog poremećaja na pojedince i društvo.

Ključne reči: kompulzivna kupovina; instrumenti za procenu; izazovi javnog-zdravlja

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ZAVISNOST OD HRANE: AKTUELNI JAVNO-ZDRAVSTVENI PROBLEM

Bojana Matejić

Gojaznost predstavlja značajan javno-zdravstveni izazov na globalnom planu i jedan je od vodećih rizika prevremene smrtnosti savremenog čoveka. Gojaznost može biti rezultat brojnih faktora, a sve češće se govori i o doprinosu zavisnosti, odnosno „gubitka kontrole“ u vezi sa konzumacijom određene hrane (posebno visoko-procesuirane hrane, koja je dospevala na tržište u proteklim decenijama). Zavisnost od hrane, za razliku od drugih bihejvioralnih zavisnosti, poput patološkog kockanja, sličnija je zavisnostima u odnosu na psihoaktivne supstance po tome što postoji fizički agens koji izaziva neurohemijske efekte u mozgu. Ipak, ovo je koncept o čijoj valjanosti se vode brojne rasprave u naučnoj zajednici. Do sada nema formalne definicije zavisnosti od hrane, kao ni studije koja bi na osnovu strogih naučnih kriterijuma utvrdila posebna svojstva hrane koja izizivaju zavisnost.

Da bi se u kliničkom okruženju ispitivala zavisnosti od hrane, istraživači sa Univerziteta Yale su razvili upitnik sa 25 pitanja-YFAS (Yale Food Addiction Scale), kojim se operacionalizuje ovaj konstrukt i identifikuju različiti aspekti zavisnosti od hrane, a to su: ponovljeni neuspešni pokušaji smanjenja količine pojedene hrane, kontinuirana upotreba određene hrane uprkos ispoljenim tegobama u vezi konzumiranja te vrste hrane i trošenje velike količine vremena za pripremu hrane, konzumiranje, ali i oporavak od tegoba u vezi sa konzumiranjem te vrste hrane.

U literaturi se sve ozbiljnije razmatra javno-zdravstvena dimenzija ovog problema i implikacije na javno-zdravstvene politike, koje bi mogle da doprinesu rešavanju ne samo zavisnosti od hrane, izolovano gledano, već i generalno gojaznosti u populaciji. U tom smislu, donosioci odluka treba da budu upoznati sa mogućnostima različitih strategija, kao što su subvencionisanje voća i povrća, urbano zoniranje prostora u cilju ograničavanja postojanja restorana brze hrane u blizini škola ili akcize na zaslađena pića i proizvode sa visokim udelom masti i soli (kao što su različite grickalice ili čips).

Ključne reči: zavisnost od hrane, gojaznost, javno-zdravstvene politike

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IZAZOVI U USPOSTAVLJANJU RAVNOTEŽE IZMEĐU POSLA I OSTALIH ŽIVOTNIH AKTIVNOSTI: JAVNODRAVSTVENE I INDIVIDUALNE ODGOVORNOSTI

Bosiljka Đikanović

Uspostavljanje ravnoteže između plaćenog posla i ostalih životnih aktivnosti ili tzv. „work-life” balans, predstavlja dinamičan proces i veliki izazov sa kojim se zaposleni svakodnevno suočavaju, a koji je veoma važan za očuvanje i unapređenje zdravlja. Iz istorije radničkog pokreta dobro je poznat primer štrajka radnika u Čikagu 1868. godine, usled prisiljenosti na iscrpljujuće uslove rada od 12 sati i više, a čiji je legat ostao 1. maj, Međunarodni praznik rada i osmočasovno radno vreme. Iako se ovaj praznik obeležava u mnogim državama širom sveta, njegove tekovine se nažalost često ne poštuju. Zaposleni su neretko, eksplicitno ili implicitno, primorani da rade i duže od 8 časova dnevno, šest ili svih sedam dana u nedelji, što im ne ostavlja dovoljno vremena da realizuju druge društvene uloge i lične aspiracije. Društveni izazovi za uspostavljanje „work-life“ balansa odnose se na ekscesivne radne zahteve poslodavaca; nedostatak fleksibilnosti u vezi sa radnim vremenom i mestom rada; nedovoljan broj zaposlenih, socijalni pritisak da se odgovori na očekivanja poslodavca, i brojni drugi. Kod individualnih izazova, najčešće se navodi nedostatak veština za postavljanje granica u komunikaciji sa poslodavcem i kolegama, izazovi u menadžmentu vremenom, strah od gubitka posla, lične navike, perfekcionizam, i brojni drugi.

U novije vreme, sve češće se spominje i pojam „workaholizam“, koji se odnosi na kompulsivnu ili opsesivnu posvećenost radu, često na račun ličnog zdravlja i odnosa. Osobe koje pate od workaholizma osećaju neodoljivu potrebu da rade prekomerno i obično svoj posao stavljaju iznad svih drugih aspekata života, uključujući lične veze, slobodne aktivnosti, pa čak i zdravlje, što može da dovede do negativnih posledica i problema u njihovom fizičkom, mentalnom i socijalnom zdravlju i blagostanju. Stoga, veoma je važno je da pojedinci pronađu zdrav balans između posla i privatnog života, u čemu mogu da pomognu javnozdravstvene intervencije i povećanje svesti o važnosti uspostavljanja ove ravnoteže.

Ključne reči: „work-life“ balans, društveni faktori, poslodavci, individualni faktori, workaholizam, javno zdravlje

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ZAVISNOST OD LJUBAVI I SAJBERSEKS

Aleksandra Jović-Vraneš

Zavisnost od ljubavi se odnosi na intenzivnu, nekontrolisanu žudnju za romantičnim vezama, što često dovodi do ponavljanja nezdravih ili toksičnih odnosa. Osobe sa ovim oblikom zavisnosti traže stalno emocionalno potvrđivanje i naklonost, što može dovesti do opsesivnog razmišljanja, ljubomore i nemogućnosti da budu sami. Ova zavisnost može prioritetno staviti romantične odnose iznad drugih aspekata života, što često rezultira ciklusom neispunjavajućih i destruktivnih odnosa. Oni koji pate od zavisnosti od ljubavi često zamenjuju duboke emocionalne veze sa intenzivnim, ali površnim odnosima, zbog čega postaju zarobljeni u beskrajnom traganju za “idealnim” partnerom koji nikada ne zadovoljava njihove potrebe.

Sajberseks, koji uključuje seksualne aktivnosti na mreži, može se razviti u kompulsivno ponašanje koje ometa svakodnevni život. Anonimnost i dostupnost interneta olakšavaju ovo ponašanje, što može dovesti do zanemarivanja odgovornosti i odnosa. Sajberseks se često javlja kao zamena za stvarnu intimnost, naročito kod osoba zavisnih od ljubavi, koje internet koriste kao način zadovoljenja emocionalnih i seksualnih potreba bez složenosti realnih odnosa. Takvo ponašanje može dovesti do gubitka interesovanja za stvarne odnose, što dodatno otežava uspostavljanje i održavanje zdravih, stabilnih veza u stvarnom životu.

Oba oblika zavisnosti mogu imati ozbiljne posledice po mentalno, emocionalno i fizičko zdravlje pojedinca, uključujući socijalnu izolaciju, emocionalnu nestabilnost i narušavanje sposobnosti za uspostavljanje zdravih odnosa. Pored toga, ovakve zavisnosti mogu uticati na radnu produktivnost, društvene aktivnosti i sveukupno zadovoljstvo životom. Lečenje često zahteva terapiju, grupe podrške i promene načina života kako bi se pojedinci oslobodili ovih destruktivnih obrazaca i uspostavili zdravije odnose, kao i razvili zdravije načine za upravljanje emocijama i stresom.

Ključne reči: zavisnost od ljubavi, sajberseks, emocionalna nestabilnost, zavisno ponašanje

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KORAK PREVIŠE U PROMOCIJI ZDRAVIH STILOVA ŽIVOTA: ZAVISNOST OD VEŽBANJA I ORTOREKSIJA

Željka Stamenković, Marija Zdujić

Zavisnost od vežbanja i ortoreksija, odnosno patološki oblik nezdrave opsesije zdravom ishranom često idu zajedno sa idealizovanim slikama tela i poremećenim telesnim percepcijama koje doprinose i ponašanju i njegovim zajedničkim karakteristikama. Grupe poput zdravstvenih radnika, doktora medicine, praktičara joge ili ljudi koji se bave sportom pokazuju uporedno visok nivo ortoreksične ishrane i stoga se smatraju populacijama u riziku od razvoja ovih poremećaja. Iz tog razloga nije iznenađujuće što se pretpostavlja da su patološka opsesija zdravom ishranom i preteranim i kompulsivnim vežbanjem usko povezane te se iz toga razloga zajedno predstavljaju.

Zavisnost od vežbanja nije naveden kao poremećaj u trenutnim sistemima klasifikacije, ali je predloženo da bude klasifikovan u odeljku o zavisnostima i srodnim poremećajima kao zavisnost od ponašanja koja nije povezana sa upotrebom supstanci. Predloženi kriterijumi za procenu i prepoznavanje obuhvataju komponente adiktivnog ponašanja, kao i kriterijume za poremećaje povezane sa upotrebom supstanci navedenih u Dijagnostičkom i statističkom priručniku za mentalne poremećaje. Ortoreksija takođe nije navedena kao poremećaj u trenutnim sistemima klasifikacije.

Malo je istraživanja i malo dokaza na kojima bi se zasnivao tretman navedenih poremećaja, pa se iz tog razloga lečenje zasniva na motivacionim i kognitivno-bihevioralnim pristupima zasnovanih na dokazima za srodne poremećaje poput zavisnosti od uzimanja psihoaktivnih supstanci ili kockanja. Motivacioni intervju je kritičan prvi korak u takvim situacijama i može pomoći pojedincu da razvije širu sliku problematičnog obrasca ponašanja, prihvatajući koristi i probleme, kao i prepoznajući potrebu za promenom ponašanja. Kognitivno-bihejviorani pristup je značajan u identifikaciji automatskih misli koje dovode do problematičnog ponašanja („Ako sada ne odem na trčanje, osećaću se užasno"), kao i u njihovoj promeni ka zdravijim mislima i budućim navikama koje stopiraju problematične misli i ciljno ponašanje. Iako se veruje da farmakoterapija pomaže u rešavanju zavisnosti od vežbanja i ortoreksije, potrebno je značajno više kontrolisanih studije pre donošenja zaključaka.

Kjučne reči: zavisnost od vežbanja; ortoreksija; stil života

MINI SIMPOZIJUM
SAVREMENI PRISTUP ISPITIVANJU I LEČENJU UTICAJA ZLOUPOTREBE ALKOHOLA NA ZDRAVLJE

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EPIDEMIOLOGIJA ZLOUPOTREBE ALKOHOLA

Vladimir Nikolić

Zloupotreba alkohola predstavlja ozbiljan javno zdravstveni problem, sa značajnim posledicama po zdravlje osobe, ali i za društvo u celini. Prema Svetskoj zdravstvenoj organizaciji (SZO), globalni prosek potrošnje alkohola po glavi stanovnika starijih od 15 godina iznosi oko 6,4 litara čistog alkohola godišnje. U poređenju sa globalnim prosekom, evropske zemlje beleže značajno višu potrošnju, a Srbija je među zemljama sa većom potrošnjom alkohola. U evropskom regionu je, prema SZO, najviši nivo potrošnje alkohola u svetu, s prosekom koji se kreće između 9 i 12 litara dok je u Srbiji, prema podacima iz 2018. godine, upotreba alkohola iznosila 8,75 litara čistog alkohola po glavi stanovnika. Iako je ova vrednost ispod proseka drugih evropskih zemalja sa visokom potrošnjom alkohola, poput Litvanije ili Češke, ona je i dalje zabrinjavajuće visoka. Projekcija za 2025. godinu pokazuje dalji porast, predviđajući potrošnju od 11,6 litara godišnje po glavi stanovnika, sa opsegom od 10,9 do 12,4 litara. Ova predikcija ukazuje na nastavak trenda rasta potrošnje alkohola, što zahteva hitnu pažnju javnozdravstvenog sektora i uvođenje programa prevencije. Prema SZO, alkohol uzrokuje oko 5,3% svih smrtnih ishoda, što je jednako broju od tri miliona godišnje. Pored toga, alkohol doprinosi pojavi više od 200 različitih bolesti i stanja. U Evropi, regiji sa najvećom potrošnjom alkohola, zloupotreba alkohola je odgovorna za oko 7,6% svih smrtnih ishoda kod muškaraca i 4% kod žena. Srbija je među zemljama s visokim rizikom od zdravstvenih problema povezanih sa alkoholom, uključujući bolesti jetre, kardiovaskularne bolesti i povrede izazvane konzumiranjem alkohola. Posebno zabrinjavajući trendovi primećeni su među adolescentima i mladim odraslim osobama, gde se beleži povećana upotreba alkohola u rizičnim količinama, što može imati dugoročne posledice po zdravlje.

Ključne reči: zloupotreba alkohola, prevalenca, komorbiditeti

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ALKOHOLNA BOLEST JETRE – STARA BOLEST SAVREMENOG DOBA

Tamara Milovanović

Alkoholna bolest jetre predstavlja oštećenje jetre prouzrokovano upotrebom alkohola. Bolest iz stadijuma steatoze i steatohepatitisa, prolazi kroz sve stadijume fibroze i rezultuje cirozom jetre. Međutim, postoje značajne razlike u toku bolesti i njenoj prezentaciji među pojedincima u zavisnosti od prisustva ili odustva pojedinih modifikujućih faktora poput genetike, pola, etničke pripadnosti, gojanosti, drugih bolesti jetre, nutritivnog statusa, pušačkog statusa i upotrebe određenih lekova i suplemenata. Poslednjih godina primećen je upadljiv porast incidencije alkoholne bolesti jetre, udruženo sa rastućim mortalitetom. Takođe, prisutan je porast stope oboljevanja kod žena, kao i trend dijagnostikovanja alkoholne bolesti jetre u mlađem uzrastu. Osnov dijagnoze alkoholne bolesti jetre je dobra anamneza i/ili heteroanamneza, uključujući validirane upitnike za procenu upotrebe alkohola koji bi trebalo da budu sastavni deo svakodnevne kliničke prakse. Ostatak dijagnostičkog algoritma podrazumeva određivanje sveobuhvatnih laboratorijskih analiza, radiološke metode, imunološke i virusološke markere, i u pojedinim slučajevima biopsiju jetre. Alkoholna bolest jetre je jedina bolest jetre u kojoj je moguće ukloniti etiološki činilac bolesti gotovo trenutno. Iz tog razloga, lečenje alkoholne bolesti jetre mora podrazumevati lečenje alkoholne bolesti zavisnosti, i neretko zahteva učešće multidisciplinarnog tima uz socijalnu podršku.

Ključne reči: alkoholna bolest jetre, dijagnoza, lečenje

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UTICAJ ZLOUPOTREBE ALKOHOLA NA DIGESTIVNE ORGANE

Marija Branković

Akutna i hronična upotreba alkoholnih pića utiče na gastrointestinalni (GI) trakt kroz brojne i često kompleksne mehanizme. Kada je reč o gornjem GI traktu, ovi mehanizmi dovode do inflamacije sluznice jednjaka i želuca, do poremećaja motiliteta, kao i do povećane proizvodnje želudačne kiseline. Na sreću, navedeni efekti zavise od količine unetih alkoholnih pića i mogu biti reverzibilni uz apstinenciju od istih. Sa druge strane, alkohol prouzrokuje disbiozu u tankom i debelom crevu, što može doprineti alkoholnoj bolesti jetre zbog prisustva bakterijskih endotoksina u portnoj cirkulaciji. Takođe, alkohol prouzrokuje promene u motilitetu creva, permeabilnosti i protoku krvi, kao i nutritivne poremećaje, što dalje može dovesti do dijareje. Pokazalo se da alkohol na nivou creva takođe inhibira apsorpciju vode, ugljenih hidrata, lipida, vitamina (posebno tiamina i folata) i minerala (kalcijuma, gvožđa, cinka i selena). Dodatno, rizik za pojavu pankreatitisa raste sa količinom alkohola koju osoba konzumira, kao i sa vremenom trajanja kontinuiranog unošenja alkohola.

Pankreatitis ove etiologije po kliničkom toku može biti akutni, rekurentni akutni i hronični, a rekurentni akutni pankreatitisi naposletku dovode do prelaska inflamatornog procesa u hroničan tok, zbog čega vremenom dolazi do postepenog gubitka egzokrine i endokrine funkcije pankreasa i neželjenih posledica. Inače, upotreba alkohola sama po sebi je faktor rizika za nastanak poremećaja metabolizma i dijabetes melitusa tipa 2. Važno je napomenuti da je još 1988. godine Internacionalna agencija za istraživanje karcinoma definisala alkohol i njegov štetni metabolit acetaldehid kao kancerogene prvog reda. Istraživanja su pokazala da je rizik za nastanak karcinoma kod osoba koje unose velike količine alkohola na dnevnom nivou veći za razvoj karcinoma dojke, debelog creva, jednjaka, jetre, ždrela, kao i orofaringealnih karcinoma. Nažalost, sa povećanjem količine unetog alkohola raste i rizik za razvoj navedenih karcinoma. Kako bi se preveniralo sve navedeno, globalno treba podizati svest o zdravstvenim posledicama zloupotrebe alkohola.

Ključne reči: alkohol, pankreatitis, crevna microbiota, karcinom

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ALKOHOLNA KARDIOMIOPATIJA

Marija Zdravković

Alkoholna kardiomiopatija predstavlja tip sekundarne dilatativne kardiomiopatije koja nastaje usled hronične upotrebe alkohola i to više od 80g dnevno minimum 5 godina. Brojni su patofiziološki mehanizmi koji dovode do razvoja alkoholne kardiomiopatije, uglavnom uključuju oksidativni stres, apoptozu miocita, mitohondrijalnu disfunkciju, kao i disfunkciju metabolizma i transporta masnih kiselina.

Postavljanje dijagnoze alkoholne kardiomiopatije i dalje je tema mnogih ispitivanja s obzirom da postoje brojna preklapanja sa drugim podtipovima dilatativne kardiomiopatije, te je konačnu dijagnozu moguće postaviti isključivanjem ostalih mogućih uzoraka dilatativne kardiomiopatije. Klinički alkoholna kardiomiopatija manifestuje se dilatacijom i istanjenjem zidova leve komore koji potom dovode do disfunkcije komora, razvoja poremećaja srčanog ritma i dalje progresije srčane insuficijencije. Osim imidžing metoda koje igraju važnu ulogu u karakterisanju abnormalnosti srčanog mišića, bitno je ne zanemariti razgovor sa pacijentom o svakodnevnim životnim navikama i dostupna laboratorijska testiranja poput detekcije transferina sa nedostatkom ugljenih hidrata (carbohydrate deficient transferrin-CDT) i testova funkcije jetre. Magnetna rezonanca, kontinuirani EKG monitoring i CPET testiranje su izuzetno bitni u stratifikaciji rizika od naprasne srčane smrti, koja je i najteža komplikacija ovog oboljenja.

Lečenje alkoholne kardimiopatije predstavlja veliki izazov s obzirom na nedostatak standardnih kliničkih smernica. Na prvom mestu izdvaja se apsolutna apstinencija od alkohola kojom se postiže ublažavanje simptoma i postepeni oporavak srčanog mišića. Standardna medikamentozna terapija srčane insuficijencije i terapija implantabilnim uređajem (ICD) koristi se kod pacijenata sa značajnom disfunkcijom leve komore i posledičnom srčanom insuficijencijom. Poslednja linija u lečenju alkoholne kardimiopatije je transplantacija srca. Multidisciplinarni pristup u lečenju je osnova pravilnog terapijskog pristupa.

Ključne reči: zloupotreba alkohola, kardiomiopatija, srčana insuficijencija

Specijalna bolnica za bolesti zavisnosti

SAVREMENI PRISTUPI U LEČENJU ZAVISNOSTI OD ALKOHOLA

Nataša Dostanić

Negativne posledice hroničnog alkoholizma su dobro poznate. Uprkos tome efikasan tretman predstavlja izazov, jer je odgovor na lečenje heterogen. Farmakoterapija je namenjena tretiranju simptoma apstincijalnog sindroma i/ili komorbidnih stanja i komplikacija, kao i primena specifičnih lekova za lečenje alkoholne zavisnosti. Američka agencija za hranu i lekove je odobrila tri leka za lečenje alkoholom uzrokovanih poremećaja. To su disulfiram, akamprosat i naltrekson (Reus et al., 2018;). Glavna klinička efikasnost disulfirama u održavanju apstiencije i redukciji recidiva je averzivna reakcija, odnosno psihološki efekat uzimanja disulfirama i svesti o mogućoj averzivnoj reakciji (Fuller RK et al., 1986). Akamprosat primenjen u kombinaciji sa psihosocijalnom podrškom povećava procenat alkoholnih zavisnika u tretmanu koji potpuno apstiniraju duže od 6 meseci, i značajno smanjuje rizik kod pacijenata za uzimanje bilo koje količine alkohola, uz redukciju žudnje (Kufahl et al., 2014; Mann et al., 2014). Naltrekson je efikasan u tretmanu alkoholnih zavisnika, jer produžava asptinenciju, smanjuje rizik od pojave recidiva, pogotovo utiče na količinu unetog alkohola (Antoan 2008; Goh 2016). Nalmefen 2013.g. odobren je od strane Evropske agencije za lekove za lečenje alkoholne zavisnosti kod pacijenata koji žele da smanje unos alkohola, ali ne nužno i da potpuno apstiniraju, kao i kod osoba kod kojih uspostavljanje apstinencije ne zahteva primenu farmakoterapije. Francuska zdravstvena agencija odobrila baklofen kao lek drugog izbora za lečenje alkoholne zavisnosti sa ciljem prevencije recidiva ili smanjenja unosa alkohola, naročito u slučaju komorbidnih stanja sa anksioznim i depresivnim poremećajima (Pierce et al., 2018). Natrijumova so gama hidroksibuterata (GHB) je lek koji se koristi u Italiji i Austriji za održavanje apstinecije kod alkoholnih zavisnika. Lečenje alkoholne zavisnosti podrazumeva i primenui psihoterapijskih intervencija u cilju sticanja veština za suočavanje sa svakodnevnim rizičnim situacijama, prevazilaženja kriznih stanja u cilju održavanja apstiencije, promene zavisničkog obrasca ponašanja i alkoholičarskog životnog stila.

Ključne reči: zloupotreba alkohola, zavisnost, lečenje

MINI SIMPOZIJUM
PATOFORENZIČKI I EKSPERTIZNI ASPEKTI MASNE EMBOLIJE

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POREKLO MASNIH EMBOLUSA I MASNA EMBOLIJA PLUĆA

Aleksa Leković

Prirodna (endogena) adipozna embolija u forenzičkoj praksi jeste ona koja je komplikacija ili posledica bolesti. Nasilna (posttraumatska, egzogena) adipozna embolija jeste ona koja nastaje usled traume i u direktnoj je vezi sa njom. Po jednoj teoriji, masne kapi vode poreklo iz oštećenja masnih depoa u telu (npr. koštane srži ili iz potkožnog masnog tkiva) i dospevaju u cirkulaciju kroz rupture vena iz okoline traumatizovanog tkiva. Po drugoj teoriji masne partikule nastaju aglomeracijom već postojećih masnoća u krvi, zbog fizikohemijskih promena plazme kao posledica traume. Ranije se smatralo da su masni embolusi u plućima hemijski inertni: smatralo se da masne kapi štetno deluju i izazivaju ishemiju delujući isključivo mehanički, ne dozvoljavajući svojim prisustvom u krvnom sudu dalji protok krvi i izazivajući retrogradni zastoj. Danas se smatra da pored ovog efekta, masni embolusi ispoljavaju i hemijsko dejstvo na tkivo pluća: deluju iz embolusa oslobođenim slobodnim masnim kiselinama pod uticajem lokalne tkivne lipaze u plućima. Direktno oštećenje endotela kapilara pluća dejstvom slobodnih masnih kiselina vodi stvaranju plućnog edema, a kasnije i hijalinih membrana i razvoju respiratornog distres sindroma. Savremeno shvatanje o patološkofiziološkim sledu događaja kod masne embolije pluća jeste sledeće: u prvoj fazi nastaje mehaničko začepljenje arterijske sudovne mreže pluća, pa ako je ono opsežno, razvija se embolija pluća i pacijent može ubrzo umreti zbog akutnog popuštanja desnog srca, sa minimalnim patohistološkim promenama na plućima. Ukoliko je embolizacija izražena u manjoj meri, može se razviti druga faza u kojoj, pod uticajem alveolarne lipaze, dolazi do oslobađanja slobodnih nezasićenih masnih kiselina iz adipoznih embolusa, koje deluju toksično izazivajući oštećenje endotela kapilara pluća, inflamatornu reakciju, mikrotromboze, stvaranje hijalinih membrana, sve do teške respiratorne insuficijencije. Postojanje ovih dveju patološkofizioloških faza objašnjava i postojanje latentnog perioda između traume i pojave histoloških promena na plućima.

Ključne reči: masna embolija, pluća, obdukcija, akutno plućno srce, forenzička patologija.

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SISTEMSKA MASNA EMBOLIJA I SINDROM MASNE EMBOLIJE

Danica Đukić

Pitanje dospevanja adipoznih embolusa iz pluća u sistemsku cirkulaciju praktično se ne postavlja ako se prihvati da su masne kapi isključivo porekla iz plazme i da nastaju aglomeracijom već postojećih masnoća uz krvi. Ukoliko se prihvati da masne partikule imaju periferno poreklo i da iz traumatizovanih masnih depoa tela dospevaju prvo u pluća, to znači da se embolusi mogu naći u sistemskoj cirkulaciji tek posle izvesnog vremena, kada prođu mali krvotok. Prelaskom u arterije velikog krvotoka, dolazi do razvoja sistemske masne embolije, tj. embolije svih ostalih organa i tkiva organizma i različitih simptoma zbog njihove sledstvene ishemije. Sindrom sistemske masne embolije (eng. *Fat Embolism Syndrome* – FES) predstavlja kliničku manifestaciju prisustva adipoznih embolusa u organima, a karakteriše se pre svega neurološkim, respiratornim i kožnim znacima i različitim simptomima. Broj onih koji posle traume razviju kliničku sliku FES-a kreće se od 1 do 3-4%, a od njih 10% do jedne trećine umire. FES-u prethodi jedan latentni period posle traume, koji obično iznosi 24 do 72 sata. Klinički dijagnostički kriterijumi sindroma masne embolije postavili su 1974. god. Gurd i Wilson kao tzv. *major* i *minor* znake. Schonfeld je uveo 1983. godine klinički indeks simptoma i znakova za dijagnozu FES-a.

Ključne reči: FES, sistemska masna embolija, obdukcija, forenzička patologija.

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MASNA EMBOLIJA KAO VITALNA REAKCIJA

Tijana Petrović

U forenzičkoj medicini vitalna reakcija jeste pojava koja sa sigurnošću ili sa verovatnoćom ukazuje da je neka povreda nastala za vreme života. Prema dijagnostičkoj vrednosti mogu biti apsolutne i relativne. Apsolutne nastaju isključivo intravitalno, a relativne mogu nastati kako za života, tako i posle smrti, s tim što je njihov intenzitet u drugom slučaju slabiji. Vitalne rekacije mogu se ispoljiti na mestu povređivanja (lokalne vitalne reakcije: tromboza, inflamacija i sve relativne vitalne reakcije) ili na delovima tela koji su udaljeni od povređenog mesta (opšte vitalne reakcije: iskrvarenje, embolija, aspiracija, deglutacija). Masna embolija predstavlja apsolutnu opštu vitalnu reakciju. Nalaz adipoznih embolusa u plućima ili u dru-

gim organima znači da je povreda, npr. fraktura dugih cevastih kostiju ili povreda supkutanog adipoznog tkiva (kontuzija ili duboka opekotina), koja je pretpostavljeno mesto nastanka masnih partikula, nanesena zaživotno, a ne postmortalno. Embolije, pa i masna, nalaze se po brzini razvoja između aspiracije i iskrvarenja: za pojavu embolije bilo koje vrste, pa i adipozne, potrebno je nekoliko sekundi, tj. nekoliko srčanih ciklusa. Adipozni embolusi u kapilarima pluća mogu se naći i duže vreme posle nastupanja smrti, tj. kada su putrefakcione promene već dosta odmakle, što adipoznu emboliju kao vitalni fenomen u ovim slučajevima čini značajnijom u odnosu na aspiraciju i iskrvarenje koji su poništeni putrefakcijom.

Ključne reči: masna embolija, vitalna rekacija, obdukcija, forenzička patologija.

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SUDSKOMEDICINSKI I PRAVNI ASPEKTI MASNE EMBOLIJE

Vladimir Živković

Pitanje krivične odgovornosti lekara može se javiti ako se sindrom sistemske masne embolije razvije posle nekih ortopedskih operacija u čijem toku dolazi do znatnog porasta intramedularnog pritiska: npr. ugradnja veštačkog kuka ili kolena, ili ubacivanje Kinčerovog klina. Tu se postavljaju pravna pitanja koja se tiču adekvatne i dobre preoperativne pripreme pacijenta, pravovremenosti i blagovremenosti preduzete operacije, valjanosti stručnog lekarskog rada u toku operacije, valjanosti stručnog praćenja pacijenta u postoperativnom periodu, itd. Kako ishodište masnih kapi mogu biti nagnječenja telesnih depoa masnog tkiva, to se masna embolija pluća može razviti i posle opsežnih povreda potkožnog masnog tkiva, a ne samo posle preloma dugih cevastih kostiju. Masna embolija može se razviti i nakon hirurških intervencija koje uključuju manipulaciju drugim depoima masnog tkiva (dojke, potkožni masno tkivo, ali i jetra, ukoliko postoji masna promena). S pravne tačke gledišta, postavlja se pitanje da li masnu emboliju pluća, ali i sistemsku, treba posmatrati kao posledicu traume telesnih masnih depoa, ili kao komplikaciju.

Ključne reči: pravna medicina, telesne povrede, obdukcija, forenzička patologija

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RADOVI MILOVANA MILOVANOVIĆA O MASNOJ EMBOLIJI

Slobodan NIkolić

Prvi nastavnik sudske medicina na našem fakultetu i osnivač Sudskomedicinskog zavoda, kasnije Instituta za sudsku medicinu Medicinskog fakulteta u Beogradu, profesor Milovan Milovanović (1884-1948), tokom 1929-1932. godine napisao je i objavio četiri originalna rada u vezi sa masnom embolijom. Prvi je rad bio eksperimentalni, na glodarima, a druga tri su bila na humanom obdukcionom materijalu i bavila su se tzv. kadaveroznom masnom embolijom i masnom embolijom pluća kao vitalnim fenomenom, odnosno masnom embolijom kao uzrokom oboljenja i smrti. Čak i danas, neke činjenice do kojih je došao Milovanović u ovim svojim radovima, aktuelni su i sada, naročito kada je u pitanju forenzičko posmatranje masne embolije pluća kao vitalnog fenomena, kao i odbacivanje tadašnje aktulene teorije o tzv. kadaveričnoj masnoj emboliji.

Ključne reči: masna embolija, obdukcija, forenzička patologija, Milovan Milovanović

MINI SIMPOZIJUM
RAZUMEVANJE I PREVENCIJA IZNENADNE SRČANE SMRTI: MULTIDISCIPLINARNI PRISTUP ZAŠTITI ZDRAVLJA SRCA

Università degli Studi di Trieste – Istituto di Medicina Legale

THE REGIONAL REGISTRY OF SUDDEN CARDIAC DEATH OF FRIULI VENEZIA GIULIA (ITALY). PROTOCOLS, BEST PRACTICES, AND RESULTS OF A MULTIDISCIPLINARY PROJECT AFTER 4 YEARS OF ACTIVITY

Stefano D'Errico

With the regional law n. 26 of December 30, 2020, the Friuli Venezia Giulia Region wanted to promote the establishment of the Regional Register of Sudden Cardiac Death, with the aim of favoring the study of all those deaths that occurred suddenly and unexpectedly under the age of 50 years in which it is not possible to trace the cause of death with certainty. Such dramatic events, difficult to quantify considering the complexity of data collection, are often accepted with resignation without any further investigation of the possible causes.

The Regional Register of Sudden Cardiac Deaths of Friuli Venezia Giulia was born from this premise and from the awareness of the importance of going back with a rigorous scientific methodology and through a multidisciplinary approach to the diagnosis of hereditary heart diseases, which, when determined, allow the enrollment of relatives in a cardiological screening process and, therefore, primary prevention of potentially fatal events. The authors describe the operating procedures feeding the Regional Register and present the results after four years of activity.

Keywords: sudden cardiac death, young adults, autopsy, multidisciplinary prevention

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UNAPREĐENJE PRAKSE UTVRĐIVANJA UZROKA NAPRASNE SRČANE SMRTI: STANDARDI ZA OBDUKCIONU DIJAGNOSTIKU I DODATNE ANALIZE

Sofija Glumac

Iznenadna srčana smrt (engl. *sudden cardiac death*, SCD) je neočekivana smrt koja se često javlja kao komplikacija srčanih bolesti. Incidencija SCD-a varira, a Evropsko kardiološko društvo procenjuje da se kreće od 36 do 128 slučajeva na 100.000 stanovnika godišnje. Ishemijska bolest srca i srčana insuficijencija su najčešći uzroci SCD u adultnoj populaciji, dok su kod mlađih osoba mogući i drugi uzroci, uključujući i genetske defekte.

Autopsija igra ključnu ulogu u dijagnostici SCD-a, identifikaciji naslednih srčanih bolesti i identifikaciji porodica koje zahtevaju kardiološki pregled. Patolog pre početka obdukcije mora imati sve relevantne podatke o preminulom, uključujući okolnosti umiranja, medicinsku istoriju, porodičnu anamnezu i toksikološke nalaze. Autopsija uključuje standardne procedure, s naglaskom na detaljan pregled srčanog i vaskularnog tkiva. Fotografisanje tokom pregleda je korisno za dokumentaciju. Glavni cilj obdukcije je utvrđivanje neposrednog uzroka smrti, identifikacija srčanih bolesti i procena njihovog naslednog karaktera. U cilju identifikacije etioloških faktora, neophodno je obaviti toksikološke i mikrobiološke analize.

Srce treba secirati u skladu sa standardnim smernicama, pri čemu radiologija može povremeno biti od koristi u slučajevima sa stentom. Preporučeni minimum histoloških uzoraka uključuje mapirane blokove prednje, bočne i zadnje desne i leve komore i septuma, kao i isečke iz reprezentativnog srednje-ventrikularnog poprečnog preseka i izlaznog trakta desne komore. Intenzivnije uzorkovanje bi uključivalo deo/sve koronarne arterije, tkiva iz sinoatrijalnog čvora i AV čvora i kompletan srednje-ventrikularni presek. Uzorci desne i leve pretkomore generalno nisu potrebni, osim ako postoji fokalna lezija. Dodatna histohemijska i imunohistohemijska bojenja mogu biti od koristi za donošenje zaključka.

U izuzetnim slučajevima treba razmotriti zadržavanje celog srca i slanje netaknutog u specijalistički centar na stručno mišljenje. U slučaju sumnje na nasledni poremećaj ili torakalnu disekciju aorte kod mlađih osoba, treba čuvati uzorke za genetsko testiranje. Post mortem *imaging* se sve više koristi u slučajevima iznenadne smrti. Uzrok smrti treba precizno definisati, izbegavajući termine poput „srčana insuficijencija". Detaljno definisanje, npr. "akutne srčane insuficijencije usled infarkta miokarda" je u skladu sa principima dobre patološke prakse.

Ključne reči: ishemijska bolest srca, srčana insuficijencija, obdukcija, postmortalne genetske analize

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KLINIČKI ZNAČAJ NAPRASNE SRČANE SMRTI: KLJUČNI FAKTORI U PREVENCIJI IZNENADNE SRČANE SMRTI IZ KARDIOLOŠKE PERSPEKTIVE

Ivana Nedeljković

Incidenca iznenadne srčane smrti (ISS) kod sportista kreće se od 1:40 000 do 1:250 000 i na ovu varijaciju uti-

če heterogenost u metodologijama, populacijama i sportskim disciplinama između studija. Smrtni slučajevi među mladim sportistima (starosti ≤ 35 godina) se uglavnom javljaju u dobi od 14 do 30 godina i najčešći su u drugoj deceniji života.

Preko 80% ISS se javlja tokom intenzivnog treninga ili takmičenja. Takođe, sa porastom broja rekreativaca koji se ne javljaju na skrining preglede niti na kontrolne preglede, zapaža se sve veća učestalost smrtnih ishoda koji su nastupili u teretanama i tokom drugih napornih rekreacija.

Ovaj rizik se razlikuje u zavisnosti od starosti sportista i prethodnog prisustva kardiovaskularnih bolesti (KVB). Dok je ISS uglavnom posledica aterosklerotične bolesti koronarnih arterija kod sportista starijih od 35 godina, genetski ili strukturni srčani poremećaj je glavna etiologija kod mladih. Svaka starosna grupa treba da ima stroge preporuke koje se tiču vrste, trajanja i snage sporta kojim je dozvoljeno da se bave.

Ključni faktori prevencije podrazumevaju sveobuhvatnu medicinsku procenu pre bavljenja sportom, koja bi uključivala upoznavanje lične i porodične anamneze, fizikalni pregled i ev. skrining elektrokardiogram (EKG). Podjednako je važan i razvoj obrazovanja i svesti sportista, trenera i sportskog osoblja o znacima i simptomima kardiovaskularnih problema i drugih potencijalnih uzroka iznenadne smrti, uključujući i znanje kada treba tražiti medicinsku pomoć i kako reagovati u hitnim slučajevima.

Takođe, sportske organizacije treba da imaju dobro definisan plan akcije za hitne medicinske slučajeve, uključujući i iznenadne srčane događaje, koji podrazumeva pristup automatizovanim eksternim defibrilatorima i obučeno osoblje.

Odgovarajući programi kondicije i treninga prilagođeni uzrastu sportiste, nivou kondicije i sportu mogu pomoći u sprečavanju prenaprezanja i sa tim povezanih neželjenih kardiovaskularnih događaja. Takođe, sportisti treba da budu edukovani i zaštićeni od bolesti povezanih sa izlaganjem prekomernoj toploti, koje mogu dovesti do iznenadnog kolapsa, pa čak i smrti ako se ne leče blagovremeno.

Pravilna ishrana i hidratacija su od suštinskog značaja za opšte zdravlje i performanse, što može indirektno doprineti smanjenju rizika od iznenadne smrti. Ključna je i uloga redovnog praćenja zdravlja sportista tokom njihove karijere, kao jednog od načina ranog otkrivanja i upravljanja svim patološkim stanjima. Obrazovanje sportista o opasnostima zloupotrebe lekova i supstanci za poboljšanje performansi, koje mogu imati ozbiljne kardiovaskularne i sistemske efekte, je od ključnog značaja. Konačno, rešavanje psiholoških stresora i zabrinutosti za mentalno zdravlje među sportistima je važno, jer stres i određena psihološka stanja mogu uticati na kardiovaskularno zdravlje.

Ključne reči: iznenadna srčana smrt, sportisti, prevencija, fizička aktivnost

KBC „Bežanijska kosa“, Medicinski fakultet Univerziteta u Beogradu

EFIKASNO UPRAVLJANJE RIZIKOM OD IZNENADNE SRČANE SMRTI U SPORTU: INTEGRACIJA PERSPEKTIVA SPORTSKE MEDICINE I KARDIOLOGIJE

Marija Zdravković

Iznenadna srčana smrt (ISS) sportiste je tragičan događaj koji potrese širu javnost. Iako se sportisti smatraju najzdravijim delom opšte populacije, prema podacima iz istraživanja *Corrado* i saradnika, incidencija iznenadne srčane smrti je 2.8 puta veća u populaciji aktivnih sportista u poređenju sa opštom populacijom istih godina.

Uzročnik naprasne srčane smrti kod sportista mlađih od 35 godina najčešće su neprepoznate strukturne i funkcionalne srčane bolesti - na teritoriji Severne Amerike najčešća je hipertrofična kardiomiopatija, dok u Evropi preovladava aritmogena kardiomiopatija. Česti uzročnici ISS su i nedijagnostikovani miokarditisi, kao i druge kardiomiopatije i anomalije koronarnih arterija. U grupi sportista starijih od 35 godina najčešći uzročnih ISS je koronarna bolest srca.

Iako skrining, uključujući i EKG pregled, omogućava identifikaciju sportista obolelih od bolesti srčanog mišića i to u fazi pre pojave simptoma, zbog čega može dovesti do smanjenja rizika od ISS, značajno ograničenje ove metode je to što se srčana oboljenja najčešće prepoznaju tek u uznapredovaloj fazi.

Ergospirometrijsko testiranje može biti značajno kod sportista srednjeg ili starijeg uzrasta sa značajnim faktorima rizika za koronarnu bolest, dok je uloga ove metode u podgrupama niskog rizika, koji i jesu ciljna populacija, limitirana.

Ehokardiografski pregled nam omogućava uvid u strukturu srca kao i funkcionalne i hemodinamske parametre, ali i dalje ima svoja ograničenja - zbog specifičnosti tumačenja nalaza, bitno je da ehokardiografski pregled sprovodi ekspert za sportsku kardiologiju, a superdijastolna funkcija je specifičnost sportskog srca.

Zlatni standard u diferencijalnoj dijagnostici simptoma kod profesionalnih sportista je nuklearna magnetna rezonanca srca i velikih krvnih sudova, koja nam osim objektivno procenjenih mera srčanih šupljina, zidova srca i fukcionalnosti valvularnih aparata, daje i uvid u karakterizaciju tkiva srca, što je od krucijalnog značaja za rano otkrivanje bolesti srca kod sportista i stratifikaciju rizika za nastanak ISS.

Integracija perspektiva sportske medicine i kardiologije predstavlja novi predloženi dijagnostički algoritam za prevenciju ISS.

Ključne reči: iznenadna srčana smrt, sport, kardiovaskularni skrining, hipertrofična kardiomiopatija, nuklearna magnetna rezonanca

Institut za socijalnu medicine, Medicinski fakultet Univerziteta u Beogradu

VALIDNE POTVRDE O IZNENADNOJ SRČANOJ SMRTI I PREPORUKE ZA POUZDANO EVIDENTIRANJE I KODIRANJE SA STANOVIŠTA SOCIJALNE MEDICINE

Željka Stamenković

Kardiovaskularne bolesti predstavljaju prvi uzrok smrti u Srbiji, a jednu petinu njih predstavlja ishemijska bolest srca (IBS). Lekari koji potvrđuju uzrok smrti ponekad nisu adekvatno uključeni u popunjavanje potvrda o smrti prema trenutnoj Međunarodnoj statističkoj klasifikaciji bolesti ili zbog visokog nivoa administrativnih zadataka ne uspevaju da završe adekvatno proces njenog izdavanja. Kada se kao osnovni uzrok smrti u potvrdu o smrti unese dijagnoza koja neadekvatno opisuje stanje koje je dovelo do smrtnog ishoda govorimo o takozvanim „kodovima za bacanje" (*garbage codes- GC*). Urađena je studija koja je za cilj imala da istraži *GC* i efekte njihove preraspodele na procene osnovnog uzroka smrti za IBS.

Podaci iz mortalitetne statistike za grad Beograd za 2015. i 2020. godinu su korišćeni za opisivanje pojave i preraspodele *GC*, koji su bili definisani kao nespecifični, nepoznati ili nemogući. Kako bi se uradila preraspodela *GC*, posmatrani su osnovni, prethodni, neposredni uzroci smrti i drugi uslovi koji su doprineli smrti. Preraspodela je izvršena korišćenjem metodologije globalnog opterećenja društva bolestima (GBD) za proporcionalnu redistribuciju *GC*.

Rezultati su pokazali da je u Beogradu 17% (4022/23663) i 20,9% (5818/27775) umrlih šifrovano nekim od *GC* u 2015. i 2020. godini. U 2015. godini, 2102 smrti (10,7% svih dobro definisanih osnovnih uzroka smrti) su pripisane IBS, dok je 2020. godine 1806 smrti (8,2% svih dobro definisanih osnovnih uzroka smrti) pripisano IBS. Konačno, preraspodeljeno je ukupno 452 i 572 smrtnih slučajeva zbog IBS 2015. i 2020. godine. Ovi proračuni ukazuju na ukupan broj od 2554 i 2378 smrtnih slučajeva od IBS u 2015. i 2020. godini.

Imajući u vidu da je zaista veliki broj smrtnih slučajeva pripisan IBS tokom 2015. i 2020. godine, ključno je fokusirati se na pouzdaniji sistem nadzora bolesti, uključujući i bolje prakse kodiranja. Detaljnija analiza lokalne prakse, kao i kontinuirana medicinska edukacija u oblasti izdavanja i popunjavanja potvrde o smrti, mogli bi biti korak napred u budućem procesu smanjenja broja *GC* -a.

Ključne reči: ishemijska bolest srca, potvrda o smrti, *garbage codes,* globalno opterećenje društva bolestima

Institut za socijalnu medicine, Medicinski fakultet Univerziteta u Beogradu

SOCIJALNO-MEDICINSKA EKSPERTIZA IZNENADNE SRČANE SMRTI - INDIKATORI OPTEREĆENJA DRUŠTVA BOLEŠĆU

Jovana Todorović

Studija globalnog opterećenja društva bolešću je najveća studija usmerena na kvantifikaciju gubitka zdravog života tokom vremena i širom sveta. Cilj je poboljšanje funkcionisanja zdravstvenih sistema i eliminacija nepravilnosti u zdravlju. Sprovodi se od 1990. godine, sa idejom da se kvantifikuju efekti po zdravlje, 459 različitih ishoda bolesti i faktora rizika.

U okviru opterećenja društva bolešću razvijeni su novi indikatori i to: godine života korigovane u odnosu na nesposobnost (*Disability adjusted life-years - DALY)*, godine života uz nesposobnost (*Years lived with disability - YLD*) i godine života izgubljene usled prevremene smrti *(Years of life lost - YLL*).

Udeo hroničnih nezaraznih bolesti u ukupnom mortalitetu, globalno, u 2021. godini bio je 64,49%, a kardiovaskularnih bolesti 28,61%. U našoj zemlji je udeo hroničnih nezaraznih bolesti u ukupnom mortalitetu u 2021. godini iznosio 77,80%, a kardiovaskularnih bolesti 46,16%. Ukupna stopa *DALY* povezana sa kardiovaskulranim bolestima globalno, u 2021. godini je iznosila 5427,81/100.000, a u Srbiji 12800,75/100.000.

Stopa godina izgubljenog života zbog prevremene smrtnosti od kardiovaskularnih bolesti globalno u 2021. godini je iznosila 5016,34/100.000, a u našoj zemlji je iznosila 12176,10/100.000. Broj godina izgubljenog života globalno povezan sa ishemijskom bolešću srca bio je 2335,55/100.000, a u Srbiji 5370,45/100.000. Ukupni *YLL*povezan sa hipertenzivnom bolešću globalno je iznosio 309,76/100.000, a u Srbiji 733,48/100.000. Ukupni *YLL* povezan sa kardiomiopatijom i miokarditisom iznosio je 142,06/100.000, a u našoj zemlji 561,47/100.000.

Udeo kardiovaskularnih bolesti u ukupnoj smrtnosti u našoj zemlji predstavlja i dalje veoma značajan javno-zdravstveni problem i skoro polovina svih smrtnih slučajeva je tokom 2021. godine pripisana kardiovaskularnim bolestima. Stope *YLL*povezane sa kardiovaskularnim bolestima - ishemijskom bolešću srca, hipertenzivnom bolešću, kao i kardiomiopatijom i miokarditisom, u našoj zemlji su bile značajno više u poređenju sa globalnim prosekom za posmatranu godinu.

Ključne reči: iznenadna srčana smrt, *Disability-adjusted life-years, Years lived with disability, Years of life lost*

Biološki fakultet Univerziteta u Beogradu

GENETIKA I IZNENADNA SRČANA SMRT: POSTMORTALNE GENETIČKE STUDIJE KAO ALAT ZA IDENTIFIKACIJU RIZIKA I PREVENCIJU

Milica Keckarević Marković

Molekularna autopsija se odnosi na postmortalne genetičke analize i ima poseban značaj kada standardnom forenzičkom autopsijom nije moguće odrediti uzrok, kao i kada se sumnja na genetičku osnovu nastanka iznenadne smrti. Neinformativni rezultati standardne forenzičke autopsije su češći u situacijama iznenadne smrti kod mlađih osoba, i kao takvi upućuju na postojanje naslednog aritmogenog sindroma kod preminule osobe, odnosno na iznenadnu srčanu smrt. Ovakva srčana smrt može biti izazvana primarnim poremećajem ritma, koji ne dovodi do strukturnih promena na srcu, kao i aritmijom kao posledicom kardiomiopatije, koja kod mlađih osoba može da dovede do smrti, a uz odsustvo vidljivih strukturnih promena na srcu. U oba slučaja uzrok smrti nije moguće utvrditi standardnom forenzičkom autopsijom.

Iako može biti indukovana faktorima sredine, iznenadna srčana smrt, posebno kod mlađih osoba i kod dece, ima izraženu genetičku komponentu. Do danas je identifikovan veliki broj gena u kojima retke varijante nedvosmisleno dovode do poremećaja u radu jonskih kanala ili do poremećaja u strukturi srčanog mišića i koje mogu dovesti do zastoja u radu srca odnosno do iznenadne srčane smrti. Takođe, veliki broj uobičajenih genetičkih varijanti je asociran sa povećanim rizikom za iznenadnu srčanu smrt.

Nasledni aritmogeni sindromi uzrokovani retkim genetičkim varijantama se uglavnom nasleđuju autozomno – dominantno i odlikuju se nekompletnom penetrabilnošću, varijabilnom ekspresijom bolesti, kao i preklapajućom genetičkom osnovom, te su bliski rođaci osoba preminulih od iznenadne srčane smrti takođe u visokom riziku, bez obzira na eventualno prisustvo i karakteristike simptoma koji bi mogli da ukazuju na poremećaj u radu srca.

Za identifikaciju genetičke osnove naslednih aritmogenih sindroma, a koja bi omogućila personalizovani pristup u prevenciji iznenadne srčane smrti, danas se koristi sekvenciranje nove generacije. U najvećem broju slučajeva analizira se 20 glavnih i 100 sporednih gena uzročnika, a zajedno sa kliničkom evaluacijom srodnika moguće je identifikovati genetičku osnovu bolesti u oko 30% slučajeva.

Ključne reči: iznenadna srčana smrt, molekularna autopsija, nasledni aritmogeni sindromi

King's College London, Department of Population Health Sciences

INFORMACIONI SISTEMI U PROCENI RIZIKA ZA NAPRASNU SRČANU SMRT

Vasa Ćurčin

Veštačka inteligencija (AI) i mašinsko učenje (ML) sve se više primenjuju u predviđanju i upravljanju tretmana iznenadnog srčanog zastoja (ISZ) analizom velikih količina podataka kako bi se identifikovali obrasci koji možda nisu očigledni kroz tradicionalne metode.

Radi prevencije, cilj je obezbediti tačnija, individualizovana predviđanja rizika od ISZ i preporučiti personalizovane opcije lečenja, kao što su lekovi ili promene načina života, koje smanjuju rizik od ISZ kod pacijenata sa visokim rizikom. Podaci o pacijentima koji se koriste za ove analize uključuju medicinske istorije iz elektronskih zdravstvenih kartona, genetske informacije, faktore životnog stila, kao i podatke sa EKG-a i nosivih tehnologija (npr. pametni satovi ili trake za grudi koje pružaju podatke u realnom vremenu). AI algoritmi mogu pomoći u interpretaciji srčanih snimaka identifikovanjem strukturnih abnormalnosti srca, kao što su miokardijalna fibroza ili disfunkcija ventrikula, koje predisponiraju pacijente za ISZ.

Uprkos napretku u sistemima za hitne intervencije, stopa preživljavanja nakon srčanog zastoja van bolnice ostaje niska. Kako bi se poboljšali uspeh reanimacije i stopa uspešnosti defibrilacije, neki AI sistemi pomažu timovima za hitne intervencije da identifikuju najverovatnije slučajeve ISZ kroz algoritme trijaže u realnom vremenu. AI se integriše u automatizovane spoljne defibrilatore i sisteme za hitnu pomoć kako bi efikasnije vodio proces reanimacije, optimizujući vreme defibrilacije i analizirajući kvalitet kompresija grudnog koša tokom kardiopulmonalne reanimacije.

U bolničkim uslovima, AI modeli prioritizuju pacijente na osnovu rizika od ISZ, omogućavajući kliničarima da efikasnije rasporede resurse. Uređaji poput implantabilnih kardioverter-defibrilatora mogu da otkriju abnormalne srčane ritmove i automatski primene spasilačke defibrilacione šokove.

Nakon što pacijent preživi ISZ, AI modeli analiziraju podatke o naknadnom praćenju kako bi procenili rizik od ponavljanja, omogućavajući bolje dugoročno praćenje i preventivne strategije, kao i pomoć u rehabilitaciji kroz ponudu personalizovanih režima vežbanja i praćenje pridržavanja plana nege.

Ključne reči: veštačka inteligencija, mašinsko učenje, naprasna srčana smrt, prevencija

MINI SIMPOZIJUM
100 GODINA KATEDRE FIZIKALNE MEDICINE I REHABILITACIJE NA MEDICINSKOM FAKULTETU UNIVERZITETA U BEOGRADU

Medicinski fakultet Univerziteta u Beogradu, Klinika za fizikalnu medicinu i rehabilitaciju

Univerzitetski Klinički Centar Srbije

100 GODINA OD ODRŽANOG PRVOG PREDAVANJA NA KATEDRI FIZIKALNE MEDICINE I REHABILITACIJE

Dragana Matanović

Na samom početku osnivanja Medicinskog fakulteta u Beogradu, 2.2.1923. godine osnovana je i katedra fizikalne medicine i rehabilitacije izborom dr Laze Nenadovića u docenta Instituta za fizikalnu terapiju aprila 1923. godine i održanim prvim predavanjem 28.10.1924. godine kada i zvanično katedra fizikalne terapije i balneologije počinje sa radom. U početku praktična nastava se obavljala u banjama, a od 1930. godine vežbe iz elektroterapije bile su na Internoj I klinici. Školske 1948-49. godine farmakoterapija, fizikalna terapija i medicinska hidrologija i terapija ujedinuju se u Katedru terapije, da bi školske 1958-59. katedra dobila naziv „Fizikalna medicina i rehabilitacija“. Medicinska hidrologija i klimatologija školske 1964-65. godine postaju Balneoklimatologija.

Prvi konkurs za osnivanje katedri i mesto nastavnika na novoosnovanom Medicinskom fakultetu u Beogradu raspisan je 1921. godine, a među 17 predmeta bila je pod rednim brojem 13 i fizikalna terapija.

Od osnivanja katedre jedini član bio je dr Laza Nenadović, kome se kasnije pridružuje asistent Vanđel Tasić, a potom se i studenti demonstratori pridružuju držanju nastave. Članovi katedre su učestvovali u osnivanju katedri pri Stomatološkom fakultetu u Beogradu, kao i Medicinskim falultetima u Nišu, Kragujevcu, Banja Luci, ali i višim i srednjim medicinskim školama u Beogradu.

Od prvobitnog prostora na Internoj klinici stvaraju se baze Institut za rehabilitaciju „Dr Aleksandar Rotović“, a kasnije i baza na Dečjoj klinici u Tiršovoj, UKC Srbije, zavod za protetiku u Klinici za rehabilitaciju „Dr Miroslav Zotović“.

U svim ovim bazama nastavnici i saradnici su držali teoretsku i praktičnu nastavu kako studentima osnovne nastave, tako i studentima poslediplomske nastave u svim oblicima, a pre svega na specijalizaciji fizikalne medicine i rehabilitacije; učestvovali su i u nastavi u okviru drugih užih specijalizacija, pratili tokove i napredovanje samog fakulteta i u nastavi koja se odvija na engleskom jeziku.

Ključne reči: istorijat, 100 godina katedre, prvo predavanje

Medicinski fakultet Univerziteta u Beogradu, Klinika za rehabilitaciju „Dr Miroslav Zotović“

OSNIVANJE BAZE ZA FIZIKALNU MEDICINE I REHABILITACIJU - KLINIKA ZA REHABILITACIJU „DR MIROSLAV ZOTOVIĆ“

Ljubica Konstantinović

Klinika za rehabilitaciju „Dr Miroslav Zotović“ osnovana je 1952. godine na osnovu sporazuma sa UN/SZO. Ugovor je sadržao sve elemente iz međunarodno prihvaćenih dokumenata savremene multidisciplinarne rehabilitacije. Klinika je promenila nekoliko puta naziv, a sadašnji je iz 1998. godine. Klinika za rehabilitaciju „Dr Miroslav Zotović“ je sekundarna i tercijarna ustanova za usluge rehabilitacije u zdravstvenom sistemu Srbije. Klinika raspolaže sa 330 postelja, od kojih je nešto više od 200 namenjeno neurorehabilitaciji dece i odraslih, što je čini najvećim pružaocem rehabilitacionih usluga u zemlji i čitavom regionu. KlinikA je nastavna baza Medicinskog fakulteta od 1999. godine i sedište specijalizacije za fizikalnu medicinu i rehabilitaciju.

Takođe, klinika je nastavna baza za srodne struke posebno za članove rehabilitacionog tima. Saradnja sa Elektrotehničkim fakultetom, Institutom za fiziku i Institutom za medicinska istraživanja, kao i učešće u evropskim projektima omogućilo je razvoj metodologije, posebno u multidisciplinarnim oblastima, kao i ispunjavanje edukativnih ciljeva u oblastima osnovnih, master i doktorskih studija. Klinička istraživanja mogu se grupisati oko dve glavne teme: motorička rehabilitacija nakon moždanog udara i nove tehnike rehabilitacije. Glavni fokus kliničkih istraživanja u Klinici za rehabilitaciju „Dr Miroslav Zotović“ je stimulacija za jačanje senzorno-motornih sistema pomoću električne stimulacije za gornje ekstremitete kod tetraplegičnih i hemiplegičnih pacijenata; poboljšana lokomocija hibridnom ortozom i treningom hoda i *low cost* robotskim uređajima, za donje i gornje ekstremitete tetraplegičnih i hemiplegičnih pacijenata.Veliki broj nastavnika i saradnika, kao i doktora nauka zaposlenih u Klinici stalno je angažovan u izvođenju svih vidova nastave, kao i na unapređenju kliničke prakse i realizaciji kliničkih istraživanja.

Ključne reči: Rehabilitacija, nastavna baza, klinička istraživanja

Medicinski fakultet Univerziteta u Beogradu, Klinika za rehabilitaciju „Dr Miroslav Zotović", Centar za fizikalnu medicinu i rehabilitaciju-Univerzitetski klinički centar Srbije

PRVI SAMOSTALNI KORACI RAZVOJA KATEDRE FIZIKALNE MEDICINE I REHABILITACIJE, NASTAVNE BAZE ZA FIZIKALNU MEDICINU I REHABILITACIJU

Aleksandra Vidaković, Tamara Filipović

Katedra fizikalne medicine i rehabilitacije na Medicinskom fakultetu Univerziteta u Beogradu osnovana je 1924. godine i tokom proteklih 100 godina bila je lider u oblasti fizikalne medicine i rehabilitacije u Srbiji i regionu. Njena uloga je ključna u edukaciji medicinskih stručnjaka, istraživanjima i implementaciji naprednih terapijskih metoda.

Institut za rehabilitaciju je formiran maja 1989. godine integracijom Zavoda za fizikalnu medicinu „Dr Aleksandar Rotović", Zavoda za interne bolesti „Vlastimir Godić", Zavoda za medicinu rada i rehabilitaciju Mladenovac i Zavoda za rehabilitaciju Prčanj.

Danas Institut za rehabilitaciju ima dva organizaciona dela: prvi je u Sokobanjskoj 17 u Beogradu sa 80 kreveta za kardiopulmološku rehabilitaciju, a drugi predstavlja banja Selters, jedna od najvećih u Srbiji, sa 300 kreveta u mreži zdravstvenog osiguranja i 200 ležajeva dostupnih za bavljenje zdravstvenim turizmom. Od svog nastanka do danas se u Institutu odvija redovna i poslediplomska nastava iz predmeta Fizikalna medicina i rehabilitacija. Nastavni kadar ove ustanove, tokom niza decenija činili su profesori: Živojin Conić, Olga Manojlović, Nadica Rotović, Olga Jovanović, Gordana Popović, Snežana Conić, Milica Lazović, Milisav Čutović i asistent Miloš Obrenović. Trenutno nastavni kadar čine: docent Tamara Filipović, asistenti Marija Hrković i Jovana Kojović i VNS Olivera Ilić.

Institut za rehabilitaciju u Beogradu, kao integralni deo ove katedre, pruža sveobuhvatan spektar rehabilitacionih usluga iz oblasti fizikalne medicine i rehabilitacije. Ove usluge obuhvataju ambulantno-poliklinički i stacionarnu rehabilitaciju pacijenata sa širokim rasponom oboljenja, uključujući bolesti mišićno-skeletnog, nervnog i kardiopulmonalnog sistema. Takođe, u ovom centru vrši se i edukacija lekara i drugih medicinskih stručnjaka iz oblasti balneoklimatologije. Institut je prepoznat kao sertifikovani trening centar Evropskog Borda za fizikalnu i rehabilitacionu medicinu.

Osobenosti ove eminentne institucije jesu brojna indikaciona područja koja pokriva, broj postelja kojima raspolaže, veličina objekta, a posebno visoko obrazovani naučni i stručni kadar, koji Institut za rehabilitaciju čini jednom od najzačajnih rehabilitacionih ustanova u našoj zemlji.

Ključne reči: rehabilitacija, nastava, Medicinski fakultet

Medicinski fakultet Univerziteta u Beogradu
Služba fizikalne medicine i rehabilitacije, Univerzitetska dečja klinika, Beograd

ISTORIJSKI RAZVOJ BAZE ZA FIZIKALNU MEDICINU I REHABILITACIJU – UNIVERZITETSKA DEČJA KLINIKA

Dejan Nikolić

Služba fizikalne medicine i rehabilitacije na Univerzitetskoj dečjoj klinici u Beogradu postaje nastavna baza Medicinskog fakulteta Univerziteta u Beogradu 1980. godine sa Ass. dr Gordanom Nikolić kada se stvaraju uslovi za pedagoški i naučni razvoj dečje fizijatrije. Od osnivanja do danas članovi nastavne baze su: prof. dr Gordana Nikolić, prof. dr Ana Maršavelski, prof. dr Ivana Petronić-Marković, prof. dr Dragana Ćirović, doc. dr Dejan Nikolić, kl. ass. dr Jasna Stojković i kl. ass. dr Tatjana Knežević. U sklopu ove nastavne baze na Univerzitetskoj dečjoj klinici u Beogradu sprovode se svi vidovi edukacije u okviru Integrisanih akademskih studija, specijalističkih, subspecijalističkih, doktorskih, master strukovnih studija, kao i nastave na engleskom jeziku, a sprovodile su se magistarske studije i specijalističke akademske studije.

Sa prof. dr Gordanom Nikolić započinje se uvođenje elektrodijagnostičkih ispitivanja (elektromioneurografije) u ovoj nastavnoj bazi, koja su dalje unapređivali prof. dr Ana Maršavelski, prof. dr Ivana Petronić-Marković (uvođenje evociranih potencijala i elektromiografije sfinktera) i doc. dr Dejan Nikolić (uvođenje testa repetitivne nervne stimulacije, kasnih odgovora i refleksološka ispitivanja). Takođe se sa prof. dr Gordanom Nikolić uvodi i rana rehabilitacija posle kardiohirurških intervencija, koja se kasnije razvijala i proširivala na sve jedinice intenzivnog lečenja na Univerzitetskoj dečjoj klinici. Prof. dr Dragana Ćirović je unapređivala urodinamska ispitivanja.

Uža specijalizacija dečje fizijatrije na Medicinskom fakultetu Univerziteta u Beogradu uvedena je 1992. godine. Rukovodioci uže specijalizacije dečje fizijatrije od njenog osnivanja do danas su: prof. dr Gordana Nikolić u periodu od 1992-2005. godine, prof. dr Ivana Petronić-Marković od 2005-2019. godine, prof. dr Dragana Ćirović od 2019-2023 godine i doc. dr Dejan Nikolić od 2023. godine. Tokom svog razvoja nastavni plan i program veština iz uže specijalizacije dečje fizijatrije je prolazio kroz mnogobrojne promene kako bi se prilagodio izazovima u vremenu koje je dolazilo i pratio savremeni korak sa svetskim trendovima. Predavači na ovom studijskom programu su nastavnici i saradnici Medicinskog fakulteta Univerziteta u Beogradu iz različitih užih naučnih oblasti u koje spadaju fizikalna medicina i rehabilitacija, pedijatrija, dečja hirurgija, anesteziologija, radiologija i u poslednje vreme, genetika. U sklopu teorijske nastave rukovodioci tematskih celina su nastavnici Medicinskog fakulteta Univerziteta u Beogradu, specijalisti fizikalne medicine i rehabilitacije i subspecijalisti dečje fizijatrije, dok su na praktičnoj nastavi rukovodioci nastavnici i saradnici Medicinskog fakul-

teta Univerziteta u Beogradu, specijalisti fizikalne medicine i rehabilitacije sa dugogodišnjom praksom u radu sa pedijatrijskom populacijom.

Ključne reči: istorijski razvoj, nastavna baza Univerzitetska dečja klinika, inovacije

Medicinski fakultet Univerziteta u Beogradu, Centar za fizikalnu medicinu i rehabilitaciju-Univerzitetski klinički centar Srbije

NASTAVNA BAZA ZA PREDMET FIZIKALNA MEDICINA I REHABILITACIJA MEDICINSKOG FAKULTETA UNIVERZITETA U BEOGRADU, UNIVERZITETSKOG KLINIČKOG CENTRA SRBIJE

Sanja Tomanović-Vujadinović

Centar za fizikalnu medicinu i rehabilitaciju Univerzitetskog Kliničkog centra Srbije (UKCS) je nastavna baza Medicinskog fakulteta Univerziteta u Beogradu za predmet Fizikalna medicina i rehabilitacija. Osnivanje nastavne baze vezuje se za 1993. godinu, prelaskom prof. dr Vladislave Vesović Potić, redovnog profesora na predmetu Fizikalna medicina i rehabilitacija na Medicinskom fakultetu u Beogradu, iz Instituta za rehabilitaciju, Beograd u Klinički centar Srbije, čime su se stekli uslovi za osnivanje nastavne jedinice koja je integrisana u tadašnji Centar za fizikalnu medicinu i rehabilitaciju u okviru Kliničkog centra Srbije. Od tog trenutka se u Centru razvija obrazovna i naučno-istraživačka delatost i nastavna baza se uvećava, čime su se stekli uslovi za sprovođenje studentske i specijalističke nastave na srpskom i engleskom jeziku. Od 1993. do 2001. godine nastavna baza broji 7 članova i to: prof. dr Vladislava Vesović Potić, doc. dr Dragana Matanović, asistent pripravnik dr Predrag Vidaković, asistent pripravnik dr Miloš Obrenović, asistent pripravnik dr Nataša Mujović, asistent pripravnik dr Sanja Vranić, asistent pripravnik dr Milena Pavićević Stojanović. Danas, nakon 30 godina od osnivanja, nastavna baza broji 10 članova od kojih 2 redovna profesora: prof. dr Draganu Matanović i prof. dr Emiliju Dubljanin Raspopović; 4 vanredna profesora: prof. dr Natašu Mujović, prof. dr Mirka Grajića, prof. dr Nelu Ilić i prof. dr Anđelu Milovanović; 2 docenta: doc. dr Sanju Tomanović Vujadinović i doc. dr Unu Nedeljković i 2 klinička asistenta: dr Nevenu Krstić i dr Ivana Selakovića. Od 2023. godine rukovodilac nastavne baze je prof. dr Anđela Milovanović. Članovi nastavne baze su predavači po pozivu na istaknutim domaćim i inostranim konferencijama, mentori brojnih magistarskih i doktorskih disertacija, mentori diplomskih radova i specijalističke nastave. Objavili su veliki broj radova sa JCR liste čiji se rezultati istraživanja citiraju u stručnoj literaturi širom sveta i svoje stručno usavršavanje su obavljali u velikim svetskim medicinskim centrima.

Ključne reči: nastavna baza UKCS, istorijat

MINI SIMPOZIJUM
25 GODINA ONLAJN NASTAVE NA MEDICINSKOM FAKULTETU U BEOGRADU I 20 GODINA RETIKULUMA, PORTALA ZA ONLAJN NASTAVU

Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić“, Medicinski fakultet Univerziteta u Beogradu

KRATAK ISTORIJAT ONLAJN NASTAVE NA MF U PERIODU 1999-2024

Miloš Bajčetić

Prvi onlajn kurs iz histologije na Institutu za histologiju i embriologiju “Prof. dr Aleksanda Đ. Kostić” organizovan je školske 1999/2000. godine. Te godine je prva grupa od 19 studenata zajedno sa tadašnjim asistentima dr Kirilom Gligorovskim i dr Milošem Bajčetićem i studentima demonstratorima – moderatorima onlajn kursa imala prilike da nastavu histologije prati po hibridnom modelu. Pored predavanja i standardnih mikroskopskih vežbi, studentima je na raspolaganju bilo i nekoliko različitih veb servisa – osim statičnog veb sajta posebno kreiranog za ove potrebe, kao glavni način interakcije tj. komunikacije između asistenata i studenta korišćen je *e-mail*. U periodu 1999 – 2004. godine, osim navedenih korišćeni su i neki drugi internet servisi za sinhrono i asinhrono onlajn učenje (forumi, mejling liste itd.). Decembra 2004. godine (u školskoj 2004/2005. godini), za ciljem daljeg unapređenja onlajn nastave na Medicinskom fakultetu u Beogradu pokrenuta je prva instalacija Moodle LMS-a (inicijalna verzija je bila 1.3.4), tj. portal za onlajn nastavu pod nazivom **Retiiikulum**. Do 2010. godine onlajn nastava u hibridnom obliku korišćena je na tek nekoliko predmeta dodiplomskih studija (histologija i embriologija i humana genetika od školske 2006/2007). Školske 2010/2011. godine svoje prve onlajn kurseve na *Reticulumu* pokrenule su još četiri katedre na dodiplomskim studijama, da bi u narednom periodu, do izbijanja KOVID-19 pandemije, to učinilo još nekoliko katedri, i to ne samo na dodiplomskim, već i na poslediplomskim katedrama.

Danas na portalu za onlajn nastavu *Reticulum*, postoji više od 500 aktivnih onlajn kurseva, koji osim obaveznih i izbornih predmeta na dodiplomskim studijama (IAS medicine) i OAS sestrinstvo, pokrivaju veći broj predmeta na nekoliko master studijskih programa, doktorskim studijama, kao i u okviru poslediplomskih specijalističkih studija. Aktuelna verzija Moodle LMS-a koja se koristi je 4.2.6. Kao standardno WAMP okruženje koristi se Apache veb server (2.4.39), PHP (8.2.8) i MariaDB baza podataka (ver. 10.11.4).

Na samom portalu ima preko 14 hiljada otvorenih naloga (od 2012. godine), od kojih je trenutno aktivnih preko 6.000 naloga studenata, specijalizanata, nastavnika i saradnika Medicinskog fakulteta.

Ključne reči: onlajn nastava, medicinska edukacija, e-učenje

Institut za epidemiologiju, Medicinski fakultet Univerziteta u Beogradu

ONLAJN NASTAVA NA DOKTORSKIM AKADEMSKIM STUDIJAMA NA MEDICINSKOM FAKULTETU UNIVERZITETA U BEOGRADU

Gorica Marić

Iako je Retikulum – zvanični portal za onlajn nastavu Medicinskog fakulteta Univerziteta u Beogradu, imao svoju ulogu u nastavi na doktorskim studijama od njihovog osnivanja, njegova šira primena počela je u martu 2020. godine, sa početkom epidemije oboljenja KOVID-19 u Srbiji i prelaskom kompletne nastave iz realnog u virtuelno okruženje. Nastava na doktorskim akademskim studijama je u kratkom vremenskom periodu potpuno prilagođena novonastaloj situaciji, te se pristupilo pripremi svih oblika nastave (predavanja, vežbe, seminari) za onlajn okruženje. Sva teorijska nastava pripremljena je u vidu snimaka predavanja koje su studenti mogli da preslušavaju više puta u vreme kada to njima odgovara. Vežbe i seminari su organizovani na nekoliko načina, od postavljanja materijala koje su studenti prolazili jednom i dobijali ocene na osnovu postignutih poena, preko izrade domaćih zadataka prema uptstvima na Retikulumu, do interaktivnih sesija uživo sa predavačima u virtuelnim učionicama. Takođe, u vreme pandemije, Retikulum je, pored fakultetskog sajta, predstavljao glavno mesto informisanja studenata o svim relevantnim aspektima predmeta koje su slušali na doktorskim studijama, uključujući raspored nastave, informacije o načinu održavanja nastave, kao i termin i način polaganja ispita iz različitih predmeta. Osim toga, na Retikulum su kačeni i materijali za nastavu koje su studenti mogli da preuzimaju i koriste kao literaturu za učenje.

Ključne reči: onlajn nastava, medicinska edukacija, doktorske studije

Institut za medicinsku i kliničku biohemiju, Medicinski fakultet Univerziteta u Beogradu

KAKO BISMO BEZ RETIKULUMA – OD BOJAŽLJIVIH POKUŠAJA E-UČENJA PREKO PANDEMIJSKE NEOPHODNOSTI DO KOMBINOVANOG BLENDED UČENJA NA KATEDRI ZA MEDICINSKU I KLINIČKU BIOHEMIJU

Anđelka M. Isaković

Korišćenje savremenih tehnologija u procesu učenja i nastave kroz koncept onlajn edukacije, tj. E-učenja na Katedri za medicinsku i kliničku biohemiju je otpočelo 2016. godine, na obaveznom predmetu za studente četvrte godine integrisanih akademskih studija medicine - Klinička biohemija, kada je postavljen prvi kurs na *Moodle* platformi Medicinskog fakulteta, *Reticulum*-u. Uvođenje tehnologija za menadžment učenja (engl. *Learning managment system, LMS*) na predmetu sa relativno malim brojem časova (15, a zatim 30) na predmetu koji se ocenjuje opisno, je omogućilo postupno prilagođavanje tradicionalne *ex cathedra* nastave savremenijem, *blended* konceptu učenja koji kombinuje prednosti korišćenja elektronskih medija sa učenjem kroz direktnu komunikaciju, „licem u lice". Naime, tehnologije i alatke koje se koriste u E-učenju su davno prepoznate i potvrđene kao one koje, obezbeđujući studentima kontrolu nad brzinom i napretkom učenja, individualizovanim, fleksibilnim i adaptivnim pristupom, dovode do većeg zadovoljstva studenata, unapređuju stečeno znanje i poboljšavaju razumevanje složenih koncepata. Postupno poboljšanje kompentencija nastavnika i saradnika Katedre u okviru koncepta E-učenja u prethodnim godinama je obezbedilo studentima pristup kako asinhronom tako i sinhronom onlajn učenju u realnom vremenu, gde studenti uče ne samo kroz gotove prezentacije nastavnih jedinica i snimljena predavanja, već i kroz pripremljene interaktivne lekcije, prateće formativne testove znanja, grupne i indivualne izrade seminarskih radova, kao i forume za diskusiju koji podržavaju vršnjačko učenje uz nadzor nastavnika. Ovo je omogućilo da u vreme pandemije nastava iz Medicinske biohemije za svega par nedelja bude gotovo u potpunosti preneta u onlajn okruženje dajući podršku studentima da u datim okolnostima na najbolji mogući način usvoje predviđena znanja i veštine i pripreme se za ispit. Danas, Katedra biohemije organizuje *blended* kurseve na *Reticulum*-u na dva obavezna predmeta za studente integrisanih akademskih studija medicine, jednom obaveznom predmetu za studente osnovnih akademskih studija Sestrinstvo, 4 izborna predmeta na doktorskim akademskim studijama, kao i 8 izbornih predmeta za studente integrisanih akademskih studija medicine koji se u celosti organizuju u onlajn okruženju.

Ključne reči: onlajn nastava, medicinska edukacija, e-učenje, nastava medicinske i kliničke biohemije

Centar za informacione i komunikacione tehnologije, Medicinski fakultet Univerziteta u Beogradu

EDUKACIJA MEDICINARA TOKOM PANDEMIJE KOVID-19

Nikola Ilić

20. marta 2020. godine je naredbom ministra zdravlja proglašena epidemija KOVID-19 u Republici Srbiji. Pet dana pre toga je proglašeno vanredno stanje u Republici. Nagli porast broja zaraženih pacijenata i broja smrtnih slučajeva uz nepostojanje efikasne vakcine doveli su do toga da je ponašanje opšte populacije i lekara, kao i njihov odnos prema epidemiji bilo od izuzetnog značaja u obuzdavanju epidemije. Zbog nedostatka adekvatne zaštitne opreme kontakt između nastavnika, studenata i pacijenata više nije mogao da se održava. Pojavila se hitna potreba za socijalnim distanciranjem i prekidom kliničke prakse za student, te medicinski fakulteti odlučuju da sa klasične nastave pređu na dostavljanje unapred snimljenih predavanja studentima uz dalju izradu i dostavljanje novih edukativnih materijala u onlajn okruženju.

Glavne dileme koje su nastale prilikom prelaska studenata sa klasične nastave na potpuno onlajn okruženje u edukaciji, bile su način dostavljanja materijala i interakcija sa studentima, organizacija nastave, opterećenje studenata i nastavnika novim oblicima održavanja nastave i tehnički kapaciteti neophodni za održavanje onlajn nastave.

Ključne reči: onlajn nastava, medicinska edukacija, e-učenje, KOVID-19 pandemija

Medicinski fakultet Univerziteta u Beogradu, Katedra za humanističke nauke

ONLAJN NASTAVA ENGLESKOG JEZIKA MEDICINSKE STRUKE U PANDEMIJSKIM USLOVIMA

Danka Sinadinović

Usled pandemije Kovida-19, Katedra humanističkih nauka Medicinskog fakulteta Univerziteta u Beogradu bila je prinuđena da pune dve i po godine izvodi nastavu iz engleskog jezika isključivo u onlajn formatu. Iako je ovakav pristup nastavi predstavljao svojevrstan izazov i nepoznanicu, i nastavnici i studenti su veoma brzo uvideli brojne prednosti koje on nudi, te su zahvaljujući svom trudu i entuzijazmu došli do izvrsnih rezultata.

Ovom prilikom ću predstaviti na koji način je, posredstvom Retikuluma, izvođena nastava iz engleskog jezika medicinske struke, kao i kako se takva nastava razlikovala od uobičajenog, pre-pandemijskog načina rada. Analiza će obuhvatiti sve četiri jezičke veštine (slušanje, čitanje, pisanje i govor), upotrebu autentičnih materijala (video klipova, tekstova sa medicinskom tematikom, studija slučaja, itd.), gramatička vežbanja, snimljena predavanja, kvizove namenjene pripremi za ispit, forum-diskusije...

Biće reči i o komunikaciji između studenata i nastavnika u izmenjenim okolnostima, kao i svim izazovima i prednostima ovakvog načina rada u odnosu na uobičajeni pristup nastavi engleskog jezika na Medicinskom fakultetu Univerziteta u Beogradu. Najzad, biće navedena i pojedinačna mišljenja nastavnika o ovakvom vidu nastave i rezultatima koji su za to vreme postignuti.

Ključne reči: onlajn nastava, medicinska edukacija, e-učenje, COVID-19 pandemija, nastava engleskog jezika.

Institut za medicinsku i kliničku biohemiju, Medicinski fakultet Univerziteta u Beogradu

PERSPEKTIVE O NASTAVI NASTAVNIKA MEDICINSKOG FAKULTETA UNIVERZITETA U BEOGRADU

Milica Velimirović Bogosavljević

Nastavnici igraju centralnu i ključnu ulogu u oblikovanju obrazovnog sadržaja. Osim što treba da budu stručnjaci u oblasti o kojoj podučavaju, trebalo bi da vladaju i pedagoškim veštinama. Ovo podrazumeva da poznaju strategije za rešavanje problema i da imaju kapacitet da donose odluke, da budu prilagodljivi različitim učenicima u smislu nivoa znanja koje poseduju i motivisanosti da uče, da imaju uvid u zbivanja u učionici, kao i osetljivost na kontekst i da se prema učenicima ponašaju sa poštovanjem. Prepoznajući značaj nastavnika i široku lepezu veština koje zahteva posao, pažnja je usmerena na njihovu obuku i profesionalni razvoj. Uprkos naglasku na formalnom obrazovanju i programima obuke za nastavnike, brojne studije pokazuju da se nastavnici često oslanjaju na lične, implicitne, pedagoške „teorije“ u svojoj praksi koje su oblikovane individualnim iskustvima, verovanjima i percepcijama efikasnih nastavnih metoda, što dovodi do odstupanja od ustaljenih obrazovnih praksi. Ovo naglašava složenost nastave kao profesije i važnost razumevanja individualnih perspektiva nastavnika i pristupa nastavi. Premošćavanje jaza između formalnog obrazovanja i ličnih pedagoških teorija nastavnika je od vitalnog značaja za povećanje efektivnosti nastavne prakse i poboljšanje obrazovnih ishoda.

Na Medicinskom fakultetu Univerziteta u Beogradu u ovom trenutku je zaposleno preko 1000 nastavnika (redovni profesori, vanredni profesori i docenti) i saradnika (asistenata u nastavi, asistenata sa doktoratom, kliničkih asistenata i saradnika u nastavi). Većina nastavnika na Medicinskom fakultetu diplomirala je na istoj ustanovi, sa izuzetkom nastavnika i saradnika na predmetima humanističkih nauka, hemije i biofizike u medicini. Do 2015. godine na fakultetu nije bilo predmeta koji su se posebno fokusirali na pedagogiju i nastavne metode, a od tada za studente druge godine fakulteta postoje 2 izborna predmeta iz metodike nastave. Takođe, tokom poslednjih deset godina pojedini nastavnici su imali prilike da pohađaju kurseve pedagogije i metodike, tačnije AMEE kurs „Osnovne veštine u medicinskom obrazovanju” 2017. godine i dvomesečni kurs Erazmus projekata ReFEEHS „Unapređenje nastavnih i mentorskih kompetencija za zdravstvene radnike”, u 2019. godini. Tokom leta 2020. godine organizovano je 8 kurseva koji su nudili praktična uputstva uz pedagoške i metodološke komponente za vođenje nastave u onlajn okruženju. Ukupno 266 članova fakulteta pohađalo je ove kurseve, tokom kojih je takođe zatraženo da popune Inventar perspektiva o nastavi (Teaching Perspectives Inventory - TPI). Ovim putem dobili smo uvid u dominantne perspektive o nastavi nastavnika i saradnika MFUB-a, kao i da li dužina radnog staža i pedagoška obuka imaju uticaj na perspektive o nastavi.

Ključne reči: medicinska edukacija, uloga nastavnika, perspektive o nastavi, TPI

Institut za histologiju i embriologiju „prof. dr Aleksandar Đ. Kostić“, Medicinski fakultet Univerziteta u Beogradu

UPOTREBA VEŠTAČKE INTELIGENCIJE U MEDICINSKOJ EDUKACIJI

Ivan Zaletel

Tokom poslednje dve godine, svetska pažnja bila je usmerena na pojavu i masovno širenje veštačke inteligencije zasnovane na različitim velikim jezičkim modelima. Komunikacija korisnika sa ovim oblicima veštačke inteligencije omogućena je putem softverskih alata, koji se nazivaju četbotovi, a koji predstavljaju softverske aplikacije koje omogućavaju i imitiraju humanu interakciju. Primena ovih jezičkih modela postaje sve prisutnija u različitim oblastima naših života, a jedno od područja na kojem je korišćenje ovih alata posebno privuklo značajnu pažnju jeste visoko obrazovanje, a pre svega oblast medicinske edukacije. Iako su mnogi izrazili zabrinutost zbog mogućih problema koje ova nova tehnologija nosi sa sobom (plagijarizam, davanje neproverenih informacija, različiti oblici varanja na ispitima, itd.), ona ipak može biti dragoceni alat za poboljšanje kvaliteta različitih aspekata medicinskog obrazovanja. Samim tim ovo predavanje imaće za cilj da prikaže prednosti i mane upotrebe velikih jezičkih modela u medicinskoj edukaciji, kao i naša iskustva u primeni ove tehnologije.

Ključne reči: veštačka inteligencija, medicinska edukacija

Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić“, Medicinski fakultet Univerziteta u Beogradu

VIDEOKONFERENCIJSKI SISTEMI U NASTAVI – OD MITA DO REALNOSTI

Miloš Bajčetić

Upotreba savremene info-komunkacione tehnologije u nastavnom procesu, ima veoma dugu tradiciju i svoje korene datira na početke šezdesetih godina 20. veka kada je na Univerzitetu Ilionis (SAD) razvijen sistem pod imenom PLATO (*Programmed Logic for Automatic Teaching*

Operations) u okviru kog su studenti imali mogućnost da rešavaju zadatke i testove i dobijaju povratne informacije u realnom vremenu, što je bilo revolucionarno za to doba. Prvi počeci onlajn učenje (*online learning*) se mogu vezati za osamdesete godine dvadesetog veka, kada su univerziteti počeli da koriste računarske mreže u obrazovne svrhe. Za razmenu informacija između nastavnika i studenata prvo su korišćeni forumi i e-pošta, ali pravu ekspanziju onlajn učenje doživljava devedesetih godina, prošlog veka sa pojavom i razvojem interneta.

Nastavne aktivnosti u procesu učenje/nastava u onlajn okruženju, se zavisno od vremenskog okvira u kojem se dešavaju mogu podeliti na sinhrone i asinhrone. Iako glavne prednosti onlajn učenja/nastave leže u asinhronim aktivnostima, upotreba sinhronih aktivnosti, posebno videokonferencijskih alata (servisa) kao što su npr. *Zoom*, *Microsoft T*eams, *BBB*, *Google M*eet itd. je, iz sasvim razumljivih razloga, privukla pažnju i dobila na popularnosti među univerzitetskim (ali i među nastavnicima osnovnih i srednjih škola) u periodu KOVID-19 pandemije. Iako je mogućnost neposredne komunikacije sa studentima/učenicima u realnom vremenu delovala kao logično rešenje (u situaciji kada nije bila moguća nastava u tradicionalnom okruženju) brojna istraživanja su pokazala da je korišćenje videokonferencijskih alata tokom pandemije imalo brojna ograničenja. Slični rezultati dobijeni su i kada su analizirani onlajn kursevi koji su tokom pandemije bili organizovani na Retikulumu, zvaničnom portalu za onlajn nastavu Medicinskog fakulteta.

Ključne reči: onlajn nastava, medicinska edukacija, videokonferencijski sistemi

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