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LIFE QUALITY OF PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH BIOTHERAPY

KVALITET ŽIVOTA PACIJENATA SA REUMATOIDNIM ARTRITISOM LEČENIH BIOLOŠKOM TERAPIJOM

Jelena OBRADOVIĆ GAJIĆ[1], Ksenija BOŠKOVIĆ[1,2], Jelena ZVEKIĆ SVORCAN[1,2] and Nataša IGIĆ[1]

Summary

Introduction. Rheumatoid arthritis is a chronic disease that causes joint damage and loss of function, thus impairing quality of life. Administration of biological drugs can change the course of the disease and improve life quality and functional capacity of patients. The objective of the study is to examine the quality of life in patients with rheumatoid arthritis treated with biological therapy. **Material and Methods.** The prospective cross-sectional study followed 56 patients of both sexes treated with biological drugs at the Special Hospital for Rheumatic Diseases, Novi Sad. The data were collected using a standardized questionnaire for monitoring the quality of life (Health Assessment Questionnaire-disability index) and a general questionnaire, containing socio-demographic data, disease and therapy data. Computer program Statistical Package for the Social Sciences version 24 was used for data processing. **Results.** The results of the assessment of the life quality of patients with rheumatoid arthritis undergoing biological therapy showed that the values of the Health Assessment Questionnaire-disability index range from Min=0.00 to Max=2.25, with the mean M=0.76. Observed by category, 39.3% of participants are in remission, while the rest (60.7%) have low disease activity. The Health Assessment Questionnaire-disability index has a statistically significant correlation with the place of residence ($p<0.05$), as well as with the duration of morning stiffness ($p<0.01$). The Health Assessment Questionnaire-disability index has no statistically significant correlation with other general data, disease and therapy data. **Conclusion.** Application of biotherapy on patients with rheumatoid arthritis leads to low disease activity and remission, which results in good quality of life.

Key words: Quality of Life; Arthritis, Rheumatoid; Biological Therapy; Surveys and Questionnaires; Disability Evaluation

Sažetak

Uvod. Reumatoidni artritis je hronična bolest koja uzrokuje oštećenje zglobova i gubitak njihove funkcije, čime se narušava kvalitet života. Primena bioloških lekova može menjati tok bolesti i popraviti kako kvalitet života, tako i funkcionalnu sposobnost obolelih. Cilj ovog istraživanja je ispitivanje kvaliteta života pacijenata sa reumatoidnim artritisom lečenih biološkom terapijom. **Materijal i metode.** Prospektivnom studijom preseka obuvaćeno je 56 pacijenata oba pola, koji se leče biološkim lekovima u Specijalnoj bolnici za reumatske bolesti u Novom Sadu. Podaci su prikupljeni korišćenjem standardizovanog upitnika za praćenje kvaliteta života (*Health Assessment Quiestionnaire-disability index*) i opšteg upitnika koji sadrži sociodemografske podatke, podatke o bolesti i terapiji. Za obradu podataka korišćen je kompjuterski program *Statistical Package for the Social Sciences* verzija 24. **Rezultati.** Rezultati merenja kvaliteta života pacijenata sa reumatoidnim artritisom lečenih biološkom terapijom pokazali su da se vrednosti *Health Assessment Quiestionnaire-disability index*-a kreću se od min = 0,00 do max = 2,25, dok prosečna vrednost iznosi m = 0,76. Posmatrano po kategorijama, u remisiji je 39,3% ispitanika, dok ostali (60,7%) imaju nisku aktivnost bolesti. *Health Assessment Quiestionnaire-disability index* je u statistički značajnoj vezi sa mestom stanovanja ($p < 0,05$), kao i sa dužinom trajanja jutarnje ukočenosti ($p < 0,01$). Sa ostalim opštim podacima, podacima o bolesti i terapiji *Health Assessment Quiestionnaire-disability index* nije u statistički značajnoj vezi. **Zaključak.** Primena biološke terapije kod pacijenata sa reumatoidnim artritisom dovodi do niske aktivnosti bolesti i remisije, što daje dobar kvalitet života.

Ključne reči: kvalitet života; reumatoidni artritis; biološka terapija; ankete i upitnici; procena onesposobljenosti

Introduction

Rheumatoid arthritis (RA) is a symmetrical polyarticular arthritis primarily affecting the small joints of hands and feet [1]. Inadequately treated, it leads to irreversible joint deformities and consequent disability as well as premature mortality [2].

Treatment is carried out by non-pharmacological and pharmacological methods. Non-pharmacological and pharmacological treatment methods have a syn-

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Abbreviations

RA – rheumatoid arthritis
DMARD – disease modifying anti-rheumatic drugs
bDMARD – biological disease modifying anti-rheumatic drugs
cDMARD – conventional disease modifying anti-rheumatic drugs
HAQ-DI – Health Assessment Questionnaire-disability index
RF – rheumatoid factor

ergistic effect in RA treatment, as well as in maintaining joint mobility and delaying the progression of the disease [3]. Pharmacological therapy involves the use of different drug groups, which include disease modifying anti-rheumatic drugs (DMARDs), as well as symptomatic therapy using non-steroidal anti-inflammatory drugs and glucocorticoids [4]. DMARDs represent the most important measure in successful RA treatment. DMARDs can be divided into conventional (cDMARDs) and biological (bDMARDs). Methotrexate stands out among cDMARDs as the gold standard in RA therapy. Biological DMARDs is a group of drugs that target specific molecules or molecular pathways involved in the inflammatory processes in RA [5]. These drugs have played a significant role in improving clinical symptoms and life quality of patients [6]. They have been in use in Serbia since 2006 and have significantly improved the treatment of patients with RA [7]. The Special Hospital for Rheumatic Diseases in Novi Sad has used biological drugs since 2007. According to the 2019 recommendations of the European Alliance of Associations for Rheumatology (EULAR), treatment of RA patients should begin immediately upon the diagnosis. Treatment should be goal-oriented, i.e., aiming at remission or low disease activity in each patient [8].

According to the World Health Organization (WHO), the quality of life is defined as "an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns" [9]. Self-assessment of the quality of life can be obtained in a systematic way through interviews, as well as qualitative assessments and questionnaires [10]. Fries et al. developed the Health Assessment Questionnaire-disability index - HAQ-DI [11, 12]. This is a self-assessment questionnaire and is the most frequently used questionnaire for assessing quality of life and physical function of patients with rheumatic diseases [10]. Quality of life in patients with RA is affected by the degree of disease activity and functional ability, which depends on the effectiveness of the applied therapy [13].

The aim of our study is to examine the quality of life in patients with rheumatoid arthritis treated with biological therapy.

Material and Methods

The study was conducted as a prospective cross-sectional study at the day hospital of the Special Hospital for Rheumatic Diseases in Novi Sad. The sample included 56 patients of both sexes who were diagnosed with RA and treated with biological therapy. The participants were chosen by a random selection method. All participants included in the study were assessed according to the biotherapy inclusion criteria by the Drug Use in the Treatment of Insured Persons Approval Committee of the Health Insurance Fund of the Republic of Serbia. The study was approved by the Ethics Committee of the Special Hospital for Rheumatic Diseases in Novi Sad (14/32-6/1-22).

Data were collected using a standardized questionnaire for monitoring the quality of life (HAQ-DI) of the RA patients included in the study. The questionnaire includes questions about independence in dressing, maintaining personal hygiene, rising, eating, ability to reach or lift objects, and other daily activities. The value of the questionnaire ranges from 0 to 3, where 0 indicates that the patient has no limitations in daily functioning, while 3 indicates complete disability. The participants also filled out a general questionnaire made by the researcher, which contains socio-demographic data (age, sex, place of residence, work status) and seven questions that include information on the diagnosis and therapy.

The study examined whether the HAQ-DI has a statistically significant correlation with the participants' general data, disease data, as well as therapy data.

The results obtained from the research were statistically processed with an adequate selection of statistical methods, depending on the type and distribution of data, in order to ensure an optimal model for observing dependencies and differences between the analysed data obtained in the study. Some of the measures of the used descriptive statistics were the arithmetic mean, with the corresponding standard deviation, the minimum and maximum. Both frequencies and percentages were used. Differences between groups were determined with use of the χ^2-test. Statistical significance is defined at the null hypothesis probability level of $p \leq 0.05$. Statistical processing and analysis were done in the computer program Statistical Package for the Social Sciences ver. 24.

Results

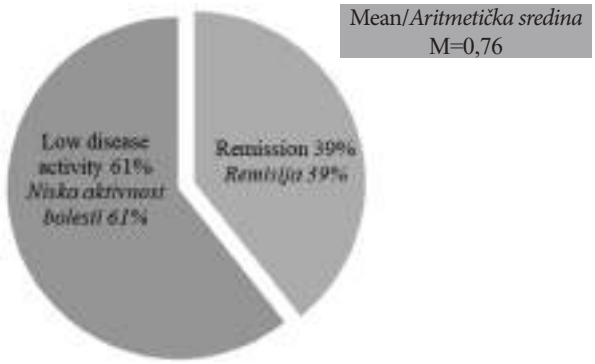
56 patients with rheumatoid arthritis treated with biological therapy participated in the study. The average age of the participants is 56 years. The sample comprised of 26.8% male and 73.2% female patients. The majority (64.3%) live in urban and 25% live in rural areas. The majority of the participants (73.2%) live with their families, 17.9% are single, while 8.9% of the participants live in multigenerational households. 48.2% of the participants are employed, 16.1% are unemployed, and 35.7% are retired. Up to 5 years have passed since the diagnosis of RA in 7.1% of patients, the duration of RA from 6 to 10 years is present in 46.4% of patients, while 46.4% of the examined patients have suffered from RA for more than 10 years. Positive rheumatoid factor (RF) was recorded in 92.9% of patients, and negative in 7.1%. Positive anti-CCP antibody was recorded in 26.8% of the participants, and negative in 73.2%. 28.6% of the patients

do not experience morning stiffness, 66.1% experience stiffness for 2 hours after rising, whereas 5.4% experience stiffness for more than 2 hours after rising. 35.7% of the participants have had current therapy for under a year. 23.2% of the participants have had current therapy for 1-3 years, 7.1% for 3-5 years, whereas 33.9% of the participants have received current therapy for more than 5 years. Of the total number of the participants, 91.9% are on methotrexate, while the other 8.1% are on hydroxychloroquine. Glucocorticoids are taken by 14.3% of the participants, 7.1% are occasionally on glucocorticoids, while 78.6% of the patients have never taken corticosteroids.

The HAQ-DI values range from Min=0.00 to Max=2.25, with the mean M=0.76. Observed by category, 39.3% of the participants are in remission, while the rest (60.7%) have low disease activity **(Graph 1)**.

The HAQ-DI has a statistically significant correlation with the place of residence ($p<0.05$). The highest percentage of the participants from urban areas is in remission (86.4%), whereas the percentage of the participants from rural areas is significantly lower (13.6%). Low disease activity is found in 50.0% from urban areas, 32.4% from rural areas and 17.6% from the suburbs. The HAQ-DI does not have a statistically significant correlation with other disease data **(Table 1)**.

The duration of morning stiffness has a statistically significant correlation with the HAQ-DI ($p<0.01$). Of the total number of participants in remission, about a half (54.5%) do not have morning stiffness, while most of those with low disease activity (79.4%) have stiffness that lasts for 2 hours. The HAQ-DI does not have a statistically significant correlation with other disease data.



Graph 1. HAQ-DI in patients with rheumatoid arthritis treated with biological therapy
Grafikon 1. *Health Assessment Questionnaire-disability index kod pacijenata sa reumatoidnim artritisom lečenih biološkom terapijom*

The therapy data do not have statistically significant correlation with the HAQ-DI. The statistical significance of the χ^2-test is above the threshold of 0.05 **(Table 2)**.

Discussion

The majority of the participants in our study were female (73.2%), which is expected as RA is the most common disease in women; three times more common than in men [14]. The average age of the participants was 56, which corresponds to the period of onset of the disease, between the ages of 35 and 50 [14]. The obtained data showing that 46.4% of patients have suffered from RA for 6-10 years and the same percentage

Table 1. General data on participants and HAQ-DI
Tabela 1. *Opšti podaci o ispitanicima i Health Assessment Questionnaire-disability index*

		HAQ-DI						p/*p*
		Remission *Remisija*		Low disease activity *Niska aktivnost bolesti*		Total *Ukupno*		
		F	%	f	%	f	%	
Average age *Prosečna starost*	56	22	100%	34	100%	56	100%	
Sex *Pol*	Male/*Muški*	6	27.3%	9	26.5%	15	26.8%	0.947
	Female/*Ženski*	16	72.7%	25	73.5%	41	73.2%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
Place of residence *Mesto stanovanja*	Urban/*Grad*	19	86.4%	17	50%	36	64.3%	0.014
	Rural/*Selo*	3	13.6%	11	32.4%	14	25%	
	Suburban/*Prigradsko naselje*	0	0%	6	17.6%	6	10.7%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
I live with *Živim sa*	Family (spouse and children) *Porodicom (suprug/a i deca)*	17	77.3%	24	70.6%	41	73.2%	0.150
	Multigenerational household *U široj zajednici*	0	0%	5	14.7%	5	8.9%	
	Alone/*Sam/sama*	5	22.7%	5	14.7%	10	17.9%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
Employment *Radni odnos*	Yes/*Da*	11	50%	16	47.1%	27	48.2%	0.870
	No/*Ne*	4	18.2%	5	14.7%	9	16.1%	
	Retired/*Penzioner/ka*	7	31.8%	13	38.2%	20	35.7%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	

Table 2. Disease and therapy data and HAQ-DI
Tabela 2. *Podaci o bolesti i terapiji i Health Assessment Questionnaire-disability index*

		HAQ-DI						
		Remission *Remisija*		Low disease activity *Niska aktivnost bolesti*		Total *Ukupno*		p/*p*
		f	%	f	%	f	%	
Duration of RA disease *Dužina trajanja bolesti RA*	1-5 years/*1-5 godina*	0	0%	4	11.8%	4	7.1%	0.211
	6-10 years/*6-10 godina*	10	45.5%	16	47.1%	26	46.4%	
	+10 years/*+10 godina*	12	54.5%	14	41.2%	26	46.4%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
RF	RF+	21	95.5%	31	91.2%	52	92.9%	0.544
	RF-	1	4.5%	3	8.8%	4	7.1%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
Anti-CCP antibody *Anti-CCP antitela*	Anti-CCP antibody+ *Anti-CCP antitela+*	6	27.3%	9	26.5%	15	26.8%	0.947
	Anti-CCP antibody– *anti-CCP antitela–*	16	72.7%	25	73.5%	41	73.2%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
How long does morning stiffness last? *Koliko dugo traje jutarnja ukočenost zglobova?*	Not present/*Nema*	12	54.5%	4	11.8%	16	28.6%	0.002
	Up to 2h/*Do 2 h*	10	45.5%	27	79.4%	37	66.1%	
	+2 h/*+2 h*	0	0%	3	8.8%	3	5.4%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
When was the current biological drug therapy introduced? *Kada je uvedena sadašnja terapija biološkim lekom?*	<1 year/*<1 godine*	5	22.7%	15	44.1%	20	35.7%	0.244
	1-3 years/*1-3 godina*	6	27.3%	7	20.6%	13	23.2%	
	3-5 years/*3-5 godina*	3	13.6%	1	2.9%	4	7.1%	
	+5 years/*+5 godina*	8	36.4%	11	32.4%	19	33.9%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
Therapy *Terapija*	Methotrexate/*Metotreksat*	11	84.6%	23	95.8%	34	91.9%	0.233
	Sulfasalazine/*Sulfasalazin*	0	0%	0	0%	0	0%	
	Hydroxychloroquine *Hidroksihlorohin*	2	15.4%	1	4.2%	3	8.1%	
	Total/*Ukupno*	13	100%	24	100%	37	100%	
Glucocorticoids *Glukokortikoidi*	Yes/*Da*	2	9.1%	6	17.6%	8	14.3%	0.137
	No/*Ne*	20	90.9%	24	70.6%	44	78.6%	
	Occasionally/*Povremeno*	0	0%	4	11.8%	4	7.1%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	

for more than 10 years speak in favour of the fact that the participants' age fits into the most common period of the disease onset. These results are similar to the results of the study by Al-Jabi et al. who investigated the impact of socio-demographic characteristics of RA patients on functional disability and quality of life. The study included 300 RA patients, most of whom were female (76.3%) with an average duration of the disease of 6 years [15]. Similarly, in their study, Direskeneli et al. looked into the quality of life, disease activity and whether there is a preference for administration routes by doctors and RA patients. Their study included a larger number of women (76%), with an average age of 50 [16]. In their study, Tipsing et al. looked into the influence of general data – age, sex, comorbidities, as well as data related to RA, including disease duration, treatment methods and lab results with the level of disease activity. The average age in that study was 52.33, while RA duration was 7.65 years [17].

The study results show that 35.7% of participants have been on current therapy for less than a year and 33.9% of participants have been receiving current therapy for more than five years. For most participants, this was the first therapy with a biological drug (76.8%). A study conducted in the territory of Vojvodina in 2018 showed that the average elapsed time from the RA diagnosis to the application of biotherapy in participants who received Etanercept was 6.12±5.62 years, while it was 7.54±7.15 years in patients who received Adalimumab, which indicated the necessity of increasing the availability of treatment with biotherapy in order to prevent the development of deformities and contractures and preserve the functional status and work ability of the patients [18]. The average duration of the disease before the commencement of biotherapy is not surprising because the official application of biotherapy for RA treatment in Serbia began in 2006, and in the Special Hospital for Rheumatic Diseases in Novi Sad in 2007 [7]. A ten-

year French study showed that although access to biological drugs in France was available, less than one-third of patients with early RA detection started treatment with biological drugs during the ten-year research [19]. Machado-Alba et al. collected information on the time from the initiation of conventional treatment in RA patients to the initiation of biological therapy. After 5 years of cDMARD therapy, 6% of RA patients started bDMARD therapy [20].

Analysing the impact of biological therapy on the quality of life and functional status of RA patients measured by the HAQ-DI questionnaire, it was found that patients treated with biological drugs were in remission (39.3%) or had low disease activity (60.7%), which is consistent with the results of other studies. Direskeneli et al. proved in their study that RA patients who are on biological therapy have better disease control and health status compared to patients who met the requirements for biotherapy but did not receive it [16]. In their study, Azevedo et al. followed 30 patients diagnosed with RA before and after the introduction of the first biological drug over the period of 6 months. Their study showed that there was a significant improvement in quality of life and functional status in just 3 months of biological drug administration [10]. In their study, Boyadzieva et al. followed 124 patients who were transferred from cDMARDs to bDMARDs for 1 year and assessed the quality of life using a questionnaire. The assessment was carried out at the beginning of therapy, 6 months and 1 year after the therapy. Their study confirmed that the quality of life rapidly improved after the introduction of biological therapy [21]. Boyadzhieva et al. did a similar study in 2022. In the prospective study, they concluded with use of the HAQ-DI and the 36-item short form health survey questionnaires that the application of biological therapy in RA patients led to improvement in the quality of life and functional capacity of RA patients. Intensity of RA activity and pain sensation were lower among the patients treated with cDMARDs and bDMARDs compared to the patients treated only with cDMARDs [22]. Bogojević et al. looked at whether there were any differences between the impact of biological therapy and conventional treatment on productivity and quality of life in patients suffering from RA. The HAQ-DI showed that the level of difficulty in daily functioning was higher with patients treated with cDMARDs compared to the ones treated with biological drugs. They also obtained results that health status, emotional status and quality of life are better in patients treated with biological therapy [23].

The results in our study showed that the HAQ-DI has a statistically significant correlation with the place of residence. The largest percentage of participants from urban areas (86.4%) is in remission as compared to a significantly smaller percentage of participants from rural areas (13.6%). Pinarosa et al. studied whether there was any difference in the distribution of RA disease and lack of health services in rural areas compared to urban areas. They came to the conclusion that the prevalence of RA is not increased in rural areas but that it is more difficult to provide adequate access to health services in such an environment. The problem occurs due to untimely visit to the doctor after the onset of symptoms, leading to late diagnosis, as well as due to frequent discontinuity in disease and therapy monitoring [24]. In their study, Hollick et al. showed that there are greater functional disability and disease activity in patients living in rural areas [25]. Study conducted in Taiwan showed that lower socioeconomic status or living in a rural area may be a risk factor for the development of RA and that it also may influence disease activity [26]. Movahedi et al. obtained results that a higher RA disease activity, measured by the number of swollen joints, was observed in patients living in rural areas [27]. Iltchev et al. showed that morbidity in residents of rural areas of Poland is higher than in residents of urban areas [28]. Codreanu et al. evaluated the influence of socioeconomic factors on the availability of biological therapy in RA patients in Romania. They found that people living in rural areas have difficulty in accessing biological drugs [29].

Study conducted at the Special Hospital for Rheumatic Diseases in Novi Sad in 2022 showed that the duration of morning stiffness has a statistically significant correlation with the HAQ-DI, which is also shown by the results of our study [30]. Of the total number of participants in remission, about a half (54.5%) do not have morning stiffness, while most of the ones with low disease activity (79.4%) have stiffness lasting up to 2 hours. These results coincide with the results of the study showing that the presence of morning stiffness was associated with higher HAQ-DI scores and thus significantly influenced the degree of disability, as well as a low level of the quality of life [15]. The authors of the Polish study compared the level of the life quality in patients with RA during cDMARD therapy and in combination with bDMARDs. They concluded that the intensity of the disease activity, pain and duration of morning stiffness were significantly lower in patients from the group that used biological drugs [31].

Conclusion

Patients suffering from rheumatoid arthritis who are treated with biological therapy have low disease activity and are in remission. Compared to the ones living in rural areas, respondents who live in urban areas have better quality of life and almost 1/3 of them do not have the feeling of morning stiffness.

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SPEECH AND LANGUAGE THERAPY FOR CHILDREN WITH PHONOTRAUMA

LOGOPEDSKI TRETMAN KOD DECE SA FONOTRAUMOM

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Summary

Introduction. Proper voice production requires coordinated, synchronous and efficient functioning of the larynx, respiratory, resonance and articulation mechanisms. Phonotrauma is trauma to the laryngeal mechanism and includes any behavior that results in injury to the vocal folds. The aim of this research was to identify and describe the characteristics of voice disorders in children that occur as a result of phonotrauma, approaches and techniques in speech and language therapy of these speech disorders, and the effects of their application. **The characteristics of phonotrauma in children** reflect the characteristics of hyperfunctional voice disorders, as they usually arise as a result of voice abuse. **Speech and language therapy of children with phonotrauma** includes identification and reduction, i.e. elimination of the vocal behavior that had caused the voice disorder. In addition, treatment focuses on a vocal hygiene program and the use of various direct treatment techniques to achieve appropriate voice production. **Effects of applying direct and indirect treatment techniques** is demonstrated by the reduction of the size of the lesion, the degree of dysphonia and voice disorders, hoarseness, breathiness in the voice, the absence of recurrence, and the achievement of optimal values of the acoustic parameters of the voice. **Conclusion**. In most cases, children can master the correct way of producing speech after a short period of speech and language therapy. However, in order to achieve this goal, it is necessary to actively involve children, their parents, and other people from the immediate and wider social environment**.**

Key words: Speech Therapy; Language Therapy; Voice Disorders; Voice Training; Child; Dysphonia; Hoarseness

Sažetak

Uvod. Pravilna produkcija glasa zahteva koordinisanu, sinhronu i efikasnu funkciju larinksa, kao i respiratornog, rezonatornog i artikulatornog mehanizma. Fonotrauma predstavlja traumu laringealnog mehanizma i obuhvata svako ponašanje koje dovodi do povrede glasnica. Cilj ovog rada bio je da se sistematskim pregledom dostupne i relevantne literature utvrde i opišu karakteristike poremećaja glasa kod dece koji nastaju kao posledica fonotraume, pristupi i tehnike u logopedskom tretmanu ovih govornih poremećaja, kao i efekti njihove primene. **Karakteristike fonotraume kod dece** odražavaju osobine hiperfunkcionalnih poremećaja glasa s obzirom na to da oni najčešće nastaju kao posledica zloupotrebe glasa. **Logopedski tretman dece sa fonotraumom** obuhvata identifikaciju i smanjenje, odnosno, eliminisanje onog vokalnog ponašanja koje je izazvalo poremećaj glasa. Pored toga, tretman je usmeren na program vokalne higijene i primenu različitih direktnih tehnika tretmana u cilju postizanja adekvatnog generisanja glasa. **Efikasnost primene direktnih i indirektnih tehnika tretmana** ogleda se u smanjenju veličine lezije, stepena disfonije i poremećaja glasa, hrapavosti, šumnosti, izostanku recidiva, kao i u postizanju optimalnih vrednosti akustičkih parametara glasa. **Zaključak**. U većini slučajeva deca nakon kratkog perioda logopedskog tretmana mogu da savladaju pravilan način govorne produkcije. Međutim, za postizanje ovog cilja neophodno je aktivno uključivanje dece, njihovih roditelja, kao i drugih osoba iz neposrednog i šireg socijalnog okruženja.

Ključne reči: terapija glasa; terapija govora; poremećaji glasa; trening glasa; dete; disfonija; promuklost

Introduction

Proper voice production is the result of vibration of the vocal cords and other modifications made with the help of the pharynx, lips and the nasal cavity. Thus, voice is produced by the work of the vocal cords, which belong to the phonation organ, with the synchronous action of the respiratory organs and resonators [1]. Correct vibration of the vocal cords is an important prerequisite for the production of an adequate voice, and any asymmetry within the larynx can lead to disturbances in the movements of the vocal cords [2].

Phonotrauma, which is also referred to as voice abuse, is any behavior or phenomenon that results in strain and/or damage to the vocal cords [3]. It is

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trauma to the laryngeal mechanism, i.e., the vocal cords, resulting from various vocal behaviors that include inappropriate use of vocal pitch and volume, and activities such as yelling, screaming, cheering, and throat clearing. These vocalizations are often accompanied by an elevated tone and hyperactivity of the larynx [4]. In addition, phonotrauma can be caused by improper hydration, improper breathing patterns, excessive stress or tension, inadequate coping mechanisms in dealing with negative emotions, and insufficient recovery time of the vocal cords [5].

Some authors believe that the term phonotrauma is more appropriate than the term voice abuse because the former does not contain negative connotations. Parents may equate the term abuse with the act of bullying, insulting, or harming the child and, consequently, adopt a hostile attitude toward the speech therapist. They also often confuse the terms "verbal abuse" and "name-calling". In addition, the term "abuse" suggests that the behavior is intentional and that the child has "violent personality".

The characteristics of vocal habits present in childhood help to find and analyze possible causes and factors that contribute to the development of vocal changes [6]. The habit of "shouting" and speaking loudly during and outside of play is common in childhood and may be the cause of chronic hoarseness resulting from impaired muscle coordination necessary for proper phonation [7]. As many children participate in activities in which voice is abused, it is very important to understand the effects of such behaviors on the development of dysphonia and other anatomical and functional changes in the phonation organ [8].

The aim of this research was to identify and describe the characteristics of voice disorders in children that occur as a result of phonotrauma, approaches and techniques in the speech and language therapy of such speech disorders, and the impact of their application through a systematic review of the available and relevant literature.

Characteristics of phonotrauma in children

Early recognition of behaviors that are considered misuse of voice is very important, because voice is not only a sound produced by the vibration of the vocal cords, but also affects the communication competence of the speaker. This competence depends on the modulation of the sound, the adjustment of the intensity, the resonance, and the type of voice that conveys the appropriate emotional aspects and allows the characterization of the child's personality [6]. It is considered that disorders resulting from voice misuse are the most widespread and common voice disorders [3]. The three most common diagnoses associated with voice disorders in children younger than three years of age are subglottic stenosis, laryngomalacia, and vocal fold nodules, while vocal fold nodules, subglottic stenosis, and papillomas are most common between the age of 4 and 11 [9]. Vocal fold nodules and papillomas, as benign lesions of the vocal cords, are the main causes of voice disorders in children with phonotrauma [10].

Functional injuries of the larynx occur as a result of voice misuse. Voice functional disorders are caused by inadequate use of the phonatory apparatus [1]. Phonotrauma leads to increased effort and tension of the throat muscles, which is a risk factor for the development of hyperkinetic dysphonia and vocal nodules [11]. Most voice disorders in children belong to the group of hyperfunctional voice disorders, which are mainly manifested by poor breath control, tension in the neck and root of the tongue, typical contractions and tension in voice, and hoarseness [4]. The majority of chronic hoarseness is due to structural changes resulting from phonotrauma and includes numerous changes in voice quality [12]. The most common conditions resulting from voice abuse are laryngitis, vocal fold nodules, polyps, cysts, thickening of the vocal cords, and contact ulcers [3, 13, 14].

When considering the consequences of phonotrauma, it is important to give equal attention to the negative psychological and/or behavioral effects. These consequences may be related to bad habits that lead to excessive effort or tension during vocalization, resulting in misdirected and ineffective communication, as well as negative reactions from communication partners and the appearance of negative stereotypes [15]. Aggressiveness and disturbed relationships with peers may occur in these children. All of these factors can lead to difficulties in participating in social interactions, as well as the development of shyness, fear, and social anxiety in children with phonotrauma [6, 15].

Speech and language therapy of children with phonotrauma

Rehabilitation of children with phonotrauma involves much more than just eliminating behaviors associated with voice abuse. As most disorders caused by voice abuse are considered reversible, the treatment approach should include careful identification and gradual elimination of voice behavior causing the voice disorder [3]. Identification and reduction, i.e., elimination of voice abuse, are the primary goals of speech and language therapy for hyperfunctional disorders with or without anatomic changes, such as vocal nodules, polyps, or contact ulcers [16]. In assessing and determining the treatment program, it is important for the speech-language pathologist to inform the child and parents about how to limit or reduce the vocal behavior that reflects the phonotrauma. In many cases, a short course of speech therapy may be sufficient for the child to master the appropriate vocal techniques and the correct way to produce speech. For this reason, the treatment of voice disorders lends itself to the application of primary and secondary prevention models [17]. Primary prevention involves eliminating or preventing the onset and development of voice and communication disorders. Primary prevention programs in functional voice disorders aim to reduce excessive use of voice in preschool- and school-age

children, which is achieved through educational programs for asymptomatic children at this age. Secondary prevention involves early detection and treatment to prevent worsening of the condition and includes mass screening and early intervention [18].

One of the programs for prevention of voice change in school-age children [18] involves training children and teachers in two half-hour sessions per week for two weeks. The speech production methods and the vocal apparatus anatomy are explained in the first lesson. Terms such as vocal cords, voice quality, and hoarseness are explained to the participants. In addition, voice recordings are presented to the children followed by a discussionabout the voice quality of the participants in the recording. The second lesson includes a discussion of adequate and inadequate voice quality. The participants will be asked about various childhood activities and behaviors associated with specific vocal behaviors and possible vocal abuse. Children are then introduced to the characteristics of impaired vocal qualities and a discussion begins about situations associated with voice abuse. The speech therapist lists possible situations while the children list additional activities that may cause phonotrauma and hoarseness. In addition, the children are presented with a list of nonviolent vocal behaviors, and they contribute in the same way. Afterwards, short stories can be read to the participants that feature characters who abuse their voices and use them correctly to encourage them to identify different vocal behaviors on their own.

Early intervention is considered critical for children who have developed a voice disorder and for children who are assessed to be susceptible to the development of such disorders.

In addition to applying these models, the treatment of voice disorders resulting from phonotrauma includes the application of direct and indirect techniques [11]. The aim of using direct techniques is to change incorrect phonatory patterns, voice production methods, and breathing mechanisms, while indirect techniques target the psychological and social aspects of vocal emission [11].

Direct and indirect treatment techniques

Direct treatment techniques focus on the part of the vocal system where anatomical changes and pathology are present, and on modifying vocal behavior to achieve appropriate voice production [19]. This goal is achieved by modifying neuromotor planning and requires the child's active participation in the exercises [20]. Direct treatment techniques include voice function exercises, resonance therapy, and the use of a semi-occluded vocal tract [19].

Exercises to improve vocal function involve direct manipulation of parts of the effector communication system to achieve physiological balance between them [21]. In addition, the exercises aim to strengthen the muscles of the larynx and improve adduction of the vocal cords. This treatment approach involves the use of a series of four systematically organized exercises [22]. The first exercise is a warm-up exercise for the voice. The second exercise allows the vocal cords to stretch by gradually changing the pitch range from low to high notes. The third exercise serves to contract the vocal cords where the child needs to change the pitch rangefrom higher to lower notes in this case. The last exercise is a 'strength exercise' aimed at achieving full adduction of the vocal cords.

Exercises for achieving the optimal vocal resonance aim to create a feeling of vibration on the lips and face and to achieve adequate vibration of the vocal cords without straining the muscles of the larynx [23]. This mainly includes different singing techniques and their variations [22]. Right at the beginning, the child is asked to purr their lips as if asking their communication partner for additional clarification ('mmm?'). After that, singing, chanting or reciting words and non-words containing the sounds 'm' and 'v' is used to detect the feeling of vibration or 'tickling' on the lips [23]. Singing is eliminated over time when the child reaches the appropriate resonance in natural speech.

The goal of using a semi-occluded vocal tract is to alter the vibration pattern of the vocal cords [24]. Increased subglottic and decreased glottic pressure allow adequate adduction and abduction of the vocal cords without the need to use excessive muscle force [25]. The term semi-occluded vocal tract implies various maneuvers that increase the interaction between the airflow directed by the vibration of the vocal cords and the resonance properties of the vocal tract [22]. In the treatment, the mouth is opened in a reduced manner during phonation with the help of a tube or straw [26]. Making bubbles in water with the help of a straw, gargling, and prolonged phonation of the vowel 'u' are the main components of this approach [23]. As with the previously described exercises, these activities gradually progress to the production of syllables, words, and sentences.

As mentioned earlier, indirect treatment techniques target cognitive, psychological, and physiological aspects, as well as changes in the child's behavior and physical environment. They are divided into external, which are performed by a speech therapist, and internal, which are applied independently by the child [27]. To change behavior, the child, parents, and people in the immediate and wider social environment must be educated on how to recognize and eliminate inappropriate vocal behavior.

After the speech-language pathologist identifies the situations in which vocal inflexion occurs, s/he should work with the child and the parents to determine how many times a day the child participates in such activities. If it is an older child, s/he can independently make a graph of the frequency of such situations, which is a kind of 'visual reminder' [16]. This chart raises the person's awareness of what activities they participate in throughout the day, which gradually leads to a reduction in those behaviors that can lead to voice abuse. Depending on the child's age, siblings, peers, and teachers may also be involved in this process. Any reduction in inappropriate vocal behavior should be

highlighted and praised, as positive reinforcement is considered more effective than criticism [5]. The effectiveness of this and similar approaches depends largely on the speech therapist's ability to motivate the child to stop inappropriate behavior [1]. Speech and language therapy can only lead to a positive outcome when the frequency of behaviors that lead to voice abuse is significantly reduced.

In addition to behavior, modification of vocal physiology is another indirect treatment technique. This includes the use of vocal hygiene, which is often the first step in beginning speech and language therapy. Structured vocal hygiene programs reduce or eliminate the risk of vocal trauma and promote appropriate vocal behavior [28]. The main goal of the program is to identify, modify and eliminate the factor that caused the disorder [1]. Vocal hygiene refers to the correct use of voice to eliminate hyperactivity or excessive contraction of the laryngeal mechanism [29]. It is considered the basis for the treatment of voice disorders because it helps the child develop awareness of their problem and voice disorder [30]. The vocal hygiene program for children with vocal cord trauma caused by vocal fracture includes auditory skill development, reduction of total time of speech production during the day, vocal intensity and frequency, vocal rest periods after vocal stress, adequate hydration, and patterns of proper diaphragmatic breathing for better support during phonation and reduction of laryngeal hyperactivity during speech [31].

Effects of applying direct and indirect treatment techniques

The effectiveness of speech and language therapy requires the obtained results to indicate a clinically significant change that is generalized and persists during long-term follow-up, and that the estimated voice parameters reach threshold values [32]. The results of a study on the voice quality change after the application of exercises to achieve optimal voice resonance in children with vocal nodules [33] showed that there was a change in fundamental frequency, and in parameters related to frequency variability and voice intensity. These parameters change due to the presence of vocal nodules, and their inadequate function can significantly affect the voice quality. In addition, positive changes were noted in hoarseness, roughness and breathiness in voice. The six-week speech and language therapy included exercises for relaxationof the throat, lips, tongue, and pharynx muscles, and the establishment of proper breathing. Subsequently, the subjects repeated the sequence 'mama' to feel the vibration in the nasal cavity, sinuses and face area. Words, phrases, and texts beginning with the sound 'm' were used as the treatment progressed. Reduction of roughness, hoarseness, and breathiness in voice was reported as a positive result of treatment of children aged five to ten with cysts and nodules on the vocal cords, using semi-closed vocal tract exercises [25]. The treatment involved blowing air through a straw placed between the teeth and lips, producing sounds. A decrease in hoarseness and breathiness in voice was noted after three minutes of such phonation, while a lesser degree of dysphonia and hoarseness in the voice was noted after five minutes. The improvement in voice quality was determined by assessing acoustic andauditory-perceptual parameters. A significant reduction in the degree of dysphonia, the presence of vocal nodules, and a change in the level of fundamental frequency were reported as positive results of the eight-week vocal hygiene program [34]. However, no positive changes were observed in the values of fundamental frequency or in the parameters related to the variability of vocal intensity in this study. A combination of direct and indirect treatment techniques is thought to provide optimal results, as they include both neurophysiological and behavioral changes in children with voice disorders [20].

Positive results of simultaneous application of direct and indirect treatment techniques were shown in a study of children under the age of 18 with dysphonia caused by benign changes in the vocal cords [35]. Vocal hygiene, semi-occluded vocal tract exercises, and exercises to achieve optimal vocal resonance were used in the treatment. Auditory-perceptual and acoustic measurements showed improvement in the subjects' voice quality in terms of fundamental frequency, effort in speaking, pitch and intensity of voice, hoarseness, loudness, and degree of voice disturbance. Significant changes in the values of these parameters indicate a functional improvement in voice quality.

The results of a study on the use of vocal hygiene and exercises to achieve optimal vocal resonance in children with vocal nodules showed a significant improvement in the severity of dysphonia as well as in the Voice Impairment Index as a parameter of auditory-perceptual voice analysis [36]. The treatment consisted of six consecutive one-hour exercises performed once a week. Positive results were observed in terms of voice quality, psychosocial functioning, and communication, although no changes were observed in the values of acoustic parameters, i.e., fundamental frequency, and parameters related to variability of frequency and intensity of voice.

The effectiveness of treatment can be further improved by active parental involvement. The results of studies on the effects of involving mothers in the treatment of voice disorders show that the use of voice function and vocal hygiene exercises with the active participation of parents can increase the child's motivation and the fulfillment of treatment goals [37]. During the first week of treatment, the children were introduced to the vocal hygiene program and ways to reduce vocal fracture. They were given instructions on how to improve vocal hygiene, which included avoiding speaking in a noisy environment, during play and physical activity, consuming fluids, ensuring adequate humidity in the environment, and observing periods without speech production during the day. During the following week, they were trained to perform vocal exercises, such as relaxation, warm-up and stretching exercises, mouth and tongue

fluttering, and proper breathing. They also practiced producing the "molm" sequence, changing the pitch range. The mothers were present during the treatment and were involved in performing the exercises and vocal hygiene programs. In this study, an increase in the value of fundamental frequency, maximum phonation time, a decrease in the variation of fundamental frequency and intensity, and the score in the voice impairment assessment instrument were recorded.

The studies investigating the effects of using different speech and language therapy techniques mainly ninvolved children with vocal nodules, cysts, and papillomas, which are the main causes of voice disorders in children with phonotrauma. The study results indicate statistically significant changes in the children's voice characteristics after treatment. They refer to the reduction of the size of the lesion, the degree of dysphonia and voice disorders, hoarseness, breathiness in the voice, the absence of recurrence, and the achievement of optimal values of the acoustic parameters of the voice. In addition, no deterioration was observed after the speech and language therapy, and no side effects of the application occurred. Because different direct and indirect treatment techniques and their combinations were used, no explicit or specific treatment protocol was followed because of the different needs of the subjects. When it comes to comparing different treatment techniques, it is too early to determine which technique is more effective in practice. This is due to a variety of variables, such as the characteristics of the children, the type of treatment technique, the appropriateness of the diagnosis, and the instruments used in the assessment. In addition, a greater number of studies in this area are needed to better define the meaning of the term "effectiveness of speech and language therapy" and to determine the specific components of treatment that affect its outcome. The most common limitations of the studies were related to insufficient sample size and the lack of control groups to be included to exclude the placebo effect. In addition, the effects of different treatment durations and exercise intensities during this period need to be compared.

Application of computer technology in the treatment of children with phonotrauma

In the early 21st century, various computer hardware and software began to be used in speech and language therapy of voice disorders, mostly in the form of "therapeutic games" for children. Computerized treatment approaches offer the possibility of automatically recording, analyzing, and providing feedback on certain speech parameters, as well as storing the resulting data. In this way, more accurate, easier and faster diagnosis and rehabilitation of voice disorders is ensured [38]. These systems can be focused on the end product or the process itself. Various computer programs provide important visual feedback about the quality of the voice, such as the correct pitch or intensity. When the child speaks into the microphone, the computer program detects the pitch and volume of the voice and displays it on the screen. This provides feedback on whether the specified goal has been achieved [39]. The integration of auditory and visual information about the nature of speech production leads to improvement in speech perception [40]. In addition to visual feedback, other programs, such as a computerized voice laboratory, provide acoustic or aerodynamic information that has a positive effect on the success of the treatment and is a great help for both the child and the speech therapist [41]. This type of treatment can provide the necessary motivation for modulating the child's vocal behavior as well as for the process of generalizing what has been learned.

Conclusion

Voice disorders resulting from abuse are a very common disorder in preschool and school-aged children that can have significant social and educational implications. Because voice disorders are also communication disorders, the literature emphasizes the importance of prevention programs and the role of speech-language pathologists in their implementation. In addition, voice treatment includes the use of direct and indirect treatment techniques, as well as computer technology, the application of which has a positive impact on the success of treatment.

The efficacy and long-term effects of various specific treatment techniques are actively studied in the literature. It is believed that treatment planned based on the child's age, needs, abilities, developmental level, and learning style can lead to positive outcomes. Active participation of parents as well as other people from the social environment is also necessary to reduce and eliminate voice abuse.

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ANALYSIS OF REASONS FOR BLOOD DONOR DEFERRAL IN STUDENT POPULATION OF VOJVODINA

ANALIZA RAZLOGA ZA ODBIJANJE DOBROVOLJNIH DAVALACA KRVI U STUDENTSKOJ POPULACIJI U VOJVODINI

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Summary

Introduction. The supply of blood from healthy blood donors (BD) is essential for safe blood transfusions. As students play an important role in providing adequate blood supplies, this study analyzes the frequency and reasons for blood donor deferral among the student population of Vojvodina, with the intention of reducing the rate of deferral and improving re-entry. **Material and Methods.** A retrospective study examined blood donor deferral records of the University of Novi Sad students who donated blood at the Blood Transfusion Institute of Vojvodina, from January 1 to December 31, 2022. The deferrals have been categorized based on pre-donation deferral causes, the blood donor deferral period, in relevance to the safety of both the blood donor and the recipient. **Results.** Of 867 students in total, 121 (13.9%) were deferred from donating blood. 72/121 (59.5%) of them were female, 49/121 (11.3%) were male, and 99/121 (81.8%) were regular blood donors. Temporary deferrals of less than 3 months were recorded for 98/121 (80.99%) students, while deferrals for 6 months were applicable to 19/121 (15.7%), with 4/121 (3.3%) experiencing permanent deferrals. The number of blood donors deferred due to safety reasons of the very donors was 85/121 (70.2%). The most common reasons were low hemoglobin level 17/121 (14.1%), medication deferral (pain-killers, antihistamines, antibiotics) 17/121 (14.1%) and adverse reactions prior to blood donation 15/121 (12.3%). **Conclusion.** Educating blood donors about high-risk behaviors, medication usage, screening for iron deficiency and hypertension could be the most important tool to reduce the rate of deferral and improve blood donor re-entry.

Key words: Blood Donors; Donor Selection; Dangerous Behavior; Blood Safety; Risk Assessment; Surveys and Questionnaires; Iron Deficiencies; Hypertension; Drug Therapy

Sažetak

Uvod. Snabdevanje krvlju od zdravih davalaca krvi je od suštinskog značaja za bezbednu transfuziju krvi. Kao značajan deo populacije davalaca krvi, studenti imaju važnu ulogu u obezbeđivanju adekvatnih zaliha krvi. Studija ima za cilj da analizira učestalost i razloge odlaganja davanja krvi u studentskoj populaciji Vojvodine, sa namerom da se smanji stopa odlaganja doniranja krvi i poboljša njihov ponovni dolazak. **Materijal i metode.** Retrospektivnom studijom analizirana je evidencija o odlaganju davanja krvi u studentskoj populaciji Univerziteta u Novom Sadu od 1. januara do 31. decembra 2022. godine. Studenti su davali krv u Zavodu za transfuziju krvi Vojvodine. Odlaganja se kategorišu prema: razlozima za odbijanje davalaca na prijemu, vremenskom periodu na koji se davalaštvo odlaže od davanja krvi, u odnosu na bezbednost davaoca ili primaoca krvi. **Rezultati.** Od 867 studenata, kod 121 (13,9%) je odloženo davanje krvi: 72/121 (59,5%) bile su žene, 49/121 (11,3%) muškarci, dok je redovnih davalaca bilo 99/121 (81,8%). Privremeno odlaganje davanja krvi na manje od tri meseca zabeleženo je kod 98/121 (80,99%) studenata, na šest meseci kod 19/121 (15,7%), dok je 4/121 (3,3%) bilo trajno odbijeno. Broj odbijenih davalaca iz razloga bezbednosti donora krvi bio je 85/121 (70,2%). Najčešći razlozi za odlaganje bili su nizak nivo hemoglobina 17/121 (14,1%), terapija (analgetici, antihistaminici, antibiotici) 17/121 (14,1%) i neželjene reakcije pre davanja krvi 15/121 (12,3%). **Zaključak.** Edukacija dobrovoljnih davalaca krvi o oblicima rizičnog ponašanja, upotrebi lekova, utvrđivanju nivoa gvožđa i hipertenziji, moglo bi biti najvažnije sredstvo za smanjenje stope odlaganja davanja krvi i poboljšanje ponovnog doniranja krvi.

Ključne reči: donori krvi; izbor donora; rizično ponašanje; bezbednost krvi; procena rizika; ankete i upitnici; deficit gvožđa; hipertenzija; medikacija

Introduction

The supply of blood from healthy donors is essential for safe blood transfusions. Blood donors (BD) should be in good health at the time of donation and be in low risk of transfusion-transmitted infections [1]. Continuous promotion of healthy lifestyle, particularly among young people interested

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Abbreviations

BTIV – Blood Transfusion Institute of Vojvodina
BD – blood donor
RBD – regular blood donor
FTBD – first time blood donor
WHO – World Health Organization
Hb – hemoglobin
UAE – United Arab Emirates

in becoming volunteer blood donors, is also crucial [2]. Guidance for staff involved in donor selection should be clear and unambiguous [1].

Strict donor selection criteria should be consistently applied to all blood donors, whether they are first-time or regular donors. Health status and medical history of a prospective donor should be assessed for each donation on the day of collection. To evaluate the health and assess the risk of blood donors, a simple donor questionnaire should be employed [3]. Transfusion protocols should not jeopardize the safety of either the recipient or the donor. Blood donors may be disqualified from donating blood due to reasons pertaining to the donor and/or recipient safety and can be deferred temporarily or permanently [4].

Understanding the most common BD deferral reasons enables the prevention of the loss of potential and motivated blood donors. Conversely, it facilitates blood donor retention, ultimately leading to an increase in the number of collected blood units [4]. Young donors, such as students, play a crucial role in ensuring an adequate blood supply [5]. Understanding and being aware of the reasons behind BD deferrals within this specific demographic group can have significant implications for ensuring the long-term sustainability and safety of the blood supply in countries undergoing significant demographic shifts [4]. For blood transfusion services, it is vital to strike a balance between managing BD and maintaining an adequate blood inventory in accordance with regulatory guidelines and rules [6].

The World Health Organization (WHO) and the Council of Europe recommend that blood and blood components should be collected only from voluntary donors in order to ensure the safety of blood products. In Serbia, there are only voluntary (non-remunerated) types of donors. Voluntary blood donors are selfless people who donate blood for the sole purpose of saving lives without expecting anything in return [1]. All deferred donors expect to be treated with respect and care in a confidential manner, and staff should provide a clear explanation of the deferral reason followed by an opportunity to ask questions [4].

The aim of the study was to analyze the frequency and reasons for BD deferral among the student population of Vojvodina (the northern province of Serbia), which is underreported in Serbia. Our further intention was to develop strategies based on the study results to reduce the BD deferral rate and improve donor re-entry.

Material and Methods

The retrospective study was conducted at the Blood Transfusion Institute of Vojvodina (BTIV) to analyze the deferral records of all blood donors among the student population of the University Novi Sad, from January 1 to December 31, 2022. The total of 867 students was divided in two groups according to their donor status: regular blood donors (RBD) – who have donated blood ones or more times in the past, and first-time blood donors (FTBD). Sociodemographic characteristics such as gender, age, deferral reason, study year, type and study group were obtained from the BTIV information system.

Procedures based on national guidelines were used for donor selection and deferral. The deferrals are categorized according to:

– the pre-donation selection process: 1) hemoglobin (Hb) level check using quantitative Hb analyzer; 2) Donor Questionnaire evaluation (Questionnaire contains questions about students' health and lifestyle, disease risk factors, and other factors that potentially affect the safety of both the donor and the recipient); 3) health examination by a physician. Non-donation was not analyzed because of the inability to obtain venous access since these donors were otherwise eligible.

– the reasons for deferral in regard to the safety of: 1) the blood donor (low Hb level, hypertension and tachycardia, hypotension, lack of sleep, adverse reactions, acute/chronic disease, insufficient body weight, menstrual cycle etc.); 2) the blood recipient (medication, risk behavior, tattoo/piercing/acupuncture and other reasons).

– blood donor deferral period: 1) temporary deferrals of less than 3 months (including reasons such as low hemoglobin level, medication, hypertension, tachycardia, hypotension, lack of sleep, adverse reactions, acute infection, insufficient body weight, and the menstrual cycle); 2) temporary deferrals for 6 months (risk behavior, tattoo/piercing/acupuncture); 3) permanent deferrals (encompassing certain chronic conditions, infectious diseases, autoimmune disorders, risky sexual behavior, risky habits, and other reasons).

The Social Sciences Statistical Package (SSSSP) was used to create the database and process the statistical data. The Fisher's exact test and Chi-square (χ^2) test were used to determine the difference in variable distribution. A p-value of 0.05 and less was considered statistically significant.

The research was approved by the Ethics Committee of the Blood Transfusion Institute of Vojvodina, which adhered to medical ethics, donor anonymity, and professional secrecy.

Results

Out of a total of 867 students who voluntarily came to donate blood during the study period, 746 (86.1%) were found eligible to donate, while 121 (13.9%) were deferred. Among the donors, 549 (63.3%) were RBD, and 318 (36.7%) were FTBD. Overall, male donors accounted for 50.1% (435), and females made up 49.9% (432) of the participants. The youngest BD was 19 years old, while the oldest was 30 years old, with a mean age of 22.37 among all donors. In terms of academic levels, 752 (86.8%) were undergraduate students, and 115

Table 1. Blood donors deferrals in the pre-donation selection process.
Tabela 1. *Odlaganje davalaca krvi u procesu selekcije*

Blood donors deferrals in the pre-donation selection process/*Odlaganje davalaca krvi u procesu selekcije*	RBD	FTBD	p level *p nivo*	Male *Muškarci*	Female *Žene*	p level *p nivo*
	n (%)	n (%)		n (%)	n (%)	
Low Hb level/*Nizak nivo Hgb*	11 (9.1)	6 (4.9)		7 (5.7)	10 (8.3)	
Donors Questionnaire *Upitnik za davaoce*	62 (51.2)	7 (5.7)	0.021523*	30 (24.7)	39 (32.2)	0.664272
Medical examination *Medicinski pregled*	26 (21.4)	9 (7.4)		12 (9.9)	23 (19.1)	

Legend: RBD – regular blood donor; FTBD – first time blood donor
*Legenda: RBD – redovni dobrovoljni davaoci krvi; FTBD – davaoci koji prvi put doniraju krv; *p<0.05*

Table 2. Blood donor deferrals due to donor and patient safety.
Tabela 2. *Odlaganje davanja krvi zbog bezbednosti davaoca i primaoca krvi*

Deferral due to donor and patient safety *Odlaganje zbog bezbednosti davaoca i primaoca krvi*	RBD	FTBD	p level *p nivo*	Male *Muškarci*	Female *Žene*	p level *p nivo*
	n (%)	n (%)		n (%)	n (%)	
Donor safety/*Bezbednost davaoca krvi*	66 (54.5)	19 (15.7)	0.06756	28 (42.4)	57 (47.1)	0.009287*
Patient safety/*Bezbednost primaoca kvi*	33 (27.2)	3 (2.5)		21 (17.3)	15 (12.4)	

Legend: RBD – regular blood donor; FTBD – first time blood donor
*Legenda: RBD – redovni dobrovoljni davaoci krvi; FTBD – davaoci koji prvi put doniraju krv; *p<0.05*

(13.2%) were postgraduate students (enrolled in master's or doctoral programs).

The deferral rate was significantly higher for females 72/432 (16.7%) than for males 49/435 (11.3%) (p = 0.021724), as well as for RBD 99/549 (18.1%) compared to FTBD 22/318 (6.9%) (p = 0.00001).

The deferrals of blood donors during the pre-donation selection process are presented in **Table 1.** There are highly significant differences between RBD and FTBD in each category of blood donation (p= 0.021523).

Most of the BD were deferred due to donor safety, accounting for 85/121 (70.2%), while 36/121

Table 3. Blood donor deferral period with reasons for blood donor deferral
Tabela 3. *Period odbijanja davaoca krvi sa razlozima odbijanja*

Blood donor deferral period/*Period odbijanja davaoca krvi*	Reasons for deferral *Razlozi odbijanja*	RBD	FTBD	p level *p nivo*	Male *Muškarci*	Female *Žene*	p level *p nivo*
		n (%)	n (%)		n (%)	n (%)	
Temporary deferral for less than 3 months *Privremena odlaganja na manje od 3 meseca*	low Hb/*nizak Hgb*	11 (9.1)	6 (4.9)	0.615899	7 (5.7)	10 (8.3)	0.004682*
	medication/*lekovi*	16 (13.2)	1 (0.8)		7 (5.7)	10 (8.3)	
	Hypertension and tachycardia *hipertenzija i tahikardija*	7 (5.7)	1 (0.4)		5 (4.1)	3 (2.4)	
	hypotension/*hipotenzija*	10 (8.3)	2 (1.6)		3 (2.4)	9 (7.4)	
	lack of sleep/*nedostatak sna*	8 (6.6)	1 (0.8)		5 (4.1)	4 (3.3)	
	acute diseases/*akutne bolesti*	5 (4.1)	1 (0.8)		2 (1.6)	3 (2.4)	
	adverse reactions *neželjene reakcije*	9 (7.4)	6 (4.9)		4 (3.3)	11 (9.1)	
	insufficient body mass *nedovoljna težina*	6 (4.9)	1 (0.8)		0 (0)	7 (5.7)	
	menstrual cycle/*menzis*	7 (5.7)	1 (0.8)		0 (0)	8 (6.6)	
Temporary deferral for 6 months/*Privremena odlaganja na 6 meseci*	risky behavior/*rizično ponašanje*	11 (9.1)	1 (0.8)		9 (7.4)	3 (2.4)	
	tattoos/piercings/acupuncture *tetovaža/pirsing/akupunktura*	6 (4.9)	1 (0.8)		5 (4.1)	2 (1.6)	
Permanent deferral *Trajno odbijanje*	chronic and other diseases/ *hronične i druge bolesti*	3 (2.4)	1 (0.8)		2 (1.6)	2 (1.6)	

Legend: RBD – regular blood donor; FTBD – first time blood donor
*Legenda: RBD – redovni dobrovoljni davaoci krvi; FTBD – davaoci koji prvi put doniraju krv; *p<0.05*

(29.8%) were deferred due to patient safety (as shown in **Table 2**). In both groups, regular blood donors (RBD) were deferred more frequently than first-time blood donors (FTBD). Furthermore, both males and females were deferred more often for donor safety (42.4% vs. 47.1%) (p=0.009287).

There were 98/121 (80.99%) of temporary deferred BD for a period of less than 3 months, 19/121 (15.7%) of temporary deferred for a 6 months period, and 4/121 (3.3%) permanently deferred BD **(Table 3)**. Unlike men, women were deferred for insufficient body weight and menstrual cycle. There is a significant difference between male and female BD in reasons for deferral (p= 0.004682).

Overall, the three most common reasons for deferral were low Hb level 17/121 (14.1%), medication deferral (pain-killers, antihistamines, antibiotics) 17/121 (14.1%) and adverse reactions prior to blood donation procedure 15/121 (12.3%).

Discussion

This study includes a large sample of students from the second-largest university center in Serbia, shedding light on blood donation deferral rates and reasons at the national level. The original paper presents, for the first time, data on BD deferral causes among the student population in Serbia.

An international comparison reveals that the deferral rate in this study (13.9%) is relatively higher than the rates reported in Germany (6.2%), France (10.8%), and the United States of America (USA) (12.8%) [3, 4, 7].

However, in this study, the deferral rate was significantly higher among RBD (81.8%) compared to the deferral rate in a study among Japanese student populations, where FTBD were more frequently rejected [5]. In both cases, rejections were primarily based on answers provided in the Donors Questionnaire. Nevertheless, temporary BD deferral may discourage them from returning for subsequent donations [8]. An encouraging study finding was that more than half of the students (63.3%) had already donated blood once or twice, which is considerably higher than the data reported in other studies, ranging from 14% to 40% [6, 7, 9]. We found that temporary deferrals (96.7%) were more common reasons compared to permanent deferrals (3.3%). This data is consistent with studies conducted in France, Japan, and the USA [4, 5, 7]. In our study, high blood pressure was classified as a temporary deferral. In contrast, one of the most common reasons for permanent deferral in India (36.6%), Nigeria (22.2%), and Saudi Arabia (14.8%) was high blood pressure [6, 10, 11]. Among students in Vojvodina, chronic diseases such as asthma, vitiligo and Hashimoto's disease were the primary reasons for permanent deferral.

The study conducted in Spain reported 37.3% BD deferrals due to answers arising from the Donor Questionnaire and 62.7% because of low Hb level [12]. According to the answers from the Donor Questionnaire, female BD were deferred more frequently than male BD (53% vs. 47%). Similar findings were observed in the study conducted in the USA, United Arab Emirates (UAE) and the Netherlands [7, 9, 13]. The results of our study, with a higher deferral rate among female BD (39% vs. 30%) and a significantly higher rate among RBD (62% vs. 7%), are consistent with those findings.

The low Hb level is a leading deferral cause, accounting for 13.3% to 60.7% deferrals among male and female BD in many studies reported from Japan, Saudi Arabia, Turkey, Brazil, Tanzania, Bangladesh, Iran, India, and Pakistan. All published data support our findings. The most common reasons for deferral were low Hb level (14.1%), medication (pain-killers, antihistamines, antibiotics) (14.1%) and adverse reactions before blood donating procedure (12.3%). Female BD are most commonly deferred because of low Hb level, the adverse reactions before blood donation procedure, menstrual cycle, lower weight and low blood pressure. These deferral reasons are aimed to protect women's health [5, 11, 14–20].

Pre-donation selection is typically performed to ensure both BD safety and the safety of blood recipients. In our study, 29.8% of BD was deferred due to patient safety concerns, such as risk behavior, tattooing, piercing, and acupuncture. The deferral period for tattooing, piercing, and acupuncture, as per Serbian national guidelines, is six months, in contrast to the American Red Cross criteria, which consider BD acceptable for blood donation if the procedure was conducted by a state-regulated entity using sterile needles [21]. Similar to a study conducted in the UAE, we found that deferrals due to BD risk behavior were unexpectedly more common among RBD than FTBD (9.1% vs. 0.8%) [9].

Young adults, in general, are in good health and may have a long donor career. Identifying the most common deferral reasons for both RBD and FTBD can help in developing a strategy to improve deferral rates and donor re-entry. The study results provide insights into the extent of donor deferrals and suggest that increasing student awareness of blood donation and the causes of deferrals is scientifically and socially acceptable approach that could lead to an increased number of blood donations.

Conclusion

The study findings suggest that increasing student awareness about the blood donation eligibility criteria is crucial. Education about high-risk behavior, medication usage, iron deficiency screening, and hypertension could minimize the loss of blood donors, retain temporarily deferred donors, and enhance blood safety. Understanding the reasons for blood donor deferral can be instrumental in planning recruitment programs and obtaining more accurate estimates of the actual eligible blood donor pool.

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FACTORS AFFECTING THE QUALITY OF LIFE OF PEOPLE WITH COLOSTOMA

FAKTORI KOJI UTIČU NA KVALITET ŽIVOTA OSOBA SA KOLOSTOMOM

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Summary.
Introduction. Colon cancer is a public health problem due to its frequency. According to the number of diagnosed cases, it is the third most common malignant tumor in the world in people of both sexes, and even the second most common in terms of mortality. The incidence is higher in developed regions, although increase is recorded in the developing countries due to changes in the living habits of the population. Operation is the method of choice in the disease treatment, and the performance of colostomy affects the patient's life, although it significantly prolongs it. **Material and Methods.** Literature review available in scientific databases was used as material in order to present significant results of the latest existing research in the selected area. **Results**. A wide range of studies conducted to observe the predictive factors, which in different ways affect the quality of life of patients with colostomy, confirm that the psychological aspects of the newly created situation have the most prominent importance in further life. In addition to possible problems with nutrition, stoma care, dressing, physical activity, professional and sexual life, and travel, it seems that coping with stress and changes in physical appearance are the fields on which the most work should be directed by both the family and the patient, as well as members of the medical team. **Conclusion.** The quality of life of people with colostomy is interference of medical and rehabilitation treatment, and it depends on the patient's willingness to cooperate during the entire treatment, care and rehabilitation process. All reference bodies and institutions should undertake activities to design a comprehensive strategy for improving life quality, primarily through the prism of improving one's own body image, functional status, psychological and social support.
Key words: Colostomy; Quality of Life; Risk Factors; Colonic Neoplasms; Health Knowledge, Attitudes, Practice

Sažetak.
Uvod. Karcinom debelog creva zbog svoje učestalosti predstavlja javno-zdravstveni problem. On je po broju dijagnostikovanih slučajeva treći najčešći maligni tumor na svetu kod pripadnika oba pola, a čak drugi prema smrtnosti. Incidencija je viša u razvijenim regijama iako se sve veći porast beleži u zemljama u razvoju − zbog promene životnih navika stanovništva. Operativni zahvat predstavlja metodu izbora u tretmanu oboljenja, a izvođenje kolostome, iako značajno produžava život pacijenta, utiče na njegov kvalitet. **Materijal i metode.** Kao materijal korišćen je pregled literature dostupan u naučnim bazama, kako bi se predstavili značajni rezultati najnovijih postojećih istraživanja u izabranom području. **Rezultati.** Širok dijapazon studija koje su sprovedene u cilju opservacije prediktivnih faktora, koji na različite načine utiču na kvalitet života pacijenata sa kolostomom potvrđuju da psihološki aspekti novonastale situacije imaju najistaknutiji značaj u daljem životu. Pored mogućih problema sa ishranom, negom stome, oblačenjem, fizičkom aktivnošću, profesionalnim i seksualnim životom, te putovanjima, čini se da suočavanje sa stresom i promene u telesnom izgledu čine polja na koja treba usmeriti najviše rada kako porodice i pacijenta, tako i članova medicinskog tima. **Zaključak.** Kvalitet života osoba sa kolostomom predstavlja interferenciju medicinskog i rehabilitacionog tretmana; zavisi od spremnosti pacijenta na saradnju tokom celokupnog postupka lečenja, nege i rehabilitacije. Sva referentna tela i institucije treba da preduzmu aktivnosti na osmišljavanju sveobuhvatne strategije za poboljšanje kvaliteta života, pre svega kroz prizmu poboljšanja slike vlastitog tela, funkcionalnog statusa, psihološke i socijalne podrške.
Ključne reči: kolostomija; kvalitet života; faktori rizika; tumori kolona; znanje o zdravlju, stavovi, praksa

Introduction.

Colon cancer is a public health problem due to its frequency. It accounts for more than 9% of the world incidence of cancer, it is the third most common form of cancer in the world and an even more common cause of death [1, 2]. Globally, colorectal cancer is the third most common cancer diagnosed in men (after lung and prostate cancer), and second in women (after breast cancer) [3]. Although it is possible to detect the disease in the early asymptomatic phase when the chances of cure are much higher, unfortunately it is usually detected only after the appearance of one or more symptoms. Primary and secondary prevention are of great

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importance when it comes to the mentioned pathology, so screening for colorectal cancer has been carried out in our country for many years. More precisely, since 2012 (gradual introduction) there has been an organized mass invitation of the target population (from 50 to 74 years old, once every two years) for testing (i.e. detection of hidden bleeding in the stool) and interpretation of the screening tests, followed by strict control quality and reporting, thereby reducing mortality [4, 5].

The choice of therapeutic procedure depends on the type, localization and the degree of development of the malignant process, although primacy is given to surgical methods of treatment. After surgical intervention (intestinal resection), an opening is made in the patient's front abdominal wall in the same way so as to maintain the function of the digestive tract (colostomy) [5].

Given that facing the patient with the fact that they suffer from a malignant disease, followed by the change in physical appearance, comes along with various psychosocial difficulties, all procedures that affect the patient's quality of life, in addition to stoma care, are extremely important. Along with the family, which has a basic role in all aspects of rehabilitation and improving the life quality after hospital treatment, the doctor and nurse/stoma therapists make an integral part of the team primarily responsible for patient education [6].

Assessment of the quality of life is an important segment of evaluation of all performed diagnostic and therapeutic procedures. There are numerous definitions that try to clarify the meaning of the term "quality of life". It basically y means well-being, which is influenced by both objective indicators and the subjective perception of the individual, as well as the evaluation of physical, social, emotional, functional and material well-being [7, 8].

As colostomy can be temporary (in order to temporarily exclude the intestine from the passage) and permanent (permanent opening for the removal of gas and stool), the patient's perception/awareness changes depending on its type. The word "stoma" is of Greek origin and means an opening, which does not have to be surgically performed the anterior abdominal wall because of the malignant process only (which has been expanding in recent years), but also as a result of the so-called benign etiology [9].

The position or the place where the stoma is performed in the case of a malignant process depends on the location, although it can also be performed as a therapeutic measure in certain congenital anomalies, various processes or injuries, etc. It is round or oval in shape, pink or red in color, 2-5 cm in diameter. It does not have nerve endings, so it is not sensitive to touch [9, 10].

Facing the patient with a new way of life, nutrition, care and proper replacement of the stoma brings a series of problems that are primarily psychological in nature, and which can intensify after leaving the inpatient facility. Uncertainty, feeling of helplessness and fear of the final outcome of the disease, along with the specifics of care, are often a predictive factor that leads to loss of self-confidence, isolation from social life, alienation, and the emergence of depressive reactions. Before the surgical intervention, after it (in hospital conditions) and upon discharge, members of the medical team have a key role in educating and encouraging the patient to take control of the continuation of regular activities (equivalent to those before surgery) [6].

Research shows that people with implanted colostomy face a series of questions, problems and doubts, which have repercussions on their quality of life to a greater or lesser extent [11, 12].

Material and Methods

To draw conclusions related to the topic, a review of the scientific databases: Medline, Pubmed, Web of Science, Google Scholar, and Embase was used as a work method, whereby the words "quality of life" and "colostomy" were used for the review of literary material. After reading the summaries and individual parts of the papers/texts, papers that met the set criteria were selected, i.e. that examined and analyzed exclusively the quality of life of people with a colostomy, the results of which were presented in the discussion.

Results

Most of the studies that were conducted earlier, as well as in recent years, aimed to investigate which factors and to what extent affect the quality of life of people with a colostomy [11, 12].

The researchers predict that continuous patient monitoring for a period of three to six months after their discharge from the hospital has favorable effect on the acceptance of their new health condition, and later on everything that entails a changed lifestyle, so that it is as close as possible to the previous one. Therefore, the focus lies on monitoring by the stoma therapist and the so-called home stoma nurse. This multicenter study was conducted in France and included 12 centers that care for patients with a stoma in order to assess the impact on their quality of life with the help of a stoma therapist [11].

Some research synthesizes data sources presented in the most important scientific bases during a ten-year period, with the aim of discovering factors that contribute to the quality of life of patients who have had a stoma performed as a result of colorectal cancer. The results of one such study conducted in Thailand identified a group of five significant themes/aspects that correlate with quality of life, namely: sociodemographic and clinical, physiological, psychological, social and spiritual aspects. The obtained indicators can contribute to the creation of appropriate interventions in the promotion of quality of life, their introduction into the curricula and programs of medical students [12].

Another study conducted in Thailand aimed to determine the degree of adaptation of patients to their lifestyle after the installation of a stoma. It was conducted as a cross-sectional study among 152 people with a stoma, where three instruments were used: socio-demographic and clinical categorization, a scale for the level of adaptation of patients with a stoma, and

a questionnaire on quality of life. The obtained indicators indicated that the coefficients of the psychological and social dimensions have the biggest changes in the average results of adaptation [13].

Another study was conducted in Thailand, with the aim of determining the factors that influence the health-related quality of life of Thai people with colorectal cancer and a permanent colostomy. Data were collected from 232 respondents from six tertiary care institutions using seven instruments: demographic and health data form, social support questionnaire, bowel function test, epidemiological data, depression scale, body image scale and quality of life index. The results showed consistency with other studies. Namely, carcinoembryonic antigen, gender and age had an indirect effect on health-related quality of life, while religion, social support, bowel symptoms, depressive symptoms, disturbed body image and functional status had both indirect and direct effects on quality of life where the strongest effect was achieved by body schema/image disorder [14].

Some studies compare the quality of life in relation to whether the stoma was formed urgently or electively. The search strategy included scientific databases from the mentioned field, and incorporated 1868 patients who underwent stoma as an emergency measure, without previous planning and detailed discussion with members of the healthcare team. This systematic review of literature confirmed that patients who underwent emergency surgery had a slightly worse quality of life, compared to the ones who underwent the same procedure as a planned intervention, and that the female gender coincided with a worse quality of life [15].

Literature related to the discussed topic constantly points out the lesser or greater importance of the patient training for stoma care by the health care team members. A meta-analysis that included 17 randomized controlled trials, i.e. 1437 patients, of which 728 were in the continuous care group and 709 in the control group, indicated that continuous care of colostomy reduces wound infection and improves quality of life [16].

Also, a systematic search and meta-analysis was conducted for studies of experimental nursing interventions in relation to routine nursing interventions in patients with a stoma, in order to decisively determine which type of intervention has an advantage in improving the quality of life. Ten studies were selected, namely 460 subjects with experimental nursing intervention and 478 who were exposed to routine care. Experimental nursing intervention showed greater positive effects on quality of life compared to routine nursing interventions, which is significant information for stoma care practitioners to encourage and improve nursing conditions [17].

Similar research was conducted as a retrospective study, which included 100 patients who underwent colostomy in the period from January 2020 to June 2022 due to colorectal cancer. From the above sample, 51 patients received micro video stimulating nursing intervention, and theymade the experimental group, and 49 received routine nursing intervention (control group). The subjects of observation were psychological status, nutritional status, quality of life and rehabilitation. Micro-video content made by team members, doctors, nurses and researchers was played for 10 min to the patients. The main sequences of this educational program combined self-care, nutrition and family support. The Hamilton Anxiety and Depression Scale and the Quality of Life Scale developed by the European Group for Research and Treatment of Cancer were used as instruments, while the nutritional status was assessed using the subjective global assessment of nutrition. A higher result in the observed category of psychological manifestations was analogous to higher quality of life, i.e. higher in the assessment of nutritional status, poorer nutrition of the person. The results showed that micro video stimulating nursing intervention for patients with colostomy has an extremely positive role in improving the quality of life of patients, correcting their negative emotions and encouraging them to live positively as the results are related to clinical data, assessment of the patient's psychological state, nutritional status and quality of life and are such that there is significant difference in favor of the experimental group [18].

Micro video motivational nursing intervention constitutes a new concept of nursing practice, which encourages the patient through motivation to turn to the achievement of his set goals [19, 20].

First of all, it helps establish a friendly relationship with the patient, provides constant psychological and physiological support, increases the patient's vitality, reduces negative emotions and anxiety, promotes the patient's active participation in treatment, promotes rehabilitation procedures and thus significantly improves the quality of life [21–23].

Some studies examine the impact of electronic health platforms on patients with a stoma. E-health includes everything related to information and communication technologies, including telemedicine, mobile health and health informatics. They conclude that digital applications can bring scientific knowledge, improve information and education of individuals and families, but also recognize early symptoms and signs of possible complications. One of them aimed to determine the most relevant content for promoting stoma self-care integrated in the E-health platform, as a digital application for smartphones or a website/site, which patients use independently for the so-called stoma management, self-care, self-monitoring and interaction with the stoma therapist [24].

Stoma surgery, as previously mentioned, can lead to a series of negative psychological outcomes, which require post-operative adaptation. Clarck et al. show that there are good post-operative support ways to deal with the resulting mental outcomes, but also a lack of pre-operative psychological preparation in standard nursing models. This study examined the existing and the new models of psychological preparation in stoma surgery during the preoperative period. A systematic search of scientific databases detected 15 publications

that met the criteria for inclusion in the research, and included 1565 participants. The following interventions were conducted: psycho-educational and counseling examination, demonstration and verification of practical skills, examination of post-operative outcomes of adjustment, anxiety, depression, quality of life and self-efficacy. It was concluded that despite all the encouraging progress in this area, there is not enough evidence to evaluate the overall effectiveness of the existing and some new models of preoperative psychological preparation on the postoperative psychological outcome of each individual undergoing ostomy surgery [25].

A qualitative study based on Heidegger's phenomenological approach, using Van Manen's method, sought to discover how colostomy patients dependent on a wheelchair (due to a previous spinal cord injury) influenced their experiences. The respondents, who were 9, were directly interviewed, and the results showed that their experiences are difficult, that they constantly face challenges, and that they have different awareness about colostomy [26].

Certain research has the task of identifying the quality of life of people with a stoma, including their sexual health and sexuality after surgery. By reviewing the literature, i.e. peer-reviewed scientific journals in the last 5 years, a detailed search found that a stoma affects many aspects of a patient's life, primarily by changing the image of one's own body, the relationship with one's partner, but also the quality of one's sexual life. The evaluation concluded that perioperative educational programs for patients with ostomy qualifications would provide wholehearted and necessary support in dealing with physical and mental difficulties, which would improve all aspects of quality of life [27].

Skin complications that negatively affect the quality of life of patients are distinguished among the possible complications that patients with a colostomy are exposed to. Peristomal skin complications, in addition to having significant impact on the quality of life, increase health care costs, product consumption, etc. A randomized controlled trial was conducted over 6 months in 2022 in 5 different countries aiming to evaluate the performance of a stoma base plate with skin protection technology. The sample included people with peristomal skin complications (79 of them) who were examined for the tested product and compared with the product in use, while the health-related quality of life was quantified using the so-called questionnaire – dermatological quality of life index. Significantly more participants gave preference to the researched product compared to the used one, because the research product, i.e. the base plate with skin protection technology reduced the percentage of peristomal skin complications, thereby improving the quality of life of these patients [28]. At the same time, a pilot study was carried out on a digital stoma leakage notification system, i.e. the impact on care and quality of life. More precisely, the evaluation of the performance of the new digital stoma leakage notification system was carried out among 25 patients for 21 days. The results confirmed that the episodes of leakage outside the base plate decreased from 2.8 to 0.5 episodes after three weeks of using the tested product, which reduced anxiety, improved the emotional health and quality of life of the subjects [29].

Bowel dysfunction after colorectal cancer surgery is the subject of research by many experts. Maalouf et al. used interviews to collect data from 54 patients from a university colorectal center. Analysis of the obtained results revealed five areas related to the quality of life that are affected by bowel dysfunction: psychological/emotional stress, role and relationships in the society, limitations of recreational activities, physical limitations, as well as adaptation to changes and self-empowerment. It was established that patients with minor or major bowel dysfunction have more frequent disorders in social activities, sexual life and sleep quality [30].

Some research aims to examine new follow-up strategies for patients with colorectal cancer that affect health-related quality of life and functional outcomes. Thus, patients from four Danish centers were monitored by comparing the records, followed by the patients after the education and the control by standard follow-up with five routine visits to the doctor. Patients from both groups underwent computed tomography in Year 1 and 3. The primary outcome was assessed by the functional assessment after the therapy, while the secondary one included explicit functional involvement and overall patient satisfaction after three years. Of the initial 336 patients, the follow-up after three years ended in 248. The obtained results suggest that no differences were found between the observed groups, neither for the primary endpoint, nor for the functional outcomes [31].

Conclusion

Progress in medicine, including the care of colostomy patients, is a challenging issue, primarily due to the quality of life of stoma patients. In addition to its benefits, colostomy has a negative physical, psychological and social impact on the patient's quality of life as it primarily changes the body image the patient had had about themselves, thus lowering self-confidence and social functioning. Activities of the health care team members should focus on developing competencies for the stoma self-care as it is supposed to contribute to adaptation to a new health condition and preservation of quality of life. Technological evolution makes a useful tool for the promotion of self-help competencies. Scientific literature induces that medical team members should use the findings of current studies in designing a comprehensive strategy for improving the quality of life, with an emphasis on improving one's own body image, functional status, and social and emotional support. In recent years, the so-called clinical nurses changed from the traditional biological-medical model to the modern biological-psychological-medical model, which implies that attention is directed towards the functional component and quality of life. More and more support is given to the implementation of a micro video stimulating health/nursing intervention, the results of which show good clinical effect.

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CORRELATION OF THE DUTCH LIPID CLINIC NETWORK SCORE AS A DIAGNOSTIC TOOL AND LIPID PARAMETERS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

KORELACIJA DIJAGNOSTIČKOG DUTCH LIPID CLINIC NETWORK SKORA I LIPIDNIH PARAMETARA KOD PACIJENATA SA FAMILIJARNOM HIPERHOLESTEROLEMIJOM

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Summary

Introduction. Familial hypercholesterolemia is a congenital disorder of lipid metabolism. The Dutch Lipid Clinic Network score is used for early diagnosis of familial hypercholesterolemia. The aim of the study was to examine correlation between the above score and the first measured lipid values in patients who had not used lipid-lowering therapy. **Material and Methods.** 390 patients identified as familial hypercholesterolemia+ (n=247) and familial hypercholesterolemia- (n=143) according to the Dutch Lipid Clinic Network score. Family and personal history, physical examination, demographic and anthropometric characteristics and lipid status were analyzed. **Results.** The familial hypercholesterolemia+ group had all Dutch Lipid Clinic Network score components significantly higher than the familial hypercholesterolemia- group. The highest average number of points in familial hypercholesterolemia+ group carries low-density lipoprotein level and family history data. Significantly higher levels of total cholesterol, low-density lipoprotein and apolipoprotein B were found in the familial hypercholesterolemia+ group, while high-density lipoprotein was lower in the familial hypercholesterolemia- group. The Dutch Lipid Clinic Network score correlates best with level of low-density lipoprotein and apolipoprotein B ($p<0.001$). The cut-off point for low-density lipoprotein is 4.9 mmol/L (sensitivity 56%; specificity 8%), while the cut-off point for apolipoprotein B is 1.52 g/L (sensitivity 42%; specificity 12.5%) for diagnosis of familial hypercholesterolemia. **Conclusion.** Low-density lipoprotein and apolipoprotein B values significantly correlate with Dutch Lipid Clinic Network score values. Elevated values of low-density lipoprotein (>4.9 mmol/L) significantly affect the total value of the Dutch Lipid Clinic Network score and are considered components that carry large number of points for the diagnosis of familial hypercholesterolemia.

Key words: Hyperlipoproteinemia Type II; Early Diagnosis; Cholesterol, LDL; Apolipoproteins B; Decision Support Techniques; Predictive Value of Tests

Sažetak

Uvod. Familijarna hiperholesterolemija je urođeni poremećaj metabolizma lipida. Za ranu dijagnostiku koristi se *Dutch Lipid Clinic Network* skor. Cilj studije bio je da ispita korelaciju između pomenutog skora i prvih izmerenih vrednosti lipida kod pacijenata koji ranije nisu koristili terapiju za snižavanje nivoa lipida. **Materijal i metode.** Identifikovano je 390 pacijenata kao familijarna hiperholesterolemija + (n = 247) i familijarna hiperholesterolemija – (n = 143) prema *Dutch Lipid Clinic Network* skoru. Analizirali smo porodičnu i ličnu anamnezu, fizikalni pregled, demografske i antropometrijske karakteristike i kompletan lipidogram. **Rezultati.** Grupa Familijarna hiperholesterolemija + imala je sve komponente *Dutch Lipid Clinic Network* skora značajno veće nego grupa Familijarna hiperholesterolemija –. Najveći prosečni broj poena u grupi Familijarna hiperholesterolemija + nosi nivo lipoproteina male gustine i podaci o porodičnoj anamnezi. Nađeni su značajno viši nivoi ukupnog holesterola, lipoproteina male gustine i apolipoptoteina B u grupi Familijarna hiperholesterolemija +, dok je lipoprotein velike gustine bio niži u grupi Familijarna hiperholesterolemija –. *Dutch Lipid Clinic Network* skor najbolje korelira sa nivoom lipoproteina male gustine i sa apolipoproteinom B ($p < 0,001$). Granična tačka za lipoprotein male gustine je 4,9 mmol/L (osetljivost 56%; specifičnost 8%), dok je za apolipoprotein B granična tačka 1,52 g/L (osetljivost 42%; specifičnost 12,5%) za dijagnozu familijarne hiperholesterolemije. **Zaključak.** Vrednosti lipoproteina male gustine i apolipoprotina B značajno koreliraju sa vrednostima *Dutch Lipid Clinic Network* skora. Povišene vrednosti lipoproteina male gustine (> 4,9 mmol/L) značajno utiču na ukupnu vrednost *Dutch Lipid Clinic Network* skora, te se smatraju komponentom koja nosi veliki broj poena za dijagnozu familijarne hiperholesterolemije.

Ključne reči: familijarna hiperlipoproteinemija; rana dijagnoza; LDL holesterol; apolipoprotein B; tehnike za podršku odlučivanju; prediktivna vrednost testova

Introduction

Familial hypercholesterolemia (FH) is the most common inherited disorder of lipid metabolism. It is a monogenetic disorder characterized by high levels of low-density cholesterol (LDL-ch) from birth and an increased risk of premature atherosclerotic cardiovascular disease (ASCVD) [1, 2].

Familial hypercholesterolemia can be an autosomal dominant or an autosomal recessive disease. Autosom-

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Abbreviations

FH	– familial hypercholesterolemia
LDL-ch	– low-density cholesterol
HDL	– high-density lipoprotein
ASCVD	– atherosclerosis cardiovascular disease
Apo B	– apolipoprotein B
DLCN S	– Dutch Lipid Clinic Network Score
Apo A1	– apolipoprotein A1
Tg	– triglycerides
Lp (a)	– lipoprotein (a)
BMI	– body mass index
BW	– body weight
BH	– body height

al dominant FH in 95% of patients occurs as a result of a mutation in the gene encoding the low-density cholesterol (LDL) receptor (LDLR) [3, 4]. In 5% patients, mutations are found in the genes for apolipoprotein B (Apo B) and pro-protein convertase subtilisin/kexin type 9 (PCSK 9), and have similar functional consequences [3]. In the autosomal recessive form of FH, there is a mutation in LDLR adapter protein 1 [5].

In FH, the basis of the pathological process is inadequate removal of LDL from plasma, which increases the concentration of LDL-ch in blood and the creation of atherosclerotic changes from birth [6]. FH can be manifested in homozygous and heterozygous forms. Patients with the heterozygous form of FH have values of total cholesterol and LDL-h between 7.75-13 mmol/L, while with the homozygous form, the values are much higher and range from 15.5-31.0 mmol/L [7].

Familial hypercholesterolemia is usually underdiagnosed and undertreated leading to premature ASCVD. Early identification of FH patients is very important in order to timely reduce lipid parameters and prevent unwanted cardiovascular disorders. The use of therapy to reduce the value of lipid parameters at a younger age reduces the occurrence of premature ASCVD contributing this way to the reduction of morbidity and mortality [1, 7].

The gold standard for diagnosing FH is genetic testing, but it is not included in routine diagnostic procedures. Therefore, the diagnosis of FH is usually based on clinical findings or validated scores that include clinical and laboratory parameters. The generally accepted scoring method in the world, but also in our country, is the Dutch Lipid Clinic Network score (DLCN S). The DLCN score includes personal and family data, as well as clinical and lipid parameters. According to DLCN score points, FH patient could be identified as definite (>8), probable (6-8), possible (3-5) or unlikely (0-2) [1].

The aim of the study is to analyze the correlation between the DLCN score and the level of lipid parameters at the time of diagnosis, as well as to identify the best individual lipid parameter that correlates with the DLCN score which in routine clinical work could be an early marker of the presence of FH.

Material and Methods

For this study, we analyzed the database and the medical records of patients with lipid disorders treated in the Lipid Disorders Unit at the Clinic of Endocrinology, Diabetes and Metabolic Diseases of the University Clinical Center of Serbia (UCCS). The patients were selected according to the criteria as follows: diagnosed hyperlipoproteinemia, clearly established increased LDL-ch value (without previously applied therapy) with triglycerides level < 4.5 mmol/l, and existing data on personal and family history. Our research included a total of 390 patients who met all the above criteria.

In all patients, we analyzed demographic characteristics, lipid parameters, and all data available to determine the DLCN score. Data were collected on sex, age, body weight (BW) and body height (BH) from which we calculated the body mass index (BMI) according to the formula: BMI = BW (kg)/BH (m^2), as well as the presence of previous diseases (diabetes mellitus, ASCVD, hypertension). We have also analyzed values of the lipid parameters detected before applying any lipid lowering therapy, and that: total cholesterol, its subfractions high-density lipoprotein (HDL-ch) and LDL-ch, triglycerides (Tg) (analyzed enzymatically using commercial kit), apolipoproteins (Apo) A1 and Apo B and lipoprotein (a) (Lp(a)) (determined by immunoturbidimetry).

Dutch Lipid Clinic Network Score was use for simple diagnosis of FH based on the existing clinical and laboratory parameters. The score includes the following parameters: LDL-ch level, personal and family history (premature peripheral or cerebral vascular disease, coronary disease), presence of xanthoma and/or corneal arcus, and deoxyribonucleic acid (DNA) analysis. Based on the value of the DLCN score, the diagnosis of FH is marked as unlikely (0-2), possible (3-5), probable (6-8), or definite (>8).

The Kolmogorov-Smirnov test was used in the statistical analysis to test the normality of distribution. To compare the groups, we used either the Student's t-test or one-way analysis of variance (ANOVA with Bonferroni post hoc analysis), or the Chi-square test for nonparametric variables. The correlation of variables was tested with use of the Spearman correlation test, and cut-off points for lipid parameters were detected with use of ROC curve analysis. Results are express as mean ± standard error (SE) or as a number (percentage). The statistical significance of the difference was set at <0.05. SPSS 20.0 software was used for statistical data processing.

Results

Our research included 390 subjects, of which 159 male patients (40.8%) and 231 female patients (59.2%). From the total number of patients, 63.3% (n=247) were identified using the DLCN score as having FH (FH+ group), while in 36.7% (n=143) the diagnosis of FH (FH- group) was not confirmed (total point of DLCN score 0-2). The characteristics of the subjects included in the study are summarized in **Table 1.** The patients did not differ in age, while the majority of patients from the FH- group had diabetes, previous coronary disease and hyper-

tension, and their BMI was significantly higher in comparison to the FH+ group.

Analysis of each DLCN score component have shown that all components in the FH+ group were significantly higher than the ones in FH- group. In addition, the highest average number of points in the FH+ group carries the levels of LDL-ch and then the family data as well. At the same time, total average number of DLCN score points was almost six-fold greater compared to the FH- group **(Table 2)**.

When we analyzed the levels of the investigated lipid parameters, we found significantly higher levels of total ch, LDL-ch and Apo B in the FH+ group compared to the FH- group, while HDL-ch was significantly lower in FH- group compared to the FH+ group. At the same time, we could not find any differences in the levels of Tg, Apo A1 or Lp(a) between the two groups (data are shown on **Table 3**).

Additionally, we analyzed the mean DLCN score and lipid levels in the Group FH+ divided according to the DLCN score points. Of 247 patients with confirmed FH diagnosis, 47 patients had a definite FH diagnosis (score >8), 56 patients had a probable FH diagnosis (score 6-7) and 144 patients had a possible FH diagnosis (score 3-5). Significant difference was found between these subgroups in FH+ patients when it comes

Table 1. Demographic characteristics of the investigated patients with and without FH
Tabela 1. *Demografske karakteristike pacijenata sa familijarnom hiperholesterolemijom (FH) i bez nje*

Parameters/*Parametri*	FH+ group/*Grupa FH+* (n=247)	FH- group/*Grupa* FH- (n=143)	p/*p*
Gender (M/F)/*Pol (M/Ž)*	83/164	51/92	
Age/*Godine*	60.47 ± 1.04 [a]	59.25 ± 1.32	NS
BW/*Telesna težina* (kg)[b]	73.86 ± 0.88	78.13 ± 1.31	< 0.05
BMI/*Indeks telesne mase* (kg/m^2)[c]	26.17 ± 0.26	27.05 ± 0.33	< 0.05
Diabetes/*Dijabetes* (%)	22.0	78.0	< 0.01
Coronary disease/*Koronarna bolest* (%)	13.1	86.9	< 0.05
Hypertension/*Hipertenzija* (%)	29.9	70.1	< 0.05

Legend: [a] Results are expressed as mean ± SE; [b] BW - Body weight; [c] BMI - Body mass index
Legenda: [a] Rezultati su izraženi kao srednja vrednost ± SD; [b] BW – Telesna težina; [c] BMI – Indeks telesne mase

Table 2. Average point number of DLCN S components in patients with and without FH
Tabela 2. *Prosečan broj poena komponenti DLCN skora kod pacijenata sa familijarnom hiperholesterolemijom (FH) i bez nje*

Score components/*Komponente skora*	FH+ group/*FH+ grupa*	FH- group *FH- grupa*	p/*p*
Family history/*Porodična anamneza*	1.09 ± 0.06	0.42 ± 0.04	<0.001
Personal history/*Lična anamneza*	0.60 ± 0.06	0.12 ± 0.03	<0.001
Xanthomas/*Ksantomi*	0.53 ± 0.11[a]	0.00 ± 0.00	<0.001
LDL-ch value/LDL-h[b]	3.74 ± 0.13	0.63 ± 0.04	<0.001
Total DLCN score[c]/*Ukupni DLCN skor*	5.92 ± 0.21	1.03 ± 0.07	<0.001

Legend: [a] Results are expressed as mean ± SE; [b] LDL-ch/LDL-h – Low density lipoprotein; [c] DLCN S – Dutch Lipid Clinic Network score
Legenda: [a] Rezultati su izraženi kao srednja vrednost ± SD; [b] LDL-ch/LDL-h – Lipoprotein male gustine; DLCN skor – Dutch Lipid Clinic Network skor

Table 3. Values of lipid parameters in patients with FH vs. patients with no disease
Tabela 3. *Vrednost lipidnih parametara kod pacijenata sa familijarnom hiperholesterolemijom (FH) i kod pacijenata bez bolesti*

Parameters/*Parametri*	FH+ group/*Grupa FH+*	FH- group/*Grupa FH-*	p/*p*
Total cholesterol/*Ukupni holesterol*	7.33 ± 0.13[a]	5.84 ± 0.12	<0.001
HDL-ch/ HDL-h[b] (mmol/L)	1.37 ± 0.02	1.22 ± 0.03	<0.05
LDL-ch/LDL-h[c] (mmol/L)	5.05 ± 0.12	3.62 ± 0.10	<0.01
Tg[d] (mmol/L)	2.09 ± 0.07	2.30 ± 0.13	NS
Apo A1[e] (g/L)	1.63 ± 0.02	1.55 ± 0.03	NS
Apo B[f] (g/L)	1.46 ± 0.03	1.22 ± 0.03	<0.001
Lp(a) (mg/L)	0.33 ± 0.02	0.32 ± 0.03	NS

Legend: [a] Results are expressed as mean ± SE; HDL-ch/HDL-h[b] – High density cholesterol; LDL-ch/LDL-h[c] – Low density lipoprotein; Tg[d] – Triglycerides; Apo A1[e] – Apolipoprotein A; Apo B[f] – Apolipoprotein B
Legenda: HDL-ch/HDL-h[b] – Holesterol velike gustine; LDL-ch/LDL-h[c] – Lipoprotein male gustine; Tg[d] – Trigliceridi; Apo A1[e] – Apolipoprotein A; Apo B[f] – Apolipoprotein B

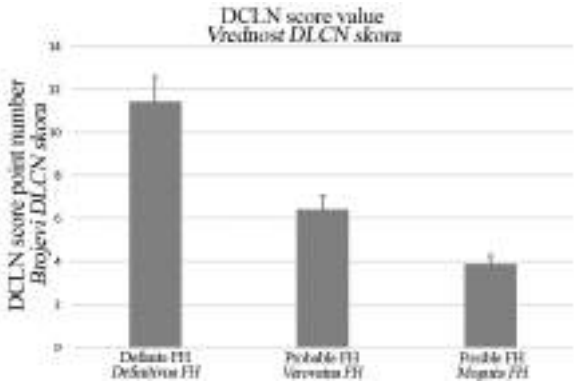

Figure 1. Mean value of total DCLN score in FH+ patients with definite, probable and possible FH
Slika 1. *Srednja vrednost ukupnog DLCN skora kod FH + pacijenata sa definitivnom, verovatnom i mogućom dijagnozom familijarne hiperholesterolemije*

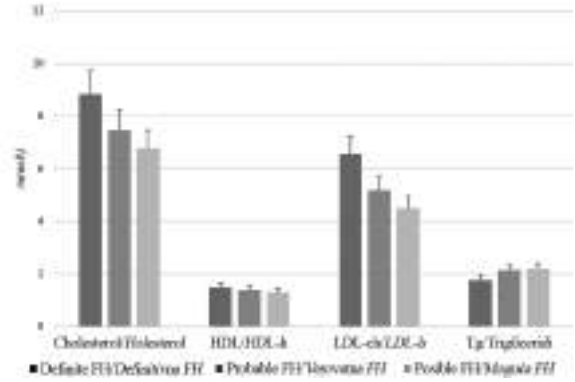

Figure 2. Mean value of lipid parameters in FH+ patients with definite, probable and possible FH
Slika 2. *Srednja vrednost lipidnih parametara kod FH+ pacijenata sa definitivnom, verovatnom i mogućom dijagnozom familijarne hiperholesterolemije*

to DLCN score values ($p<0.05$) **(Figure 1)**. Patients with a definite FH diagnosis had the highest DLCN score mean value (11.45±0.44), which was significantly higher compared to patients with a probable FH (6.43±0.06) or possible FH diagnosis (3.90±0.06; $p<0.05$ respectively) **(Figure 1)**.

Regarding the values of lipid parameters of subgroups (probable, possible, and definite) within the FH+ group, we found that total cholesterol (8.83± 0.37 mmol/l) and LDL-ch (6.55± 0.34 mmol/l) were significantly higher in with the definite FH subgroup in comparison to other two subgroups (total ch: 7.47± 0.25; 6.79± 0.12; LDL-ch: 5.18± 0.24; 4.5± 0.11 mmol/l; $p<0.01$ respectively), while we could not find any differences in HDL-ch and Tg levels **(Figure 2)**. Similarly, Apo B level was significantly higher in the definite FH subgroup (1.8± 0.09 g/l) compared to the other two subgroups (1.53± 0.06; 1.33± 0.03 g/l; $p<0.05$ respectively), while the level of Apo A1 was similar in all three subgroups **(Figure 3)**.

Finally, correlation was made between the total calculated value of the DLCN score and the level of the investigated lipid parameters. According to our results,

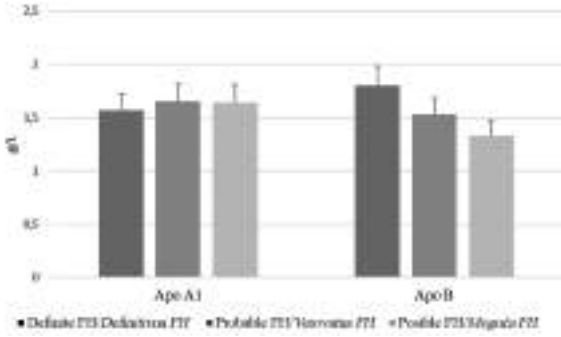

Figure 3. Mean value of Apo A1 and Apo B in FH+ patients with definite, probable and possible FH
Slika 3. *Srednja vrednost apolipoproteina A1 i B kod FH+ pacijenata sa definitivnom, verovatnom i mogućom familijarnom hiperholesterolemijom*

the DLCN score highly statistically and best correlates with the LDL-ch level ($r=0.463$; $p < 0.001$), followed by Apo B ($r=0.364$; $p < 0.001$). We performed the ROC curve analysis to investigate the LDL-ch and Apo B threshold levels that have the highest probability to diagnose FH with use of the DLCN score. The results showed that the cut-off point for LDL-ch is 4.9 mmol/l with 56% sensitivity and 8% specificity, while the cut-off point for Apo B is 1.52 g/l with 42% sensitivity and 12.5% specificity for the diagnosis of FH.

Discussion

The results of this study showed that the level of LDL-ch and Apo B in our cohort of patients with FH correlate most strongly with DLCN score values during the diagnosis. In addition, our results imply that finding of elevated LDL-ch (> 4.9 mmol/l) and/or Apo B (> 1.52 g/l) values during the routine clinical work strongly suggest that the DLCN score should be performed on the patients in order to diagnose FH.

The presence of FH leads to atherosclerotic changes in blood vessels and increases the risk of premature coronary disease [8]. Despite the mentioned facts, the FH is often underdiagnosed in most countries. Early detection of the disease is important for early application of treatment and prevention of atherosclerosis. The goal of our research was to try to improve the diagnosis in order to apply the appropriate therapy. Previous studies, including our research, show that statins were prescribed to patients with FH in only 48% cases and the administered dose was not sufficient to reduce the LDL-ch level according to the recommended guidelines [8–11].

The analysis of all the DLCN score components in our patients showed that there is a significant difference between the patients having the disease (FH+) and the ones not having the disease (FH-), which is in accordance with earlier studies [7–9, 12, 13]. The higher value of mean score points in the DLCN score in our results was found for LDL-ch followed by family data, which strongly suggests that FH should be suspected in patients with elevated LDL-ch and a positive family history (premature ASCVD or high cholesterol in a family member).

At the University of Catania in Italy, in 2017, studies were conducted with a large number of patients (n=1575), which showed that the DLCN score is a very sensitive method that can be used to identify patients with probable FH (score value >6), after which the patients were referred for genetic testing. The high sensitivity of the test is evidenced by the fact that as much as 90.5% of patients had a genetic mutation [9]. In our country, genetic testing is not an everyday clinical practice, so simpler methods such as the DLCN score are used for diagnosis. However, DLCN is a reliable method only if all information is available to calculate its value [9].

We wanted to see with our research if there is a statistically significant difference when it comes to lipid parameters in FH+ and FH-. The results show that there is statistical significance when it comes to total cholesterol, LDL-h, and ApoB, and the diagnosis is easier if these parameters are elevated during lab tests. In the further course of the research, we compared the mean values of lipid parameters between the three groups that we defined based on the DLCN score as definitely, probably, and possibly FH. The results show that patients with a definite FH diagnosis (> 6 mmol/l) had the highest mean value of LDL-ch, while that value was around 5 mmol/l in all patients with FH. Previous research has shown that the value of LDL-ch 5.9 mmol/l represents a value that is associated with the presence of mutation [8], and the diagnosis of FH can be made with great certainty based on the measured LDL-ch between 5.7 and 7.7 mmol/l [14]. Our results are in line with these recommendations and suggest that there is safe diagnosis of FH with high probability in patients with LDL-ch greater than 6 mmol/l, but may also be present with lower LDL-ch values (cut-off >4.9 mmol/l) (which are often overlooked in routine clinical work), and it is also necessary to calculate this simple DLCN score with such patients.

Conclusion

Our research shows that low-density cholesterol values, as well as apolipoprotein B, significantly correlate with Dutch Lipid Clinic Network score values. Elevated low-density cholesterol values (>4.9 mmol/l) significantly affect the total Dutch Lipid Clinic Network score value and are considered components that carry a high number of points for the diagnosis of familial hypercholesterolemia. We want the results of our work to improve diagnosing of familial hyprcholesterolemia and thus prevent unwanted cardiovascular diseases in those patients.

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CORRELATION BETWEEN ELECTROCARDIOGRAPHIC AND ECHOCARDIOGRAPHIC PARAMETERS IN THE DIAGNOSIS OF LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSIVE PATIENTS

KORELACIJA ELEKTROKARDIOGRAFSKIH I EHOKARDIOGRAFSKIH PARAMETARA U DIJAGNOSTICI HIPERTROFIJE LEVE KOMORE KOD BOLESNIKA SA HIPERTENZIJOM

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Summary

Introduction. Left ventricular hypertrophy is defined as an increase in the left ventricular mass. Electrocardiography is a widely used and cost-effective method for the initial screening of the condition, but it has limited sensitivity and specificity. The Sokolow-Lyon and Cornell criteria are still most commonly used in diagnosing the disease; their sensitivity, however, is low. On the contrary, the Romhilt-Estes scoring system incorporates atrial abnormalities and repolarization phases making this scoring system a better diagnostic tool. This study explores the correlation between electrocardiography and echocardiography in the diagnosis of left ventricular hypertrophy. **Material and Methods**. The study enrolled 30 patients with median age of 62, diagnosed with arterial hypertension, who underwent a 12-lead electrocardiogram and transthoracic echocardiogram. The analysis included the assessment of correlation between the relevant electrocardiographic parameters and the left ventricular mass index, as well as calculation of their diagnostic capability including the area under the ROC curve. **Results**. Positive correlation of moderate intensity has been observed between the left ventricular mass index and Sokolow-Lyon (ρ=0.479), Cornell index (ρ=0.366), and Cornell product (ρ=0.423). Cornell product had the highest sensitivity (0.82), while the Romhilt-Estes criteria exhibited the highest specificity (0.85). Sokolow-Lyon yielded the highest area under the curve (0.733), followed by Cornell product (0.640), Cornell voltage (0.622), and Romhilt-Estes criteria (0.570). **Conclusion**. The Sokolow-Lyon criterion exhibited the best balance between sensitivity and specificity, the highest and significant area under the ROC curve and the strongest correlation with the left ventricular mass index.

Key words: Electrocardiography; Echocardiography; Hypertrophy, Left Ventricular; Hypertension; Diagnosis; Sensitivity and Specificity

Sažetak

Uvod. Hipertrofija leve komore definiše se kao uvećanje mase leve komore. Elektrokardiografija je široko rasprostranjena i jeftina metoda koja služi za inicijalni skrining ovog oboljenja, ali je ograničene senzitivnosti i specifičnosti. *Sokolow-Lyon* i *Cornell* kriterijumi i dalje se najviše koriste u dijagnostici ove bolesti, međutim, njihova osetljivost je niska. Nasuprot njima, *Romhilt-Estes* skor sistem obuhvata atrijalne abnormalnosti i faze repolarizacije, čime ovaj skor sistem postaje bolji dijagnostički alat. Cilj ovog rada bio je istraživanje međusobne povezanosti između elektrokardiografije i ehokardiografije u kontekstu dijagnoze hipertrofije leve komore. **Materijal i metode**. U studiju je bilo uključeno 30 bolesnika medijane godina 62, sa arterijskom hipertenzijom i ranije načinjenim 12-kanalnim elektrokardiogramom i transtorakalnim ehokardiogramom. Analiza je obuhvatala određivanje jačine povezanosti elektrokardiografskih parametara od interesa sa indeksom mase leve komore kao i određivanje njhovog dijagnostičkog kapaciteta uključujući izračunavanje površine ispod ROC krive. **Rezultati**. Primećena je jaka pozitivna korelacija između indeksa mase leve komore i *Sokolow-Lyon* kriterijuma (ρ = 0,479), *Cornell* indeksa (ρ = 0,366) kao i *Cornell* proizvoda (ρ = 0,423). Najveću senzitivnosti pokazao je *Cornell* proizvod (0,82) dok je najveću specifičnost imao *Romhilt-Estes* kriterijum (0,85). Analizirana površina ispod ROC krive bila je najveća za *Sokolow-Lyon* kriterijum (0,733), zatim *Cornell* proizvod (0,640), *Cornell* indeks (0,622) i na kraju *Romhilt-Estes* kriterijum (0,570). **Zaključak**. *Sokolow-Lyon* kriterijum pokazao je najbolji odnos između senzitivnosti i specifičnosti, najviši i značajnu površinu ispod ROC krive kao i naizraženiju korelaciju sa indeksom mase leve komore.

Ključne reči: elektrokardiografija; ehokardiografija; hipertrofija leve komore; hipertenzija; dijagnoza; senzitivnost i specifičnost

Introduction

Left ventricular hypertrophy (LVH) is defined as an increase of the left ventricular mass either due to wall thickening or due to enlargement of the left ventricular cavity, or both, in response to a wide array of pathophysiological stressors [1–3]. This cardiac remodeling response is triggered by various pathophysiological stressors such as increased intraarterial pressure or intraventricular volume overload [2,4] and is prominently observed in hypertensive patients. The prevalence of LVH increases with the severity of hypertension, advancing age, and obesity. In general population, the prevalence of the LVH is between 15 and 20%

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Abbreviations

LVH – left ventricular hypertrophy
ECG – electrocardiography
DM – diabetes mellitus
BMI – body mass index
SL – Sokolow-Lyon
CI – Cornell index
CP – Cornell product
RE – Romhilt-Estes
LVM – left ventricular mass
LVMI – left ventricular mass index
LVIDd – left ventricular end-diastolic diameter
LVIDs – left ventricular end-systolic diameter
PLWd – posterior wall end-diastolic diameter
IVSd – interventricular septum end-diastolic diameter
LA – left atrium diameter
EF – ejection fraction
ROC – receiver operating characteristics
AUC – area under the curve
PPV – positive predictive value
NPV – negative predictive value

and it is similar in men and women, with rates being significantly higher in hypertensive patients [2]. As LVH evolves, it can independently serve as a risk factor for chronic heart failure, arrhythmias, and even sudden cardiac death [5], highlighting the critical need for accurate and timely detection of the condition.

Both electrocardiography (ECG) and echocardiography have emerged as indispensable tools in the comprehensive assessment of left ventricular hypertrophy. Echocardiography boasts superior diagnostic accuracy, especially in the early stages of the disease, however, it is also important to point out that it comes at the cost of being more expensive and time-consuming [6, 7]. Considering these factors, current available guidelines for arterial hypertension and appropriate utilization criteria for echocardiography do not endorse its universal application in patients with hypertension. Instead, they recommend employing echocardiography when the test results are likely to significantly impact the patient's management and treatment decisions [8–10]. ECG, on the other hand, is a relatively straightforward procedure since it poses as a complementary screening alternative that has low cost and wide dissemination, however, its diagnostic specificity and, especially, sensitivity are constrained [11]. The underlying assumption for the use of ECG is that the enlargement of the left ventricular mass leads to a more robust electrical field, resulting in heightened electrical forces directed posteriorly and leftward. Consequently, this augmentation leads to increased QRS amplitude in specific leads [12].

Traditionally, voltage criteria, such as Sokolow-Lyon (SL), Cornell voltage index (CI) and Cornell product (CP), as well as some scoring systems, one such being Romhilt-Estes (RE) criteria, are utilized in electrocardiography as a method for detecting left ventricular hypertrophy [11, 13–16], however, there is still an ongoing debate concerning their diagnostic value. The correlation between these two diagnostic modalities in detecting LVH has garnered increasing attention, as a more comprehensive understanding of their mutual relationship holds the potential to refine diagnostic accuracy and optimize patient care. By synthesizing the latest research findings, this paper aims to explore the interplay between ECG and echocardiography in the context of LVH diagnosis, particularly in hypertensive patients.

Material and Methods

We have conducted a cross-sectional retrospective study that included patients with diagnosed arterial hypertension [8] treated at the Institute of Cardiovascular Diseases of Vojvodina in Sremska Kamenica from 2017 to 2019.

Age, gender, presence of diabetes mellitus (DM), and body mass index (BMI) were recorded for each patient. All patients underwent a 2D echocardiography. Each patient underwent a standard 12-lead ECG recording at a speed of 25 mm/s and voltage gain of 10 mm = 1 mV. The SL voltage parameter, CI, CP, and RE were determined from each ECG report. Individual wave measurements were taken with a caliper to an accuracy of 0.1 mm. The SL voltage parameter was obtained by adding SV_1 and RV_5 (expressed in mm) with the cut-off value >35 mm. Cornell voltage index was obtained by adding SV_3 and RaVL (expressed in mm), while the CD was obtained by multiplying CI with the duration of the QRS complex (expressed in mm·ms). The cut-off value for the CI was sex-dependent (>28 mm for males and >20 mm for females), while the CP defined LVH when it was above 2440 mm·ms [8]. The RE criteria encompassed six categories, each scored with a specific number of points. Probable LVH was defined when the RE criteria score was 4 points, while definitive LVH was defined when the RE criteria score ranged from 5 to a maximum of 13 points [15, 16].

Moreover, the echocardiographic parameters were registered as follows: left ventricular mass (LVM), left ventricular mass index (LVMI), left ventricular end-diastolic diameter (LVIDd), left ventricular end-systolic diameter (LVIDs), posterior wall end-diastolic diameter (PLWd), interventricular septum end-diastolic diameter (IVSd), left atrium diameter (LA), and ejection fraction (EF). Myocardial hypertrophy was defined if the left ventricular mass index exceeded 115 g/m² for men and 95 g/m² for women [17].

The normality of the continuous variables was assessed using the Kolmogorov-Smirnov test. Non-normally distributed continuous variables were reported as the median with the interquartile range (Q1-Q3). Continuous variables were compared between independent groups using the Wilcoxon rank-sum test, categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Spearman's correlation coefficient was used to express the level of association between selected continuous variables. Discriminatory capacity, e.g., predictive strength of ECG criteria for the left ven-

tricle hypertrophy, was evaluated via the area under the receiver operating characteristic (ROC) curve area under the curve (AUC). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio (PLR and NLR, respectively), were calculated for each predictor based on sensitivity and specificity. All statistical tests were two-tailed and the alpha level of 0.05 was set as a significance threshold. No imputations were used for the missing data. Statistical analyses were conducted using RStudio 2023.03.1+446 "Cherry Blossom" Release.

Results

Our study included 30 patients diagnosed with hypertension, with a median age of 62 (55-69) and female predominance of 56.7%. Female participants were significantly older with median age of 67 (61-72) compared to males with median age of 56 (36-61), p=0.017. Four participants (2 male and 2 female) had DM. The median BMI was 29 (27.3-32.2) kg/m^2, with no differences between genders (p=0.241). Five participants (16.7%) had a BMI below 24.9 kg/m^2, 12 (40%) patients fell into the BMI range of 25.0-29.9 kg/m^2, while 13 (43.3%) patients had a BMI over 30.0 kg/m^2. Patient baseline characteristics are presented in the **Table 1.**

After analysing the echocardiographic parameters, it was observed that the male gender exhibited significantly higher values for left ventricular mass, with a median of 359 (231-453) g compared to 173 (105-220) g in females, p<0.001. Similarly, the left ventricular mass index was notably higher in males, 160 (106-189) g/m^2, compared to 99 (69-111) g/m^2 in females, p=0.006. Despite these differences, the presence of LVH based on left ventricular mass index cut-off values showed no statistically significant difference between genders, with 9 (53%) females and 8 (62%) males having LVH (p=0.638). Additionally, the male population exhibited significantly higher LVIDd, LVIDs, and left atrium diameter, while no statistically significant differences were found in IVSd, PLWD, and EF. Complete echocardiographic parameters are presented in **Table 2.**

The ECG analysis showed that the SL criterion had a median of 24.90 (18.88-30.58) mm with no significant differences between genders. Among all patients, five (16.7%) participants had values above the appropriate cut-off, with no gender-based frequency differences. Regarding the CI criterion, males exhibited a significantly higher median value of

Table 1. Patients' characteristics at the baseline
Tabela 1. *Osnovne karakteristike bolesnika*

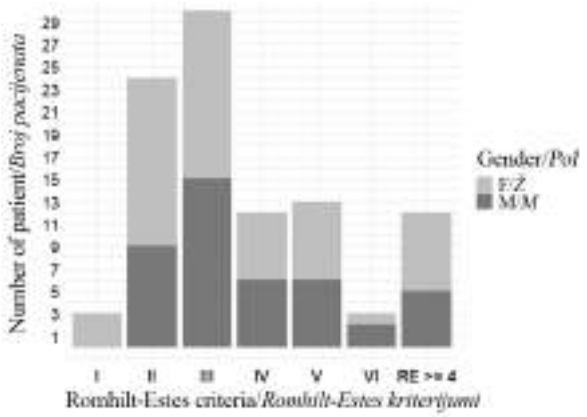
Characteristic *Karakteristika*	Total/*Ukupno*, No/*Br.* = 30	Female/*Žene*, No/*Br.* = 17	Male/*Muškarci*, No/*Br.* = 13	p/*p*
Age/*Starost*	62 (55-69)	67 (61-72)	56 (36-61)	0.017
BMI	29.0 (27.3-32.8)	28.4 (27.2-32.3)	31.7 (28.3-33.9)	0.241
< 24.9	5 (16.7)	4 (24)	1 (7.7)	
25.0-29.9	12 (40)	7 (41)	5 (38)	0.494
> 30	13 (40.3)	6 (35)	7 (54)	
Diabetes mellitus/*Dijabetes melitus*	4 (13)	2 (12)	2 (15)	1.000

Legend: BMI – Body Mass Index; Numerical data is presented as the median (Q1-Q3); categorical data is presented as n (%)
Legenda: BMI – *Indeks telesne mase; Numerički podaci su prikazani kao medijana (Q1-Q3); kategorijalni podaci su prikazani kao br. (%)*

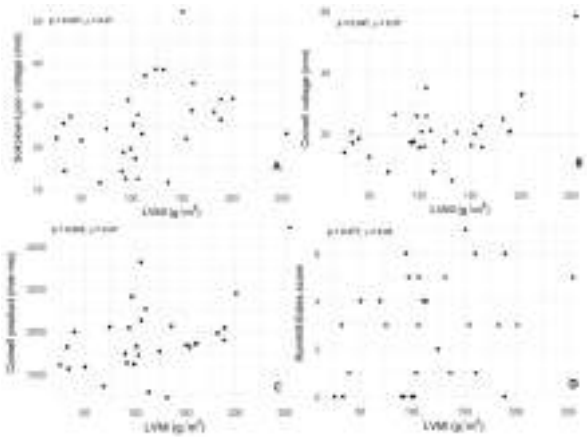
Table 2. Echocardiographic parameters
Tabela 2. *Ehokardiografski parametri*

Echocardiographic/*Parameter*	Total/*Ukupno*, No/*Br.* = 30	Female/*Žene*, No/*Br.* = 17	Male/*Muškarci*, No/*Br.* = 13	p/*p*
LVM (g)	222 (158-276)	173 (105-220)	359 (231-453)	< 0.001
LVMI (g/m^2)	106 (91-153)	99 (69-111)	160 (106-189)	0.006
LVIDd (cm)	4.90 (4.53-5.38)	4.70 (4.50-5.10)	5.30 (4.90-6.30)	0.025
LVIDs (cm)	3.20 (2.80-3.50)	3.00 (2.80-3.40)	3.40 (3.30-4.40)	0.034
IVSd (cm)	1.30 (1.20-1.40)	1.30 (1.20-1.40)	1.30 (1.30-1.40)	0.215
PLWd (cm)	1.30 (1.20-1.30)	1.20 (1.20-1.30)	1.30 (1.20-1.30)	0.151
LA (cm)	4.10 (3.42-4.40)	3.90 (3.30-4.30)	4.40 (3.90-4.70)	0.018
EF (%)	60 (54-64)	61 (57-64)	59 (52-64)	0.586

Legend: LVM – left ventricular mass; LVMI – left ventricular mass index; LVIDd – left ventricular end-diastolic diameter; LVIDs – left ventricular end-systolic; IVSd – interventricular septum end-diastolic diameter; PLWd – posterior wall end-diastolic diameter; LA – left atrium diameter; EF – ejection fraction; Data is presented as the median (Q1-Q3)
Legenda: LVM – masa leve komore; LVMI – indeks mase leve komore; LVIDd – enddijastolni dijametar leve komore; LVIDs – endsistolni dijametar leve komore; IVSd – enddijastolni dijametar interventrikularnog septuma; PLWd – enddijastolni dijametar zadnjeg zida; LA – dijametar leve pretkomore; EF – istisna frakcija; Podaci su prikazani kao medijana (Q1-Q3)

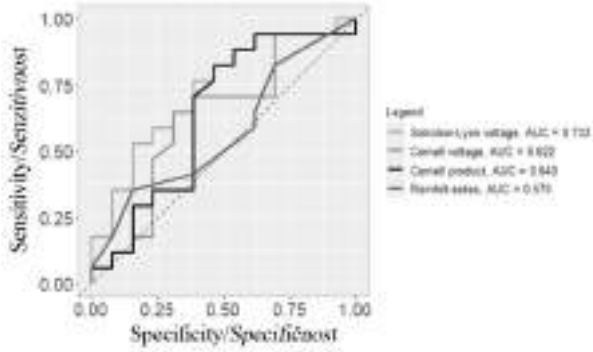


Graph 1. Romhilt-Estes criteria by gender
Grafikon 1. *Romhilt-Estes kriterijumi prema polu*



Graph 2. Scatter diagrams between left ventricular mass index and A. Sokolow-Lyon voltage. B. Cornell Voltage. C. Cornell product and D. Romhilt-Estes score
Grafikon 2. *Dijagram raspršenja između indeksa mase leve komore i A. Sokolow-Lyon voltažnog kriterijuma. B. Cornell voltažnog kriterijuma. C. Cornell proizvoda i D. Romhilt-Estes skora*

20.90 (18.45 vs. 25.65) mm vs. 17.10 (15.40-26.65) mm, p=0.035. Additionally, nine patients, with no significant gender-based frequency differences, had values indicative of left ventricular hypertrophy. The CP also yielded significant results, with males having a higher median value of 1992.80 (1716.0-2821.50) mm·ms vs. 1540.0 (1205.60-1674.40) mm·ms, p=0.012. Of note is that five patients showed CP values exceeding 2440 mm·ms, with no significant gender-based frequency differences. Four patients (13.3%) met the RE criterion with a score of 4, while eight patients (26.7%) had a score over 4, as illustrated in **Graph 1**.



Graph 3. ROC curves for the electrocardiographic criteria
Grafikon 3. *ROC krive za elektrokardiografske kriterijume*

Correlation analysis revealed that there was a significant moderate positive correlation between LVMI and SL voltage (ρ=0.47, p=0.007), CI (ρ=0.37, p=0.047), as well as CP (ρ=0.42, p=0.020). On the other hand, although the RE score correlated moderately positive with LVMI, the correlation was not statistically significant (ρ=0.33, p=0.077) (**Graph 2)**.

The CP demonstrated the highest sensitivity of 0.82, followed by SL (0.76), CI (0.65) and lastly the RE criteria (0.35). On the other hand, the RE score achieved the highest specificity of 0.85, while CP exhibited the lowest specificity of 0.54, which resulted in the lowest NPV **(Table 3).** Analysis of the ROC curves demonstrated that the SL criterion exhibited the highest AUC of 0.733, closely followed by the CP with an AUC of 0.640, the CI criterion with an AUC of 0.622, and lastly, the RE score with an AUC of 0.570 **(Graph 3).**

Discussion

Various electrocardiographic criteria were compared in this study to diagnose left ventricular hypertrophy, with echocardiographic findings of the left ventricular mass index serving as the reference diagnostic method in patients with arterial hypertension. Left ventricular hypertrophy represents an asymptomatic organ damage developing under the influence of arterial hypertension and posing high risk of adverse cardiovascular events for the patients [8].

Our study included 30 patients with the median age of 62 years, mostly overweight and obese individuals with 80.3% having a BMI that exceeds the obesity cut-off of 24.9 [18]. This observation is in line with previous research indicating higher prevalence of left ventricular hypertrophy in obese populations [19]. Diabetes has also been closely associated with the development of the LVH [20, 21]. We identified four individuals (13%) with diabetes mellitus, reinforcing the relevance of considering DM as a potential risk factor in the context of left ventricular hypertrophy.

The correlation analysis revealed that LVMI exhibited the strongest positive correlation with SL (ρ=0.47), followed by a slightly weaker but still statistically significant positive correlation with CP (ρ=0.37) and CI index (ρ=0.42). On the other hand, the RE criteria showed the weakest association with LVMI in our study. Such variations in results among different studies that explore the relationship between ECG and left ventricular hypertrophy have been attributed to the daily fluctuations in ECG voltage within the same patient, as reported by previous research [22, 23].

Table 3. Diagnostic performance of the EKG criteria
Tabela 3. *Dijagnostički kapacitet EKG kriterijuma*

ECG parameter/*EKG parametar*	Sensitivity/*Senzitivnost*	Specificity/*Specifičnost*	PPV	NPV	PLR	NLR	AUC
Sokolow-Lyon	0.76	0.62	0.72	0.67	2.00	0.39	0.733
Cornell voltage	0.65	0.69	0.73	0.60	2.10	0.51	0.622
Cornell product	0.82	0.54	0.70	0.70	1.78	0.33	0.640
Romhilt-Estes	0.35	0.85	0.75	0.50	2.33	0.76	0.570

Legend: PPV – Positive predictive value; NPV – Negative predictive value; PLR – Positive likelihood ratio; NLR – Negative likelihood ratio; AUC – Površina ispod krive
Legenda: PPV – Pozitivna prediktivna vrednost; NPV – Negativna prediktivna vrednost; PLR – Odnos verovatnoće pozitivnog rezultata; NLR – Odnos verovatnoće negativnog rezultata; AUC – Površina ispod krive

The SL criterion demonstrated relatively balanced sensitivity (0.76) and specificity (0.62), positive predictive value (PPV) and negative predictive value (NPV) predictive values (0.72 and 0.67, respectively), suggesting its potential for correctly identifying true positive and true negative cases. The CI criterion showed similar results (sensitivity 0.65, specificity 0.69, PPV 0.73, NPV 0.60), while its QRS duration product exhibited higher sensitivity of 0.82 with significantly lower specificity of 0.54, while PPV and NPV were identical, 0.70. On the other hand, the RE criterion displayed the lowest sensitivity (0.35) and NPV (0.50) but notably the highest specificity (0.85) and PPV (0.75), suggesting it might be more appropriate at correctly identifying true negatives. The wide range of sensitivity and specificity suggests the presence of both false negative and false positive results. Various studies had been conducted reporting sensitivity and specificity values that are different than the ones in our study. For instance, a study conducted in 2022 [11] reported much lower sensitivity of all analysed ECG criteria (SL 0.05, CI and RE 0.22), while, on the other hand, specificity rates were much higher, reaching up to 1 for SL criterion, 0.952 and 0.738 for CI and RE, respectively. A systemic review from 2007 performed on 21 studies [13] found that the median sensitivity for SL criterion was 0.21 (range 0.04 to 0.52), while the median specificity was 0.89 (range from 0.53 to 1). CI and CP exhibited the same median specificity of 0.96 (range 0.89 to 1 and 0.90 to 1, respectively), and the sensitivity was notably lower: 0.15 (range 0.02 to 0.41) and 0.115 (range 0 to 0.39) for CI and CP, respectively. Moreover, the RE criterion demonstrated the highest specificity with a median of 0.99 (range 0.71 to 1) and a relatively low sensitivity, median of 0.12 (range 0 to 0.41). Not all results in our study correspond although there is an alignment with certain aspects of the findings from the 2007 systemic review. This variation could be attributed to the relatively small sample size examined in our study. Regarding the observed wide range of sensitivity values, Narayanan and colleagues [24] attribute the presence of false negative results to electrical remodeling of the heart. They suggest that extracardiac factors such as the distribution of adipose tissue in the chest area and chronic obstructive pulmonary disease lead to a decrease in the ECG voltage recorded on the surface of the chest. Additionally, the same authors state that pathological changes in hypertrophied myocardium can lead to relative voltage deficit, resulting in a lack of expected increase in QRS amplitude.

The results from numerous authors who have studied the diagnostic capabilities of specific electrocardiographic criteria for diagnosing LVH are not consistent in regard to which criterion has the best diagnostic potential. Wei Zhang et al. [17] compared SL, CI and CP criteria in relation to echocardiographic diagnosis of LVH using LVMI as the reference. They concluded that the Cornell criteria had the highest AUC, indicating that it might be a more reliable diagnostic test for LVH. Their findings were consistent with the results of Hsieh et al. and Xie et al. [25, 26], where it was demonstrated that voltage criteria modified by the duration of the QRS complex, such as the CI product, were superior in diagnosing LVH defined according to LVMI. Moreover, these criteria were also identified as better predictors of cardiovascular mortality. Our study demonstrated that the SL voltage criterion was a significantly better diagnostic method, as indicated by the highest AUC value of 0.733, followed by CP (0.640), CI (0.622) and lastly the RE criterion (0.570).

Conclusion

In our patient cohort, the Sokolow-Lyon voltage criterion exhibited the best trade-off between specificity and sensitivity, substantial ROC curve area and a moderately strong correlation with the left ventricular mass index diagnosed. Although weaker than Sokolow-Lyon, the Cornell voltage index and Cornell product also displayed positive correlations with the left ventricular mass index. Notably, there was not any statistically significant correlation between echocardiographic left ventricular hypertrophy diagnosis and Romhilt-Estes electrocardiographic criteria in our study. However, the value of these criteria was seen in their high sensitivity, the highest negative likelihood ratio and negative predictive value.

To make an early and more accessible left ventricular hypertrophy diagnosis, further research is necessary to identify even more precise electrocardiographic criteria as the primary and routine diagnostic tool in hypertensive patients.

The study had several limitations. Its design was retrospective and it included a relatively small number of participants. There was a presence of selection bias and the potential for confounding variables.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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POSTTRAUMATIC PSEUDOANEURYSM OF THE INTERNAL CAROTID ARTERY EXTRACRANIAL SEGMENT DUE TO CHRONIC INTIMAL TRANSECTION – CASE REPORT

POSTTRAUMATSKA PSEUDOANEURIZMA EKSTRAKRANIJALNOG SEGMENTA UNUTRAŠNJE KAROTIDNE ARTERIJE USLED HRONIČNE TRANSEKCIJE INTIME – PRIKAZ SLUČAJA

Tijana KOKOVIĆ[1], Željko ŽIVANOVIĆ[2, 3] and Viktor TILL[1,2]

Summary

Introduction. Carotid artery pseudoaneurysms can refer to pseudoaneurysms involving any segment of the carotid arteries. Posttraumatic internal carotid artery pseudoaneurysm dilatation due to intimal transection is extremely rare entity that requires detailed clinical examination and multiple diagnostic modalities to confirm the diagnosis. The aim of the study is to present rare entity of posttraumatic extracranial internal carotid artery pseudoaneurysm dilatation due to intimal transection, diagnostic algorithm and diagnostic findings. **Case Report.** The patient was a 30-year-old, previously healthy, female who came to see a cardiologist due to intermittent tachycardia, which first appeared a week before the examination. Duplex ultrasound was performed, and aneurysm of extracranial segment of internal carotid artery was found. The patient had severe neck trauma due to bicycle accident in childhood, which was treated at home, without medical examination. Further computed tomography angiography and magnetic resonance angiography were performed. All imaging findings were in favor of chronic arterial wall small pseudoaneurysmal dilatation, with intimal transection, without signs of acute trauma. Based on the above, a decision was made to continue conservative treatment in accordance with the recommendations of current guidelines. Periodic clinical diagnostic follow-up was performed. After the applied therapy, the complaints in terms of intermittent tachycardia disappeared completely. **Conclusion.** Formation of extracranial internal carotid artery pseudoaneurysm due to intimal transection is a rare entity, and requires multiple imaging findings in order to evaluate if the trauma is acute or chronic. In most cases, chronic pseudoaneurysm does not require surgical intervention. It requires conservative medical treatment and diagnostic follow-up.

Key words: Carotid Artery, Internal; Aneurysm, False; Carotid Artery Injuries; Ultrasonography, Doppler, Duplex; Computed Tomography Angiography; Magnetic Resonance Angiography

Sažetak

Uvod. Pseudoaneurizma karotidne arterije može zahvatati bilo koji segment karotidnih arterija. Posttraumatska pseudoaneurizmatska dilatacija unutrašnje karotidne arterije usled transekcije intime je izuzetno redak entitet, koji zahteva detaljan klinički pregled i više dijagnostičkih modaliteta za potvrdu dijagnoze. Cilj ovog rada je prikaz retkog entiteta posttraumatske dilatacije pseudoaneurizme ekstrakranijalnog segmenta unutrašnje karotidne arterije usled transsekcije intime, dijagnostički algoritam i dijagnostički nalaz. **Prikaz slučaja.** Pacijentkinja je bila 30-godišnjakinja, ranije zdrava, javila se kardiologu zbog intermitentne tahikardije, koja se prvi put javila nedelju dana pre pregleda. Urađen je dupleks ultrazvuk i utvrđena je aneurizma ekstrakranijalnog segmenta unutrašnje karotidne arterije. Pacijentkinja je u detinjstvu imala tešku traumu vrata usled nezgode na biciklu, koja je lečena u kućnim uslovima, bez lekarskog pregleda. Dalje je urađena kompjuterizovana tomografska angiografija i magnetna rezonantna angiografija. Svi nalazi su ukazivali na hroničnu malu pseudoaneurizmu, sa transsekcijom intime, bez znakova akutne traume. Na osnovu navedenog, doneta je odluka o nastavku konzervativnog lečenja u skladu sa preporukama aktuelnih vodiča. Sprovedeno je periodično kliničko i dijagnostičko praćenje. Nakon primenjene terapije, tegobe u vidu intermitentne tahikardije su potpuno nestale. **Zaključak.** Formiranje pseudoaneurizme ekstrakranijalnog segmenta unutrašnje karotidne arterije usled transsekcije intime je redak entitet i zahteva višestruke dijagnostičke nalaze da bi se procenilo da li je trauma akutna ili hronična. U slučaju nalaza hronične pseudoaneurizme, hirurška intervencija u većini slučajeva nije indikovana. Neophodno je konzervativno lečenje i periodični dijagnostički pregledi.

Ključne reči: unutrašnja karotidna arterija; pseudoaneurizma; povrede karotidne arterije; Dopler ultrasonografija; CT angiografija; magnetno rezonantna angiografija

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Abbreviations

ICA – internal carotid artery
CT – computerized tomography
DUS – Duplex ultrasound
MR – magnetic resonance
EICA – extracranial internal carotid artery

Introduction

Carotid artery pseudoaneurysms can refer to pseudoaneurysms involving any segment of the carotid arteries.

As with pseudoaneurysms elsewhere, these lack all three layers of the arterial wall (intima, media and adventitia). Pseudoaneurysm development can occur within hours to several years after initial arterial injury, although normally presenting within five years [1].

Posttraumatic internal carotid artery (ICA) pseudoaneurysm dilatation due to intimal transection is extremely rare entity, which requires detailed clinical examination and multiple diagnostic modalities to confirm the diagnosis. These usually present with either "hard signs" of vascular injury or by identification of a pseudoaneurysm on imaging [2].

Pseudoaneurysms can arise from trauma, arterial dissection, vasculitis (e.g. Behcet's disease) [3, 4], infection (e.g. mycotic pseudoaneurysm) [5], as an iatrogenic complication following procedures (carotid endarterectomy, transsphenoidal surgery, surgical neck dissections) [5–8], misplaced central venous lines [9].

Internal carotid artery pseudoaneurysms may be asymptomatic, accounting of 30 – 60% of cases, or symptomatic. ICA pseudoaneurysms can be partially or completely thrombosed and may lead to embolisation with cerebral infarction. The enlarging pseudoaneurysm may present as a pulsating neck mass with mass effect and resulting cranial nerve palsies. Other complications include ruptures with haemorrhage [10].

Imaging evaluation is often with initial Duplex ultrasound (DUS), computerized tomography (CT) and magnetic resonance (MR) angiography.

Management options can range from traditional surgical repair to endovascular repair (stent placement - combined stent placement and coil embolization) [11]. Mortality rates of up to 30% have been reported in the case of external carotid arterial pseudoaneurysms. In certain situations, more conservative approaches are taken (i.e. observation) [12].

The purpose was to present a rare entity of posttraumatic extracranial internal carotid artery pseudoaneurysm dilatation due to intimal transection, diagnostic algorithm and diagnostic findings.

Case Report

We present a case of delayed presentation of extracranial internal carotid artery (EICA) pseudoaneurysm due to transection of arterial intima. The patient was a 30-year-old, previously healthy, female who came to see a cardiologist due to intermittent tachycardia, which first appeared a week before the examination. The patient had no others comorbidities, except smoking. The patient had no previous births, and no surgery in that region. The local findings were normal, without swelling or hematoma. DUS was performed, and aneurysm of EICA was found. There was no acute neck trauma. Patient had severe neck trauma due to a bicycle accident in childhood, which was treated at home, without medical examination. Further CT angiography and MR were performed.

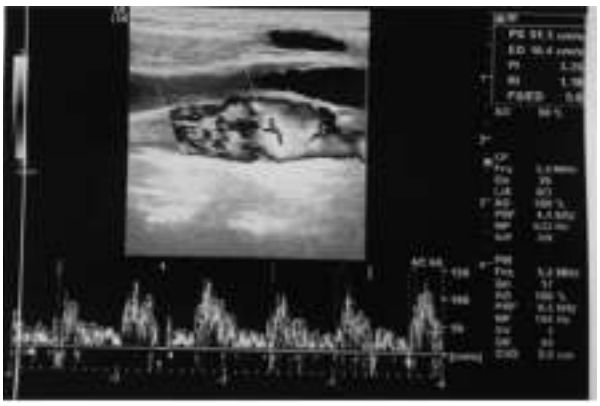

Figure 1. DUS findings showed turbulent blood flow in dilated EICA, with blood vessel wall thinning and intimal transection, and no locoregional hematoma
Slika 1. *Nalazi dupleks ultrasonografije prikazuju turbulentan protok krvi kroz dilatirani ekstrakranijalni segment unutrašnje karotidne arterije, sa istanjivanjem debljine zida i transsekcijom intime, bez lokoregionalnog hematoma*

Figure 2. CT angiography showed fusiform EICA pseudoaneurysmal dilatation, without contrast extravasation and without locoregional hematoma
Slika 2. *Kompjuterizovana tomografska angiografija prikazuje fuziformnu pseudoaneurizmu ekstrakranijalni segmenta unutrašnje karotidne arterije, bez ekstravazacije kontrasta i bez lokoregionalnog hematoma*

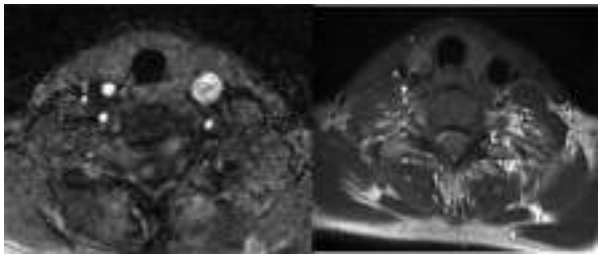

Figure 3. MR was performed with additional T1W fat/sat MRI sequence in order to evaluate the presence of intimal hematoma in the blood vessel wall known as 'crescent sign', which is seen in acute arterial wall dissection. This sign was absent.
Slika 3. *MR je urađen sa dodatnom* T1W fat/sat *MRI sekvencom, kako bi se procenilo prisustvo hematoma intime u zidu krvnog suda poznatog kao „znak polumeseca" koji se vidi kod akutne disekcije zida arterije. Ovaj znak je bio odsutan.*

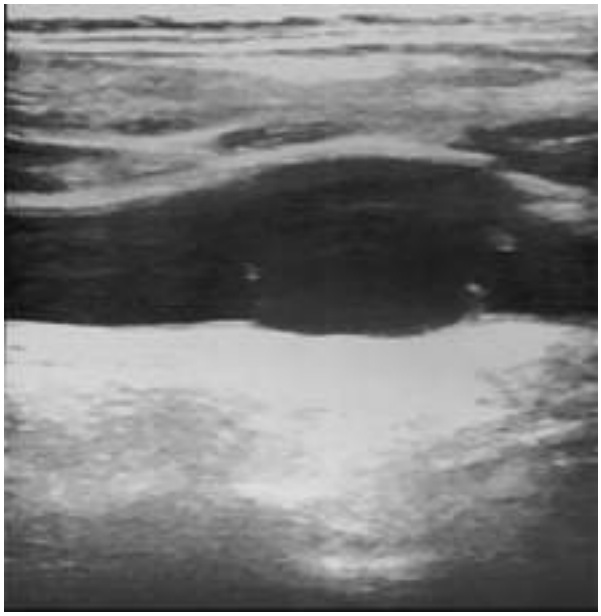

Figure 4. Two years after the initial diagnosis DUS finding did not change.
Slika 4. *Dve godine nakon inicijalne dijagnoze nalaz DUS-a je bio nepromenjen.*

Duplex ultrasound findings showed turbulent blood flow in dilatated EICA, with blood vessel wall thinning and intimal transection, and no locoregional hematoma **(Figure 1)**.

Computerized tomography angiography showed fusiform EICA pseudoaneurysmal dilatation, without contrast extravasation or locoregional hematoma, with diameter 12.5 x 19 mm (LL x CC) **(Figure 2)**. The findings on the brain parenchyma were normal.

The MR was performed with additional T1W fat/sat MR sequence in order to evaluate presence of intimal hematoma in a blood vessel wall known as 'crescent sign', which is seen in acute arterial wall dissection. This sign was absent **(Figure 3)**. The diameter was identical with the one on CT angiography.

All imaging findings were in favor of chronic arterial wall pseudoaneurysmal dilatation, with intimal transection, without signs of acute trauma.

Apart from intermittent tachycardia, the patient had no other complaints. She was a young patient with a small pseudoaneurysm. Based on the above, a decision was made to continue with conservative treatment in accordance with the recommendations of the current guidelines. Antiplatelet therapy (Aspirin) was introduced to the treatment.

Periodic clinical diagnostic follow-up was performed, with DUS 6 months later and then once a year. After the applied therapy, the complaints in terms of intermittent tachycardia disappeared completely. Two years after the initial diagnosis, DUS finding did not change **(Figure 4)**.

Discussion

Ekstracranial internal carotid artery aneurysm is a rare entity, accounting for 0.8% to 1% of all arterial aneurysms [10]. They are defined as more than 50% focal dilatation of the ICA diameter as compared with the reference values (0.55 ± 0.06 cm in men; 0.49 ± 0.07 in women) [13]. There are two types of aneurysms - true aneurysms and pseudoaneurysms. Pseudoaneurysms of the internal carotid artery are less common than true aneurysms, comprising 14% of cases [13]. True aneurysms are most commonly due to atherosclerosis or fibromuscular dysplasia. The major cause of pseudoaneurysm is previous endarterectomy. Other causes include trauma and infections. Traumatic pseudoaneurysm is most often caused by a motor vehicle accident (69%), followed by stab-wounds, iatrogenic central venous cannulation, sport accident, a fight, a fall or cervical manipulation [13]. The incidence of EICA injury in patients with blunt trauma is about 0.08% [13]. Infection was the main cause of EICA aneurysms before the antibiotic era.

Traumatic pseudoaneurysms of EICA are either caused by compression and stretching of the artery on the lateral mass of the atlas or shearing of the artery before entering the carotid canal [14]. The diagnosis is often delayed due to other associated injury and delayed manifestation of the clinical signs [14]. Conservative treatment with anticoagulants and antiplatelets can be considered for young patients without symptoms [15]. The overall estimated complication rate ranges from 20–71% with medical treatment.

Surgery is recommended particularly for symptomatic pseudoaneurysms in patients of all ages. Total aneurysmectomy with end-to-end anastomosis is the surgery of choice. Alternatively, the gap can be interposed with a synthetic graft or a saphenous vein graft. For patients who undergo surgery, the mortality rate is 10% and the incidence of severe stroke is 3%, which are both relatively high [14]. Minimally invasive treatment with endovascular stenting with or without coiling of the pseudoaneurysm has become more popular in recent years [16].

Conclusion

Formation of extracranial internal carotid artery pseudoaneurysm due to intimal transection is rare entity and requires multiple imaging findings in order to evaluate if the trauma is acute or chronic. In most cases, chronic pseudoaneurysm does not require surgical intervention. It requires conservative medical treatment and diagnostic follow-up.

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CANCER-ASSOCIATED STROKE IN A PATIENT WITH TESTICULAR CANCER – CASE REPORT

MOŽDANI UDAR UDRUŽEN SA KARCINOMOM KOD BOLESNIKA SA KARCINOMOM TESTISA – PRIKAZ SLUČAJA

Maša JOVIĆEVIĆ[1, 2], Predrag JOVIĆEVIĆ[1, 3], Željko ŽIVANOVIĆ[1, 4], Ksenija BOŠKOVIĆ[1, 3], Maja POPOVIĆ[1, 2] and Lazar POPOVIĆ[1, 2]

Summary

Introduction. Cerebral venous thrombosis is a rare cerebrovascular disease that affects about 5 in 1 million people each year and accounts for 0.5% of all strokes. There is significant overlap of many risk factors for cerebral venous thrombosis and venous thromboembolism: cancer, obesity, genetic thrombophilia, trauma, infection, and prior neurosurgery. Testicular cancer is a malignant tumor found in testicular cells and it is generally called testicular germ cell tumor. This case report puts emphasis on the importance of recognizing cerebral venous thrombosis as one of the cancer-associated symptoms that can help set the appropriate diagnosis, which, however, is not very common for this type of disease. **Case report.** A 58-year-old patient has been examined many times due to recurrent strokes. Lumbar puncture, computed tomography scan, magnetic resonance imaging, magnetic resonance angiography, magnetic resonance venography, immuno-serology and electroencephalography have been performed. Apart from the vascular changes in the brain blood vessels, the cause of the stroke was not clear. Furthermore, the patient was examined by a hematologist and an urologist. Laboratory testing showed increased levels of alpha fetoprotein and beta-human chorionic gonadotropin, however, no tumor was found in the suspected testis. Eventually, the patient underwent retroperitoneal lymph mass percutaneous core biopsy procedure and was diagnosed with non-seminoma germ cell tumor – Yolk sac tumor. **Conclusion.** Patients with cerebral venous thrombosis require multidisciplinary approach for the appropriate diagnosis.

Key words: Testicular Neoplasms; Stroke; Venous Thrombosis; Intracranial Thrombosis; Diagnosis; Biomarkers, Tumor; Biopsy; Risk Factors

Sažetak

Uvod. Cerebralna venska tromboza predstavlja retko cerebrovaskularno oboljenje koje pogađa pet od jednog miliona ljudi i čini 0,5% svih moždanih udara. Postoji značajno preklapanje različitih faktora rizika za cerebralnu vensku trombozu i venski tromboembolizam: rak, gojaznost, trombofilija, trauma, infekcija, prethodna neurohirurška intervencija. Rak testisa predstavlja maligni tumor ćelija testisa kod muškaraca i uopšteno se naziva tumor zametnih ćelija testisa. Ovaj prikaz slučaja naglašava značaj prepoznavanja cerebralne venske tromboze kao mogućeg pratećeg simptoma maligne bolesti koji može pomoći u postavljanju odgovarajuće dijagnoze. **Prikaz slučaja.** Pedesetosmogodišnji bolesnik je više puta pregledan zbog ponavljajućih moždanih udara. Načinjena je lumbalna punkcija kao i kompjuterizovana tomografija, magnetna rezonanca, magnetno-rezonantna angiografija i venografija, imunoserologija i elektroencefalografija. Osim patoloških promena u krvnim sudovima mozga, uzrok moždanog udara nije utvrđen ovim ispitivanjima. Nadalje, ovog bolesnika su pregledali hematolog i urolog. Laboratorijski nalazi pokazali su povišene vrednosti alfa fetoproteina i beta humanog horio gonadotropina, ali nije postavljana dijagnoza tumora u sumnjivom testisu. Naposletku je bolesniku načinjena perkutana iglena biopsija retroperitonelanih limfnih čvorova abdomena čime je postavljena dijagnoza tumora zametnih ćelija testisa − tumor žumančane kese. **Zaključak.** Bolesnici sa cerebralnom venskom trombozom zahtevaju multidisciplinarni pristup radi postavljanja pravovremene tačne dijagnoze.

Ključne reči: tumori testisa; moždani udar; venska tromboza; intrakranijalna tromboza; dijagnoza; tumorski biomarkeri; biopsija; faktori rizika

Introduction

Cerebral venous thrombosis (CVT) is a rare cerebrovascular disease that affects about 5 in 1 million people each year and accounts for 0.5% of all strokes [1]. It was previously thought to be most commonly caused by infections (mastoiditis, otitis, meningitis) that affect the superior sagittal sinus and often result in focal neurologic deficits, seizures, coma and death. CVT mainly affects children and young adults and is an important cause of stroke in the younger population [2]. There is significant overlap of many risk factors for CVT and the ones for venous thromboembolism (VTE): cancer, obesity, genetic thrombophilia, trauma, infection, and prior neurosurgery [3].

Testicular cancer (TC) is a malignant tumor found in testicular cells of men and it is generally called testicular germ cell tumor (TGCT) [4]. TC is

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Abbreviations

CVT – cerebral venous thrombosis
CT – computed tomography scan
VTE – venous thromboembolism
TC – testicular cancer
TGCT – testicular germ cell tumor
MRI – magnetic resonance imaging
MRA – magnetic resonance angiography
MRV – magnetic resonance venography
EEG – electroencephalography
LDH – lactate dehydrogenase
AFP – alpha fetoprotein
β- h*CG* – beta-human chorionic gonadotropin
CNS – central nervous system

a rare disease, accounting for 1 to 2% of all male neoplasms. However, TC is the most common malignancy among 20 to 34-year-old men [5, 6]. There are two main types of TGTC -seminomas and non-seminomas. Seminomas usually develop later in life, in the fourth and the fifth decade, whereas non-seminomas occur among younger men between their second and third decade of life, and they are more aggressive [7]. In Europe, TGCT is the most common cancer in young men with over 18,000 new cases diagnosed annually. Further estimations predict that there will be a 25% increase in cases by 2025 across the industrialised countries [8].

This case report puts emphasis on the importance of recognizing CVT as one of the cancer-associated symptoms that can help set the appropriate diagnosis, which, however, is not very common for this type of disease.

Case report

A 58-year-old patient was first admitted to a hospital in June 2019 due to cryptogenic stroke followed with right-sided weakness. He had controlled hypertension and no family diseases in his medical history. He was treated with intravenous thrombolytic therapy and was diagnosed with left parasagittal intracerebral hematoma. Notwithstanding the therapy, the patient continued to suffer from neurological disorders in a form of headaches and right sided facial and body paresthesia. The control computed tomography (CT) scan showed partial thrombosis of the sagittal sinus, while the magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) performed in the hospital failed to confirm the sagittal sinus thrombosis. All of the additional medical tests, including immuno-serology and electroencephalography (EEG), were referent. After been discharged from the hospital, he was readmitted only two weeks later due to right-side impairment and persistent headache.

New MRI/MRA/MRV, as well as lumbar puncture, were performed during his hospitalization. MR showed two small subacute ischemic spots in the cingulate gyrus region of the same side with suspected thrombosis of left parietal veins. The lumbar puncture showed pleocytosis and hyperproteinorrachia, but infectious inflammatory diseases were excluded by an infectious disease specialist as the virology panel was negative. Furthermore, the patient was examined under the suspicion of paraneoplastic syndrome. The full-body CT scan showed retroperitoneal and inguinal lymphadenopathy up to 25 mm, but the consulted hematology specialist excluded any hematology diseases based on values of beta-2 microglobulin, lactate dehydrogenase (LDH), peripheral blood smear and the extended immunoserology tests. The patient was discharged with prescribed oral anticoagulant therapy due to thrombosis. He was admitted to the same hospital a month later for additional diagnostics that included lumbar puncture and MRI/MRA/MRV of the brain. The lumbar puncture was referent and the MRI did not show any significant brain pathology except superior sagittal sinus thrombosis. Gastroscopy showed no evidence of tumor. During the same hospitalization, the patient experienced psycho-organic syndrome and was treated with a psychiatric drug. From then on, the patient occasionally experienced epileptic attacks. He was hospitalized in June 2020 for the fifth time due to right-sided plegia and altered state of consciousness. The CT scan showed multiple both-sided frontal hemorrhages and the MRI/MRA/MRV showed new-onset hemorrhages in the temporal region, impassible anterior communicating artery and superior sagittal sinus thrombosis. In order to expose the underlying cause of neurological symptoms, further examinations were performed in the direction of vasculitis. The hemostasis, additional immuno-serology and tumor marker results were all referent as well as the granulomatous lung disease. Without the exposed underlying cause, the patient's condition was worsening and some of the diagnostic procedures such as MRI/MRV/MRA were redone. The MRI/MRA/MRV showed the early seen radiological findings that were described as chronic. The patient was admitted to the hospital six months later due to the same neurological symptom as before, and CT scan, MRI and EEG were performed. The CT scan showed hypodense spot that may correspond to ischemia in the left parietal region. The MRI showed impairment in comparison to the earlier MRI from April 2021 in the form of edema of the parietal and partially frontal region accompanied by vein thrombosis. The EEG showed no evidence of epilepsy. Onconeural antibodies (Amphiphysin, CV2, PNMa2, Ri, Zo, Hu, Recoverin, SOX1, Titin) were negative. The patient was admitted for further examination only two months later. This time, the examination included re-consultation with a hematologist and consultation with a urologist. The ultrasound of the scrotum showed smaller size of the left testicle, estimated at about 20 mm of the long diameter, inhomogeneous. Alpha fetoprotein (AFP) and beta-human chorionic gonadotropin (β- h*CG*) were increased (AFP 1576.4 β- hCG 11.6 lactate dehydrogenase referent). Histopathology results of the left testis showed no evidence of tumor. The CT scan performed in September 2021 showed enlargement

of the retroperitoneal mass of 50x40x52 mm and 45x34x54 mm this time. After he was admitted to the same hospital in September 2021, the patient underwent retroperitoneal lymph mass percutaneous core biopsy procedure. The histopathology findings showed non-seminoma germ cell tumor (NSGCT) – Yolk sac tumor (original HP number 6816/21 – CD117+, Desmin -, S100-, HMB45-, MDM2-, AFP+/-, Glypican 3+, CKMNF116+.) The patient was finally referred to the Oncology Institute of Vojvodina for further treatment.

Discussion

The prevalence of CVT in patients with malignancy is believed to be approximately 0.3% [9, 10]. Malignancy-related thromboses of the dural sinus or cerebral veins are thought to represent roughly 7.4% of all CVT cases, with cancer increasing risk for CVT roughly 5-fold [11]. Hematologic malignancies appear to be implicated more so than solid organ malignancies; however, the underlying reasons for this are not completely understood [12]. The pathogenesis of CVT in the setting of malignancy is not well defined [13]. Several potential mechanisms have been proposed including direct tumor compression, tumor invasion, and the hypercoagulable state of malignancy [10, 14, 15]. In the absence of tumor compression or invasion, malignancy-related prothrombotic states are thought to drive development of venous thromboembolism (VTE) via a variety of mechanisms including a tumor's ability to increase the expression of tissue factor, cancer procoagulant, and inflammatory cytokines as well as to downregulate the expression of thrombomodulin and the protein C system [16].

Data from a Finland study that has investigated 589 CVT patients without prior malignancy showed that 2.3% of all patients experienced new cancer diagnosis during the follow up; the risk of a new cancer diagnosis was higher in men than in women in the same age group <50, but with no sex difference in older patients. No particular cancer type was predominant. Four of the new cancer diagnoses occurred within a year after the CVT, 3 in men and 1 in women (all in different organs) [17].

Studies of hospitalized cancer patients have noted a VTE incidence of 0.6% to 7.8%, with higher rates reported among patients receiving chemotherapy and the ones with pancreatic, ovary, kidney, lung, stomach and brain tumors [18, 19].

As a vast majority of common CVP causes was excluded in this patient's case (thrombophilia, inflammation, infection, etc.) we continued with further research towards malignancies. Knowing that hematologic malignancies appear to be implicated more than solid organ malignancies, hematological disease was excluded. We need to note that the patient's left testis was smaller but histopathology findings did not show any testicular malignancy as an underlying cause of CVT. A later CT scan showed enlargement of retroperitoneal lymph mass that appeared to be metastatic lesion of testicular cancer. Srikanthan et al. have shown that a large (maximum axial diameter more than 5cm) retroperitoneal lymphadenopathy (RPLN) is a strong risk factor for VTE in TGCT [20]. In addition to positive nodal disease factors, a metastatic disease, high LDH and age over 30 can also affect VTE in patients with testicular cancer [21]. Our patient did not have any clinical signs of peripheral venosus thromboembolism. On the contrary, he had signs of central thromboembolism even though he had not received any platinum-based therapy. Platinum based chemotherapy is associated with treatment-related toxicities like thromboembolic events [22].

Most patients with germ cell tumors are young without many comorbidities, which should lower their VTE risk. However, the cancer itself and cisplatin markedly increase their VTE risk. In a study that included 179 patients with germ cell cancer, 8.4% developed thromboembolic complications [23]. In another study that included 153 patients undergoing cisplatin-based chemotherapy, 26 (17%) developed VTE. As opposed to VTE, literature data did not show many patients with testicular cancer who experienced CVT without peripheral thrombosis [24]. Furthermore, processing this patient, we wanted to exclude angiitis of the central nervous system (CNS), where CNS remains a poorly understood form of vascular inflammatory disease. Primary angiitis of the CNS (PACNS), a disease once considered extremely rare, has recently been reported more frequently. Secondary vasculitis of the CNS can occur with a variety of other conditions and diseases; each requiring a different diagnostic and therapeutic approach [25]. Only a few data in literature describe relation between primary CNS angiitis and testicular cancer. Our patient's MRI/MRA/MRV showed minor bleeding and impassable anterior communicating artery in June 2020, so he underwent additional searches in order to exclude secondary vasculitis. He did not undergo stereotaxic biopsy of the described spots in order to elucidate the presence of primary angiitis of the CNS.

Data from the literature suggest that patients with testicular carcinoma are more likely to develop limbic, brainstem and hypothalamic anti-Ma2 antibody positive encephalitis than CVT. Our patient did not have any of the above diagnosis on his CT/MR scans or the lumbar puncture findings.

Even there are well known CVT and VTP risk factors, the most common acquired CVT risk factors are oral contraceptive use and pregnancy, which explains why CVT is 3 times more likely to occur in young and middle-aged women [3]. However, other causes must not be neglected.

Conclusion

Patients with cerebral venous thrombosis require multidisciplinary approach for the appropriate diagnosis. In every day clinical practice, cancers must not be omitted as one of the possible causes of cerebral venous thrombosis.

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A NEW DESIGN OF INDIVIDUAL MANDIBULAR ADVANCEMENT DEVICE IN THE TREATMENT OF OBSTRUCTIVE SLEEP APNEA

NOVI DIZAJN INDIVIDUALNOG INTRAORALNOG APLIKATORA U LEČENJU OPSTRUKTIVNE SLEEP APNEE

Sandra PJEVAC VLASAČEVIĆ[1], Ivan KOPITOVIĆ[2, 3], Predrag VUČINIĆ[2, 4] and Ana MILENKOVIĆ[2, 3]

Summary

Introduction. Mandibular advancement devices are used in the treatment of mild to moderate obstructive sleep apnea. We have created different types of devices over the years and come up with a design of an acrylic two-part adjustable device as the best one so far. **New design of the mandibular advancement device.** A 36-year-old male patient has been referred for polysomnography to the Sleep Medicine Center of the Institute of Pulmonary Diseases of Vojvodina due to primary problems in the form of drowsiness during the day, reduced concentration and witnessed cessation of breathing during sleep. By evaluating respiratory parameters, the patient was diagnosed with mild obstructive sleep apnea with an Apnea-Hypopnea Index of 10.3. Hygienic-dietary regimen of life and the use of mandibular advancement device were prescribed to the patient. Control polysomnography was performed six months after the use of the mandibular advancement device. Evaluation of respiratory parameters has registered the apnea-hypopnea index of 6.2 with predominant hypopneas. The average oxygen blood saturation was 94.4%. Snoring was mild and rare. Patient did not have any long-term side effects of the device and he got used to it easily. **Conclusion.** Mandibular advancement device is an effective way to treat obstructive sleep apnea in clearly indicated cases. Dentists who indicate and make it must be well educated, informed and they must cooperate with the sleep medicine centers to monitor the effectiveness of the therapy.

Key words: Sleep Apnea, Obstructive; Mandibular Advancement; Polysomnography; Treatment Outcome; Equipment Design; Dentist's Role; Sleep Medicine Specialty

Sažetak

Uvod. Intraoralni aplikatori se koriste u lečenju lakših i srednje teških oblika opstruktivne slip apnee. Tokom godina kreirali smo različite tipove aplikatora i došli smo do dizajna dvodelnog aplikatora od akrilata. **Novi dizajn intraoralnog aplikatora.** Pacijent muškog pola, 36 godina star, upućen je na poligrafiju u Centar za medicinu sna Instituta za plućne bolesti Vojvodine zbog tegoba u vidu dnevne pospanosti, smanjene koncentracije i posvedočenih prekida disanja u toku spavanja. Evaluacijom respiratornih parametara pacijentu je dijagnostikovana opstruktivna slip apnea lakšeg oblika sa apnea hipopnea indeksom od 10,3. Predložen mu je higijensko-dijetetski način života i upućen je stomatologu radi izrade intraoralnog aplikatora. Kontrolna poligrafija je urađena šest meseci od početka korišćenja intraoralnog aplikatora. Apnea hipopnea indeks se smanjio na 6,2 sa dominantnim hipopneama. Srednja vrednost saturacije krvi kiseonikom je bila 94,4%. Hrkanje je slabo i retko. Pacijent nije imao ništa od neželjenih efekata aplikatora i navodi da se na njega lako navikao. **Zaključak.** Intraoralni aplikator je efektivan način lečenja opstruktivne slip apnee u jasno indikovanim slučajevima. Stomatolog koji ih indikuje i pravi mora biti dobro edukovan, informisan i mora imati saradnju sa centrom za medicinu sna radi praćenja efikasnosti terapije.

Ključne reči: opstruktivne sleep apnea; intraoralni aplikator; polisomnografija; ishod lečenja; dizajn opreme; uloga stomatologa; specijalista medicine sna

Introduction

Mandibular advancement devices (MAD) are medical devices applied in the mouth to treat obstructive sleep apnea. They can be individual custom made by the dentist or prefabricated heat molded devices adapted to the teeth by the patient. Individual custom made devices have better efficiency and are more acceptable by the patients [1, 2].

Obstructive sleep apnea (OSA) is the most significant sleep-related breathing disorder, and occurs as a result of decreased muscle tone in upper respiratory

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Abbreviations

OSA – obstructive sleep apnea
MAD – mandibular advancement device
AHI – apnea hypopnea index
ODI – oxygen desaturation index

Figure 1. First designed one-part silicone mandibular advancement device
Slika 1. *Prvi dizajnirani jednodelni intraoralni aplikator*

tract. It represents at least five interruptions of breathing and /or other irregularities of ventilation during the hour of sleep (apnea-hypopnea index (AHI) > 5, or respiratory disturbance index (RDI) > 5) [3–6].

The treatment of obstructive sleep apnea is carried out by a multidisciplinary team. The gold standard in therapy is the continuous positive airway pressure machine (CPAP). MAD are used in the treatment of mild to moderate OSA, but sometimes also in severe cases when there is CPAP intolerance [7–9].

Obstructive sleep apnea is a serious, potentially life-threatening condition. Epidemiologic studies show that sleep apnea increases cardiovascular diseases risk factors including hypertension, obesity, and diabetes mellitus. OSA is also responsible for serious illnesses such as congestive heart failure, stroke, arrhythmias, and bronchial asthma [10]. It is important to offer patients with OSA adequate individual therapy which will be the most effective for the case and acceptable by the patient. MAD treatment in well indicated cases reduces AHI values by at least 50%: the treatment is deemed successful (success being defined as an AHI < 5) in

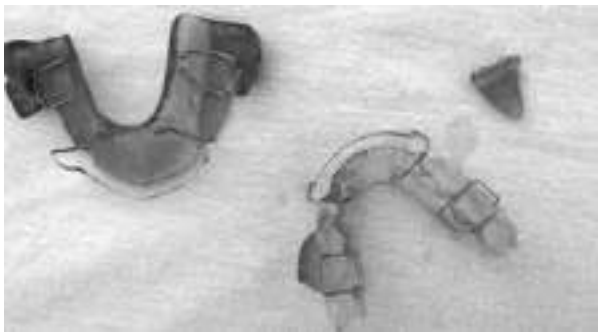

Figure 2. Cracked two-part mandibular advancement device made of acrylate and wire
Slika 2. *Polomljeni dvodelni intraoralni aplikator napravljen od akrilata i žice*

Figure 3. New two-piece mandibular advancement device made of acrylate
Slika 3. *Novi dvodelni intraoralni aplikator napravljen samo od akrilata*

17–75% of patients, while AHI values are < 10 in 30–94% of the patients [11].

Over the years, we have made different designs of individual MADs realizing their advantages and disadvantages. We have checked the efficiency of the devices with control polysomnography. We have also done regular dental check-ups to diagnose any side effects or inconvenience felt by the patient, aiming to give the best therapy needed. The first device was a one-part silicone device **(Figure 1).** It had a slit between the teeth of the lower and the upper jaw to allow breathing through the mouth, if necessary, but did not allow any movements of the lower jaw. The second designed MAD was a two-part device combining wire elements and acrylate parts with good effects but have often cracked and the wire elements were damaging the teeth **(Figure 2).**

We then designed a two-piece acrylate only MAD **(Figure 3).** This device had good results in reducing the AHI and giving the needed long-term comfort to the patients.

New design of MAD

A 36-year-old male patient was referred for polysomnography to the Sleep Medicine Center of the Institute of Pulmonary Diseases of Vojvodina due

Figure 4. Upper part of the new mandibular advancement device made of acrylate
Slika 4. *Gornji deo novog intraoralnog aplikatora napravljenog od akrilata*

Figure 5. Lower part of the new mandibular advancement device made of acrylate
Slika 5. *Donji deo novog intraoralnog aplikatora napravljenog od akrilata*

to primary problems in the form of drowsiness during the day, reduced concentration and witnessed cessation of breathing during sleep.

The Epworth sleepiness scale was 11, the Stop Bang questionnaire 3, body mass index 28.7, neck circumference 37 cm and waist circumference 96 cm. The comorbidities of the patient were allergic rhinitis, nasal septum deviation and gastroesophageal reflux disease (GERD).

By evaluating the respiratory parameters after the polysomnography, the patient was diagnosed with mild obstructive sleep apnea with AHI = 10.3 with dominant hypopnea expressed especially during back sleep (AHI supine 14.8 and AHI non supine 7). The average oxygen blood saturation was 94.2, the lowest 89% and the oxygen desaturation index (ODI) was 13.5. Snoring of mild intensity was present in all body positions, especially during back sleep. The heart rate during the night was an average of 63 beats per minute. Hygienic-dietary regimen of life and the use of MAD were prescribed to the patient.

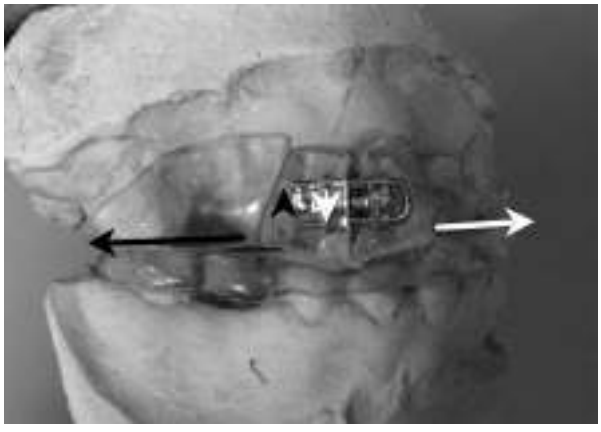

Figure 6. Movements of the lower jaw depending of the patient's need. In the so-coled "the thorn" of the device lower part of the device there is a lock that allows you to move the part of the "thorn" so it pushes the lower jaw forward or backward depending on the need. We push the lower jaw forward if the symptoms of OSA start to reappaer. We move the jaw backwards in case the patient has problems in the temporomandibular joint that do not go away.
Slika 6. *Pomeranje donje vilice u zavisnosti od pacijentovih potreba. U tzv. trnu donjeg dela intraoralnog aplikatora nalazi se bravica čijim okretanjem se omogućavaju njegovi pokreti u zavisnosti od potrebe. Pomeramo donju vilicu više napred u slučaju da se ponovo pojavljuje opstruktivna apnea. Pomeramo donju vilicu nazad u slučaju da pacijent ima tegobe u temporomandibularnom zglobu koje ne prolaze.*

After taking the impressions of the upper and lower jaw and determining the maximum comfortable protrusion, a new design of MAD was created for the patient.

The device consisted of two parts, one for the upper jaw and one for the lower jaw. It was made of acrylic. The upper part in the molar region had a rectangular bulge with the front surface slanted backwards **(Figure 4).** The lower part had a so-called 'thorn' in the region of the premolar with the back surface tilted forward to touch the front of the rectangular bulge on the upper part of the device **(Figure 5).** Touching and sliding on each other, these surfaces enable the device to function as a whole. The sliding allows limited jaw movements. The most important role of the MAD is to hold the lower jaw in the maximum comfortable protruding position and prevent it from returning to central occlusion and retruded position. In so-called 'thorn' of the device lower part there is a lock that allows the therapist to move the part of the 'thorn' so that it pushes the lower jaw forward or backward depending on the need. The lower jaw is pushed more forward if the symptoms of OSA begin to appear again. The jaw is moved back in case the patient has persisting problems in the temporomandibular joint **(Figure 6).**

The patient quickly and easily got used to the MAD. There was increased secretion of saliva while wearing it and a feeling of transient tingling of teeth upon waking up. These side effects passed in a week. The patient stated that this MAD was comfortable, he felt more rested and all his cognitive functions had improved.

Control clinical examination and control respiratory polysomnography six months after using the MAD showed good results of the device new design.

Evaluation of the respiratory parameters registered light OSA with AHI 6.2 with predominant hypopneas. The average oxygen blood saturation was 94.4%, the lowest 84%, ODI 8.3/h. Snoring was mild and rare. During the night, the average heart rate was 50 per minute.

Discussion

The MAD design can be improved further in regard to the side effects and its use in cases of missing group of teeth and mobile prosthetic replacements [6, 7].

In our case, the patient had a full and healthy dental arch, with a 2 mm second class occlusion that is favorable when making the MAD. Unfavorable is the presence of a third-class occlusion and the edge-to-edge teeth arrangement. The effect of the MAD is then significantly reduced and the side ef-

fect in terms of teeth displacement by the device influence is more expressive [14, 15].

MADs are also made in the absence of individual teeth or group of teeth or even complete edentulousness; however, the possibility of poorer adaptability and lesser device stability must be emphasized to patients. Also, if there are irregularities in the teeth position, the retention of the device may be reduced. The patient in the presented case had a dental arch without crowding or rotated teeth.

As MADs are mainly used in mild and moderate cases of the disease, these patients sometimes do not have any symptoms of OSA [8, 16]. This is one of the additional reasons why the MAD must be designed to be better accepted by the patients and not to lead to any side effects.

Conclusion

Mandibular advancement devices is an effective way to treat obstructive sleep apnea in clearly indicated cases. Dentists indicating and making mandibular advancement devices must be well educated, informed and they must cooperate with some of the sleep medicine centers to monitor the effectiveness of the therapy.

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ACUPUNCTURE AS AN ADDITIONAL ANALGESIC METHOD IN THE PERIOPERATIVE PERIOD

AKUPUNKTURA KAO DODATNA ANALGETSKA METODA U PERIOPERATIVNOM PERIODU

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Summary
Acupuncture is a traditional Chinese therapeutic method that uses a sterile thin needle technique to puncture the skin at specific strategic points on the body. World Health Organisation has acknowledged acupuncture as a complementary treatment method for over 300 diseases. Nowadays, many available studies conducted in China, the United States, and Europe confirm the efficacy of acupuncture, its analgesic effect, while providing direct health benefits without or with minimal side-effects. There are many scientific evidence mechanisms of acupuncture's analgesic effects. One of the mechanisms is described in the oldest and best-known Gate Control Theory which explains how pain pathways are modulated through normal anti-nociceptive pathways in the spinal cord. The second mechanism of analgesia shows that there are changes in descendent inhibition of pain pathway and secretion of neurotransmitters when the acupuncture needle is placed at the specific acupuncture point. In addition, it has been proved that there is an increased secretion of endogenous opioids during acupuncture procedures, which help reduce the pain sensations. Analgesic effects of acupuncture on cerebral function have been confirmed with use of functional magnetic resonance imaging and positron emission tomography scans. Although there is an increased number of relevant studies that confirm the effects and benefits of acupuncture therapy in the perioperative period, some important factors are still missing: the standardization process of acupuncture technique, the determination of types of surgery where the acupuncture method shows the best therapeutic effect, the determination of the best technique and time interval for the most effective analgesia.
Key words: Acupuncture; Analgesics; Perioperative Period; Pain; Enhanced Recovery After Surgery

Sažetak
Akupunktura je drevna kineska metoda lečenja pomoću sterilnih igala koje se ubadaju u tačno određene tačke na koži. Svetska zdravstvena organizacija je priznala akupunkturu kao metodu komplementarne grane medicine i preporučila je za lečenje više od 300 bolesti. Danas postoji veliki broj studija sprovedenih u Kini, Americi, evropskim zemljama, od kojih mnoge potvrđuju efikasnost akupunkture, analgetski efekat, doprinos poboljšavanju zdravlja bez ili uz minimalne mogućnosti štetnih efekata**.** Postoji više naučno potvrđenih mehanizama o analgetskom efektu akupunkture. Jedan od njih je opisan u najstarijoj i najpoznatijoj teoriji „kontrolne kapije" gde je objašnjena modulacija puta širenja bola kroz normalan anticeptivni put u kičmenoj moždini. Drugi mehanizam je da ubadanjem iglica u akupunkturne tačke dolazi do promene u descedentnoj inhibiciji prenosa bola i lučenju neurotransmitera. Pored ovoga, dokazano je da dolazi do povećanog oslobađanja endogenih opioida koji doprinose smanjenju osećaja bola. Analgetski efekti akupunkture na funkciju mozga su potvrđeni i pomoću funkcionalne magnetne rezonancije i pozitronske emisione tomografije. Uprkos tome što postoje relevantne kliničke studije, koje idu u prilog efikasnosti korišćenja akupunkture u perioperativnom periodu, ono što nedostaje jeste: standardizacija primene akupunkture, u kojoj vrsti hirurgije se postižu najbolji terapijski efekti akupunkture, na koji način je primeniti i u kojim vremenskim intervalima da bi akupunktura dala mnogo efikasniju analgeziju.
Ključne reči: akupunktura; analgezija; perioperativni period; bol; ubrzan oporavak nakon operacije

Introduction

Acupuncture is a traditional Chinese therapeutic method that uses a sterile thin needle technique to puncture the skin at specific strategic points on the body. In 1979, the World Health Organisation (WHO) acknowledged acupuncture as a complementary treatment method for over 50 diseases. The list of diseases has expanded over time and now there are over 300 indications for acupuncture treatment [1].

Although acupuncture is an ancient Chinese therapeutic method, the use of acupuncture has expanded in the last four decades in Europe. Western medicine hardly accepts this type of treatment as it seems there is no scientific evidence for it. Merging the two types of therapeutic approaches, the Western and the Eastern, is hard as they have different origin. Western medicine relies on anatomy and physiology while Eastern medicine has its roots in philosophy [2].

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Abbreviations

WHO – World Health Organisation
fMRI – functional magnetic resonance imaging
PAG – periaqueductal gray matter
RVM – rostroventromedial medulla
NRM – nucleus raphe magnus
GABA – gamma-aminobutyric acid
ERAS – Enhanced Recovery After Surgery
TEAS – transcutaneous electric acupuncture stimulation

Nowadays, many available studies conducted in China, the United States, and Europe confirm the efficacy of acupuncture and its analgesic effect, while providing direct health benefits with minimal side-effects [3–7].

According to the analysis done by WHO, which included several randomized controlled trials, acupuncture has proven to be a highly effective method in the treatment of headache, postoperative nausea and vomiting, migraine, chronic neck pain, shoulder periarthritis, elbow pain, chronic back pain, knee osteoarthritis and various of different pain syndromes. The results were significantly better when acupuncture was performed in addition to conventional pain treatment in comparison to only conventional pain treatment [1, 8]. In addition, acupuncture helps reduce the severity of symptoms of chronic diseases, helping patients have better quality of sleep, reducing anxiety, fatigue, and helping them have more energy, which all reflect on better quality of life [9].

Acupuncture is based on the premise that humans, as all living beings, are filled with life energy that circles the human body through specific pathways or meridians. Meridians are energetic flows of energy named *Chi*, which is composed of Yin and Yang **(Figure 1)**. When a human is healthy, Yin and Yang are balanced. The disease develops when Yin and Yang are imbalanced due to the blockage in energy flow. Acupuncture helps return the body to a balanced state by stabilizing the energy flow [2].

Figure 1. Traditional Chinese medicine – Yin and Yang
Slika 1. *Tradicionalna kineska medicina – jin i jang*
Wikipedia Contributors. Yin and Yang [Internet]. Wikipedia. Wikimedia Foundation; 2019. Available from: https://en.wikipedia.org/iki/Yin_and_Yang

Mechanism of pain

It is important to know the pain pathophysiology in order to understand the analgesic effect achieved by acupuncture [10].

Pain is an unpleasant sensory and emotional experience that accompanies the existing or potentially existing tissue damage [11].

Pain can be classified by duration, pathogenesis, localization and etiology. Pain experienced during surgery or during postoperative period is nociceptive pain resulting from tissue damage and lesion [12].

Pain pathways consist of an ascending excitatory pathway and a descendent inhibitory pathway. Ascending pathways carry excitatory information from peripheral tissues, through the spinal cord to the brain. Descending pathways carry inhibitory information from the brain to the spinal cord. The spinal cord is called the "Pain gate" and it is a place where the ascending and descending pathways meet. The predominance of the excitatory or inhibitory pathways determines the feeling of pain and its intensity **(Figure 2)** [10].

Tissue damage causes the release of proinflammatory mediators (prostaglandins, bradykinins, leukotrienes, interleukins, etc.) and activation of nociceptive receptors [10, 13].

Nociceptors are pain receptors in the form of bare nerve endings that react to mechanical, thermal and pain sensations. By activating the receptors, the stimuli are transmitted by an ascending pathway up to the spinal sensory ganglia, which represents the first-order

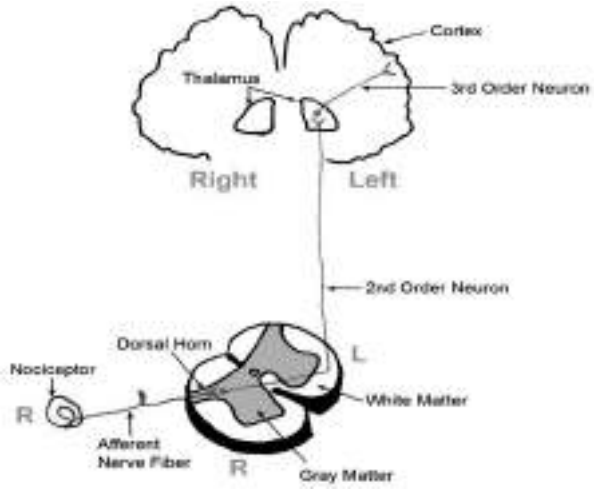

Figure 2. Pain transmission pathway
Slika 2. *Put širenja bola*
Pain Pathway Flowchart: The Complete Steps [Internet]. www.zenflowchart.com. Available from: https://www.zenflowchart.com/blog/pain-pathway-flowchart-the-complete-steps

neuron. The first-order neuron body within the ganglia projects its axons to the posterior gray horn of the spinal cord, where it builds a synapse with the body of the second-order neuron [10, 13].

The transmission of sharp, well-defined painful stimuli from nociceptors goes through two classes of nociceptive fibers to the spinal cord. These fibers are A-β and A-δ myelinated fibers. Chronic, dull pain is transmitted through slow, non-myelinated C fibers [10, 13].

The axons of the second-order neuron build an ascending pathway that crosses the medial line and ends in the thalamus, which is considered a third-order neuron. The thalamus not only represents a relay station where the synapsis between the second- and the third-order neuron is built, but also a place where impulses traveling to the cerebral cortex are transformed and modulated. A number of neurotransmitters are released during this process [10, 13, 14].

The information is transmitted from the thalamus to the cerebral cortex and subcortical structures, where the fourth-order neuron is located and the painful stimuli are finally integrated. Cerebral areas that are activated the most are primary and secondary somatosensory cortex, periaqueductal gray matter (PAG) in the upper brain stem, rostroventromedial medulla (RVM), locus coeruleus, nucleus raphe magnus (NRM) and nucleus reticularis gigantocellularis. The formation of localization, nature and pain intensity take place in cortical structures, and the emotional perception of pain is formed [10, 13, 14].

The inhibitory pathway that modifies the pain response travels in the opposite direction, from the upper brain areas to the spinal cord. With use of the inhibitory pathway, PAG and RVM send inhibitory signals by releasing endogenous opioids, gamma-aminobutyric acid (GABA) and glycine, which can produce analgesic effects. On the other hand, pain perception is enhanced by substance P, glutamate and aspartate [10, 13, 14].

Acupuncture mechanisms of action

Many acupuncture methods are known: manual, electroacupuncture, laser acupuncture, moxibustion, auriculotherapy, acupressure. Nevertheless, the application of acupuncture on specific points to achieve analgesia and other regional and systemic effects is common for all of them [15]. From the scientific point of view, the mechanism of acupuncture in reducing pain response to painful stimuli is complex. The changes occur in peripheral and central structures and include direct and indirect neurochemical effects [16–18].

One of the oldest, best known, and scientifically proven theories of acupuncture action mechanism is the "Gate Control Theory" [19, 20]. This theory suggests that the modulation of pain pathway happens through a normal anti-nociceptive pathway in the spinal cord. "The gate" in the posterior gray horn of the spinal cord controls the transmission of nerve impulses from the peripheral into the central nervous system. Under normal circumstances, the gate is open and painful stimuli can pass freely through small-diameter fibers. When the acupuncture point is stimulated by the needle, another wave of non-painful stimuli travels to the gate. These stimuli are transmitted through A-β and A-δ myelinated fibers, which are thicker and transmit information faster into the spinal cord, where they bind to specific spots in synapses in the posterior gray horn. As a result, the gate is overcrowded with signals, which causes the gate to close. C-fibers, which transmit signals slower, do not have any spots to bind to at the synapses, because the gate is closed. The competitive inhibition of painful stimuli by non-painful stimuli causes the reduction or disappearance of pain [2, 20].

The acupuncture effect that causes the analgesic effect is much more complex than what the Control Gate Theory explains. By stimulating the acupuncture spot with a needle, the signals are generated and transmitted to the specific cerebral areas. In addition, there is a change in the secretion of neurotransmitters where the excitatory neurotransmitters are inhibited. On the other hand, the concentration of inhibitory neurotransmitters increases (GABA, serotonin, norepinephrine, endogenous peptides) [21, 22] **(Figure 3)**.

Acupuncture causes the activation of the descending inhibitory pain pathway, which means that specific cerebral areas are activated so that the response to outside painful stimuli of neurons in the posterior gray horn is reduced [21]. PAG cerebral area collects

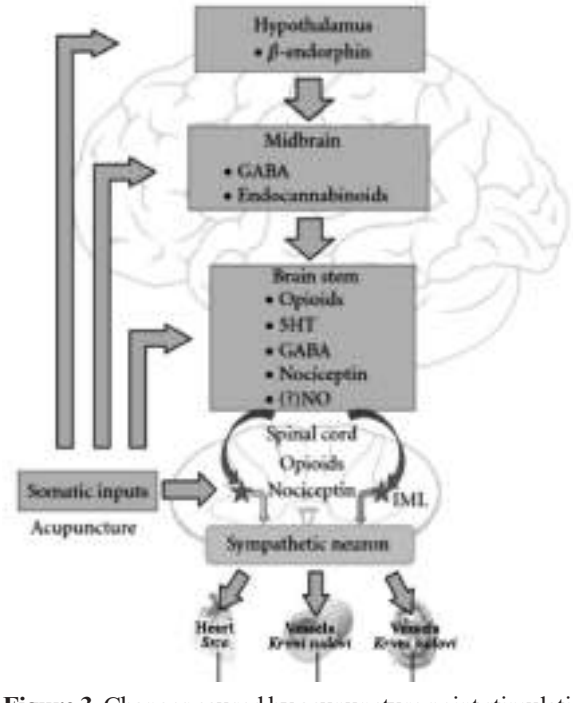

Figure 3. Changes caused by acupuncture point stimulation
Slika 3. *Promene koje nastaju stimulacijom akupunkturne tačke*
Delaney, S. The Science of Why Acupuncture Relieves Pain & Makes You Feel Great! [Internet]. West Street Wellbeing. 2019 [cited 2023 Sep 16]. Available from: https://www.weststreetwellbeing.com.au/the-science-of-why-acupuncture-relieves-pain-makes-you-feel-great/

the information from the upper cerebral centers and releases neurotransmitters norepinephrine and serotonin, thus inhibiting pain by the descending pathway. In addition, stimulating the acupuncture spots, PAG influences the hypothalamic-pituitary-adrenal axis, which, in addition to having a neuroendocrine effect, also leads to the release of endogenous peptides: endorphins, enkephalins and dynorphins. These endogenous opioids have neurotransmitter and neuromodulatory effects on the three types of receptors - μ, δ, κ, and help produce analgesia [23–25].

In the research Pomeranz and Chin conducted on mice, they examined the effect of acupuncture in reducing acute pain. The reduction of pain was greater in the group where acupuncture needles were placed on specific acupuncture spots than in the group where needles were placed on non-acupuncture spots. The analgesic effect of acupuncture was blocked by opioid antagonist naloxone, which confirms that the analgesic effect is produced by releasing endogenous opioids [26].

Analgesic effects of acupuncture on cerebral function have been confirmed by using functional magnetic resonance imaging (fMRI) and positron emission tomography scans. While painful stimuli were induced and acupuncture was performed to treat the acute pain, the fMRI showed a reduction in activity in specific pain-related cerebral areas [27, 28].

Acupuncture as an additional analgesic method

The Enhanced Recovery After Surgery (ERAS) Society has published several clinical practice guidelines designed to improve perioperative care and enhance postoperative recovery [29]. One of the main aspects of ERAS is using multimodal analgesia in pain treatment by reducing the use of opioids and their side effects [30].

Lately, the number of clinical trials that examine the efficacy of acupuncture as an additional method of analgesia during general or regional anesthesia and postoperative pain treatment is increasing. Accumulated evidence from clinical trials and updated reviews confirm the beneficial effects of acupuncture in reducing the need for opioids and consequently its side effects, which makes it a promising approach in perioperative management, especially with respect to ERAS. Further efforts need to be made to optimize the clinical application of perioperative acupuncture [31–34].

The study conducted by Sahmeddini et al. on 90 patients showed a positive effect of electroacupuncture on pain reduction after nasal septoplasty. The control group underwent sham acupuncture. The intensity of postoperative pain was similar in both groups, but nausea and vomiting occurred significantly less in the acupuncture group [35]. Another study that included 60 patients who had sinus surgery and were treated by transcutaneous electric acupuncture stimulation (TEAS) 30 minutes before the surgery, showed that the TEAS procedure reduced the intraoperative consumption of remifentanil by 39%. It also showed reduced time until extubation and a decrease in anesthesia-related side effects [36].

Sun et al. meta-analysis included 15 studies that assessed the intensity of postoperative pain where acupuncture was performed after different types of surgery. 608 patients of the total number of 1166 had acupuncture to reduce postoperative pain. The acupuncture techniques included manual needle acupuncture, moxibustion, transcutaneous electroacupuncture, and acupressure. Meta-analysis showed that the pain intensity measured by the visual-analog pain scale was significantly reduced in the group that had acupuncture. Researchers discovered that acupuncture was correlated with the reduction of cumulative opioid analgesic consumption in the postoperative period. Relative reduction of opioid consumption with acupuncture stimulation was 21% eight hours after surgery, 23% after 24 hours, and 29% after 72 hours [37].

The use of electroacupuncture in ERAS had great effects in the perioperative period, and it is believed that it will have a significant role in rehabilitation and treatment in the future [38–41].

Conclusion

According to data from the literature and the latest clinical research, encouraging results were obtained that acupuncture can be used as an additional analgesic method in the perioperative period. The use of acupuncture reduces the dose of analgesics, opioids and non-steroidal anti-inflammatory drugs. It enables patients to wake up faster from anesthesia, reduce postoperative nausea and vomiting, achieve better intestinal motility, faster mobilization of the patient and reduce treatment costs. Despite the fact that there are relevant clinical studies that support the effectiveness of using acupuncture in the perioperative period, what is missing is: standardization of the application of acupuncture, type of surgery where the best therapeutic effects of acupuncture are achieved, how to apply it and at what time intervals in order for acupuncture to provide much more effective analgesia.

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2. Originalni članci – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

3. Pregledni članci – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

4. Prethodna ili kratka saopštenja – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

5. Stručni članci – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

Priprema rukopisa

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings, MeSH.*

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

3. Tekst članka

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.