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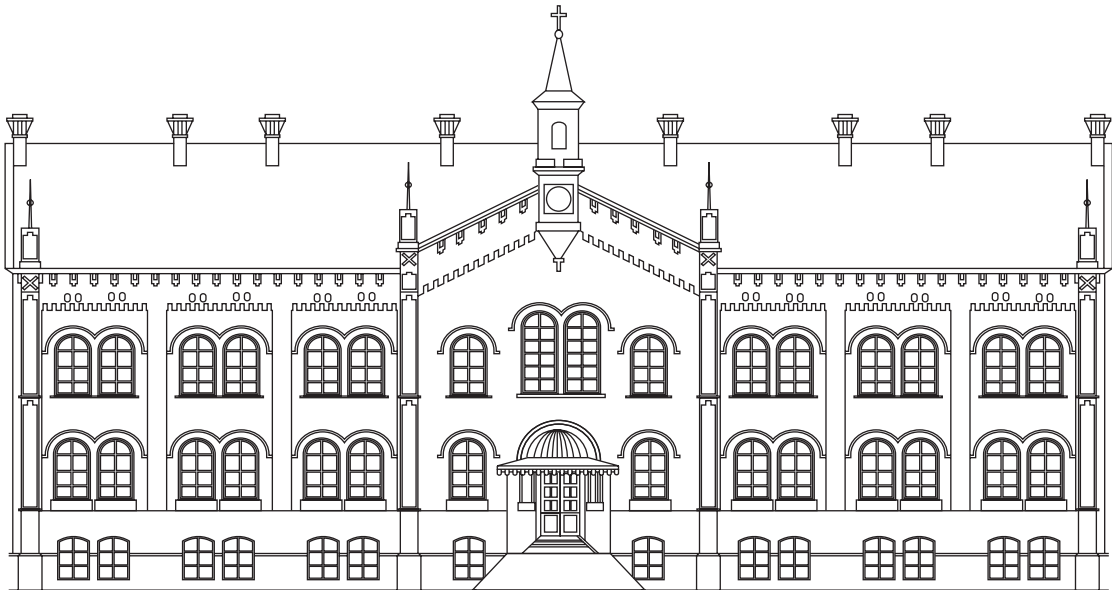
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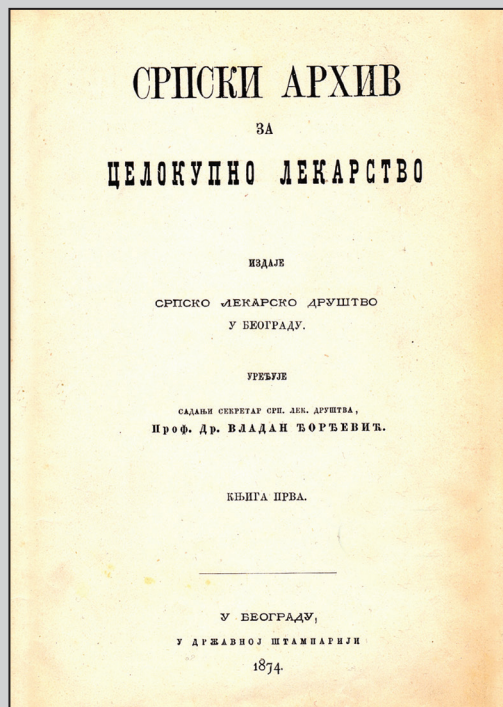


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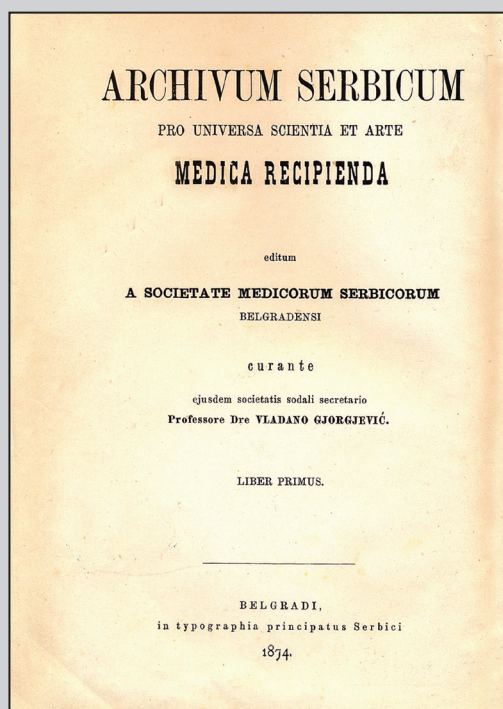
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Прва страна првог броја часописа на српском језику



The title page of the first journal volume in Latin

Српски архив за целокупно лекарство је часопис Српског лекарског друштва основаног 1872. године, први пут штампан 1874. године, у којем се објављују радови чланова Српског лекарског друштва, претплатаника часописа и чланова других друштава медицинских и сродних струка. Објављују се: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике и регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози.

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EDITORIAL / УВОДНИК



My Dear and Honorable Colleagues,

For us in the Serbian Archives of Medicine the beginning of a calendar year is a time to thank both our authors and reviewers. We apologize to authors whose manuscripts have been rejected in the previous year, but we hope that the reviews they have received, although sometimes painful, will encourage them to improve their research and writing skills. We hope this will, in return, enable them to publish their results in journals that are more prestigious than ours is.

We owe special thanks to the reviewers for their invaluable time and suggestions. Furthermore, we are grateful to those who have exchanged messages with the editors. To those very few who remained silent, we suggest to follow the Serbian Archives of Medicine in this 148th year of publication to find out the destiny of the manuscript they missed to review.

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| 261. | Rakić Snežana | 311. | Stojković Mirjana | 359. | Živaljević Vladan |
| 262. | Ranin Lazar | 312. | Stojković Siniša | 360. | Živković Rade |
| 263. | Ranković Janevski Milica | 313. | Stojšić Mirjana | 361. | Živković Slavoljub |
| 264. | Ristanović Momčilo | 314. | Stojšin Ivana | 362. | Živković Vladimir |
| 265. | Ristić Arsen | 315. | Stokić Edita | 363. | Žorić Lepša |
| 266. | Ristić Gorica | 316. | Subotić Dragan | 364. | Žugić Vladimir |
| 267. | Roby-Brami Agnès | 317. | Svetel Marina | 365. | Žuvela Marinko |
| 268. | Romić Predrag | 318. | Svorcan Petar | | |
| 269. | Ruscitti Piero | 319. | Šaponjski Jovica | | |

There is a global medical issue, which should be addressed in the best interest of clinicians of different specialties and at different phases of their training and practices. This is burnout, work-related syndrome, which nowadays reached an epidemic level, and therefore has been recognized by World Health Organization [1, 2]. Burnout does not affect physicians exclusively, it affects nurses and medical care providers as well [3, 4]. Those experiencing burnout may develop sleep disturbances, depression, alcoholism, musculoskeletal disorders, hypertension, and even ischemic heart disease.

The burnout of physicians was first described in the 1970s as syndrome of emotional exhaustion, depersonalization, and a sense of low personal accomplishment that leads to decreased effectiveness at work [5]. Burnout was investigated with emphasis on psychological presentation and management [6, 7]. The estimated prevalence of the phenomenon was reported to be 30–50% [8]. The latest report of Ganeshan et al. [9] of an online survey sent to the U.S. academic radiologists with a response rate of 27% (228/831) and estimated prevalence of burnout of 79% illustrates the magnitude of the problem. They found that the work overload, inability to balance personal and professional life, lack of autonomy, lack of appreciation from patients and other medical staff were significantly associ-

ated with high burnout. Are our clinicians exposed to those risk factors as well?

In general, medicine has made progress in the last decade, which has proven to be a challenge for health care providers and administrations everywhere [10, 11]. Medicine in Serbia has been making efforts to keep pace with the global one. Therefore, in recent years, changes have been taking place in our medical care including regulatory changes, a wide use of electronic health records, etc., but one should bear in mind that Serbia is a low-income country. Taking into consideration the 800-year-long history of Serbian medicine on one hand, and the global experiences on the other, I am sure that we will find our way to protect our profession and colleagues for the benefit of our patients.

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Editor-in-Chief

Prof. Gordana Teofilovski-Parapid, M.D., Ph.D.
Honorary President, International Committee of
Symposia on Morphological Sciences
President, European Federation for Experimental
Morphology
University of Belgrade, Faculty of Medicine
gordana.teofilovski.parapid@srpskiarhiv.rs

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The influence of the final irrigation protocol on the efficiency of root canal cleaning

Jelena Nešković¹, Neda Ninković¹, Vanja Opačić-Galić¹, Milica Jovanović-Medojević¹, Marijana Popović-Bajić¹, Miloš Maksimović², Slavoljub Živković¹

¹University of Belgrade, School of Dental Medicine, Department of Restorative Dentistry and Endodontics, Belgrade, Serbia;

²University of Belgrade, School of Dental Medicine, Department of Prosthodontics, Belgrade, Serbia

SUMMARY

Introduction/Objective Irrigation has an important role in root canal cleaning and its efficiency depends on the type of irrigants, the amount, the technique and the irrigation protocol.

The aim of this work was to estimate the efficiency of cleaning of the canal walls by using scanning electron microscope analysis after the instrumentation by rotary NiTi instruments with the use of three different irrigation solutions and two final irrigation protocols.

Methods Sixty extracted human incisors were divided into two groups after the rotary instrumentation with the iRace instruments. In both groups, the same amount (1.5 ml) of three solutions (2% sodium hypochlorite solution, 2% chlorhexidine solution, and 10% citric acid solution) and total final irrigation time (90 seconds) was the same. The final irrigation in the first group was accomplished using the technique of continuous irrigation and in the second group it was done using the intermittent protocol. The roots were cut longitudinally and analyzed by thirds (coronal, middle, and apical) on a scanning electron microscope (JSM 6460LV, JEOL Ltd., Tokyo, Japan) with 1,000× magnification.

Results The most efficient cleaning of the root canal walls in both groups was seen after the use of citric acid with the intermittent protocol of the final irrigation (90.7% clean walls), while the least efficient was the final irrigation by chlorhexidine with continuous irrigation (80.3%). The most efficient cleaning of the canal walls in both groups was observed in the coronal third and the largest amount of the smear layer in the apical third.

Conclusion The most efficient cleaning of the canal was achieved by the use of citric acid and the intermittent protocol of the final irrigation. In all tested solutions, the intermittent protocol of irrigation was more efficient than continuous irrigation.

Keywords: final irrigation protocol; irrigants; smear layer removal

INTRODUCTION

The success of endodontic treatment significantly depends on the possibility of complete elimination of microorganisms from the root canal, and prevention of reinfection of periapical tissue. Microcomputer tomographic studies have shown that a large part of the surface of the main canal remains untouched by instruments, and in the case of the presence of isthmuses, ramifications and lateral canals, this percentage ranges 30–50% indicating the extreme importance of irrigation in the cleaning and disinfection of the root canal system [1, 2].

Preparation of the root canal manually and particularly by rotating Ni-Ti instruments, leads to the formation of dentine debris and a smear layer, which are most often accumulated in the uninstrumented parts of the root canal system [3]. The smear layer prevents adequate adherence of a sealer to the walls of the root canal and can be a potential area for the growth of numerous bacteria, but also prevent antibacterial agents from reaching the residual bacteria in the dentinal tubules [4, 5]. Mechanical instrumentation eliminates the largest number of bacteria, but

maximum reduction of the number of microorganisms organized into biofilms demands an irrigant with good antibacterial effect and adequate irrigation techniques [6, 7, 8].

Irrigation of the canal whose efficiency depends on the type of irrigant, quantity, technique and the protocol of irrigation, is of crucial importance for the efficient cleaning of the complex root canal system [9, 10, 11]. Optimal irrigation today involves the use of two or more solutions and the application of appropriate protocols in order to increase its efficiency [6].

The most commonly used solution for irrigation in endodontics is NaOCl due to its strong antibacterial and exceptional soluble effect, despite the toxicity for periapical tissues [11, 12]. Chlorhexidine is also used because of the extraordinary and prolonged antibacterial effect and the absence of cytotoxicity [12, 13]. Chelating agents, EDTA (tetrasodium ethylenediaminetetraacetic acid), and citric acid effectively dissolve inorganic substances and thus significantly contribute to the removal of the smear layer [14, 15]. The precondition for the success of the endodontic treatment is clean dentinal walls of the root canal without the

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Correspondence to:

Jelena NEŠKOVIĆ
School of Dental Medicine
University of Belgrade
4 Rankeova St.
Belgrade 11000
Serbia
jelenaneskovic74@gmail.com

presence of a smear layer and debris to allow best sealing and adhesion of the sealer [16, 17].

Contemporary irrigation also involves different activation protocols in order to improve the efficiency of the irrigant. Studies have confirmed that passive ultrasonic irrigation (PUI) is more effective than the conventional one [15, 18, 19, 20], and De Moor et al. [18] found that PUI in three cycles is equally effective in debris removal as well as laser-activated NaOCl solution. Leoni et al. [20] found that the XP Endo Finisher is as effective as PUI, and they also showed that activated irrigation is significantly more efficient in cleaning the root canal than conventional irrigation.

The objective of this study was to evaluate the efficiency of cleaning root canal walls after instrumentation by rotary Ni-Ti instruments and application of three different irrigation solutions and two final irrigation protocols using scanning electron microscope (SEM) analysis.

The hypothesis of this study was that the final three-step irrigation (intermittent protocol) provides more efficient cleaning of the root canal system than the conventional irrigation protocol.

METHODS

The study was conducted on 60 extracted human incisors, which were stored up to experiments in a 0.01% solution of NaOCl at a temperature of 4°C. The crowns of the teeth were cut off so that each root sample was 15 mm long.

After the formation of the access cavity, the initial penetration of the root canal was established by K-file #10. The working length was determined to be 1 mm shorter than the apical foramen, i.e. 14 mm. At the top of each root, a pink wax ball was placed in order to prevent the irrigation solution leaking during the instrumentation. The instrumentation of all canals was carried out by one researcher. After adjusting the working length by a hand instrument and before starting the instrumentation, the canal was irrigated with 2 ml of 1% solution of NaOCl.

Mechanical preparation of all canals was performed by NiTi rotating instruments iRace (FKG Dentaire SA, La Chaux-de-Fonds, Switzerland) using three instruments: R1 #15/06, R2 #25/04, and R3 #30/04. After each instrument, the canals were irrigated with 2 ml of 1% NaOCl solution with 2 ml plastic syringes and gauge 27 needles. After each use of an instrument, irrigation was carried out in the manner described so that the total amount of the irrigant used during preparation for each sample was 8 ml of 1% NaOCl solution.

After the instrumentation of the canals, samples were randomly selected in two groups of 30 teeth, where the final irrigation was carried out in group 1 by a continuous protocol, while in group 2 an intermittent final irrigation protocol was used. In both groups, three solutions were used in the same amount (1.5 ml each) and total final irrigation time (90 seconds): 2% solution of sodium hypochlorite (Chloraxid, 2%, Cerkamed, Stalowa Wola, Poland); 2% solution of chlorhexidine (Glucohex, 2%, Cerkamed), and 10% citric acid solution was obtained by diluting 40% citric acid solution (citric acid, 40%, Cerkamed).

Group 1 – in the first group, the final irrigation was performed by the continuous flushing protocol in the amount of 1.5 ml of irrigant for the duration of 90 seconds. Ten teeth were irrigated with 1.5 ml of 2% solution of sodium hypochlorite. The amount of 1.5 ml of 2% chlorhexidine solution was used for each of the following 10 teeth, and the last 10 teeth from this group were irrigated with 1.5 ml of 10% citric acid solution.

Group 2 – in the second group, the final irrigation was carried out according to an intermittent flushing protocol of 3×0.5 ml of irrigant for a period of 3×30 seconds. Each subgroup of 10 teeth was irrigated with following solutions: 3×0.5 ml 2% solution of sodium hypochlorite for 3×30 sec, 3×0.5 ml 2% chlorhexidine solution for 3×30 sec, and 3×0.5 ml of 10% citric acid solution for 3×30 sec.

The roots were longitudinally cut with a diamond disc (so that the root canal remains intact) separated with sharp spatula into two halves. The halves obtained in this way were prepared for SEM analysis (JSM 6460LV, JEOL, Tokyo, Japan). A total of 120 samples were dried and filled with gold and scanned by an electron microscope. For each sample, five standardized microphotographs were made for coronal, middle, and apical thirds at magnification of 1,000 \times . SEM microphotographs were independently analyzed and appraised by two researchers. In the event of disagreement, the ratings were reconsidered until a consensus was reached.

The criteria set by Hülsmann et al. [21] were used to qualitatively estimate the residual smear layer, according to the cleaning efficiency:

Score 1 – the root canal wall is without a smear layer, all dentinal tubules are open;

Score 2 – a small quantity of a residual smear layer and most of the dentinal tubules are open;

Score 3 – a homogeneous smear layer covers the walls, a few dentinal tubules open;

Score 4 – the entire wall of the root canal is covered with a smear layer, there are no open tubules;

Score 5 – a non-homogeneous smear layer covers the entire surface of the root canal.

The scoring implies that grades 1 and 2 represent a clear root canal wall, and the wall with a smear layer includes grades 3, 4, and 5.

The obtained result was statistically processed in IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA) using the descriptive statistics method and the χ^2 test.

The study was approved by the Ethics Commission of the School of Dental Medicine, University of Belgrade (36/6).

RESULTS

The results of the SEM analysis are shown in Tables 1 and 2 and Figures 1–4.

In the group with a continuous final irrigation protocol when NaOCl was used as the irrigant, the lowest average value of the assessment of the smear layer presence was observed in the coronal third (1.6), then in the middle (1.7), while the weakest cleaning was recorded in the apical

Table 1. Mean value of the assessment of the residual smear layer on root canal walls by thirds

Groups		Solution for irrigation	Third of root canal	Smear layer rating					
				n	\bar{x}	SD	Med	Min.	Max.
Final irrigation	Group 1 continuous protocol	NaOCl	coronal	100	1.60	0.67	1.5	1	3
			middle	100	1.70	0.73	2	1	4
			apical	100	2.14	1.16	2	1	5
		Chlorhexidine	coronal	100	1.62	0.66	2	1	3
			middle	100	1.76	0.79	2	1	4
			apical	100	2.26	1.21	2	1	5
		Citric acid	coronal	100	1.5	0.58	1	1	3
			middle	100	1.64	0.69	2	1	3
			apical	100	2.04	1.08	2	1	5
	Group 2 intermittent protocol	NaOCl	coronal	100	1.54	0.61	1	1	3
			middle	100	1.66	0.62	2	1	3
			apical	100	2.06	0.99	2	1	4
		Chlorhexidine	coronal	100	1.62	0.66	2	1	3
			middle	100	1.66	0.65	2	1	3
			apical	100	2.11	1.03	2	1	4
		Citric acid	coronal	100	1.52	0.61	1	1	3
			middle	100	1.52	0.61	1	1	3
			apical	100	1.76	0.71	2	1	3

n – number of teeth; \bar{x} – mean value; SD – standard deviation

Table 2. Assessment of the cleaning efficiency of root canal walls regarding the final irrigation solution and applied irrigation protocol

Final irrigation protocol				Continuous irrigation		Intermittent irrigation	
Assessment of the presence of the smear layer				Clean walls Score 1, 2	Smear layer present Score 3, 4, and 5	Clean walls Score 1, 2	Smear layer present Score 3, 4, and 5
NaOCl	SEM analysis	Coronal third	n	90	10	94	6
			%	90	10	94	6
		Middle third	n	88	12	92	8
			%	88	12	92	8
		Apical third	n	71	29	72	28
			%	71	29	72	28
Chlorhexidine	SEM analysis	Coronal third	n	249	51	258	42
			%	83%	17%	86%	14%
		Middle third	n	90	10	90	10
			%	90	10	90	10
		Apical third	n	86	14	90	10
			%	86	14	90	10
Citric acid	SEM analysis	Coronal third	n	65	35	69	31
			%	65	35	69	31
		Middle third	n	241	59	249	51
			%	80.3%	19.7%	83%	17%
		Apical third	n	96	4	94	6
			%	96	4	94	6
		Coronal third	n	88	12	94	6
			%	88	12	94	6
		Middle third	n	72	28	84	16
			%	72	28	84	16
		Apical third	n	256	44	272	28
			%	85.3%	14.7%	90.7%	9.3%

SEM – scanning electron microscope

third (2.14) (Table 1). Slightly higher mean values of the evaluation of the smear layer was observed after the application of chlorhexidine, mostly in the apical (2.26), then in the middle (1.76), and the coronal third (1.62). The most effective cleansing was observed in the group with citric acid [in the coronal third (1.5), in the middle one (1.64),

and the least effective cleaning was noted in the apical third (2.04)] (Table 1).

In the group with an intermittent protocol of final irrigation, the mean values of the presence of the residual smear layer were slightly lower in regard to the first group. After using NaOCl, the lowest mean was in the coronal third

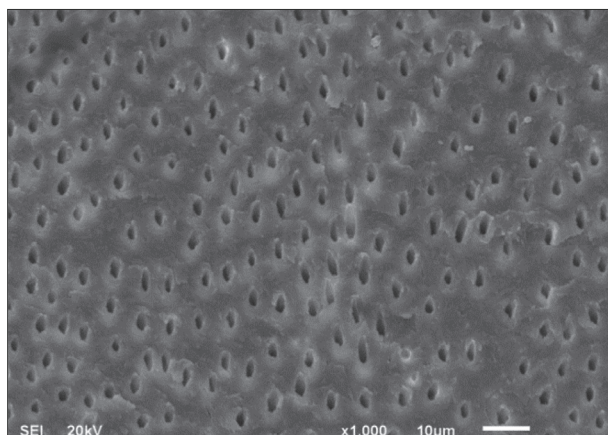


Figure 1. Representative microphotography of the coronal third (citric acid, intermittent protocol) (score 1) – scanning electron microscope, magnification $\times 1,000$

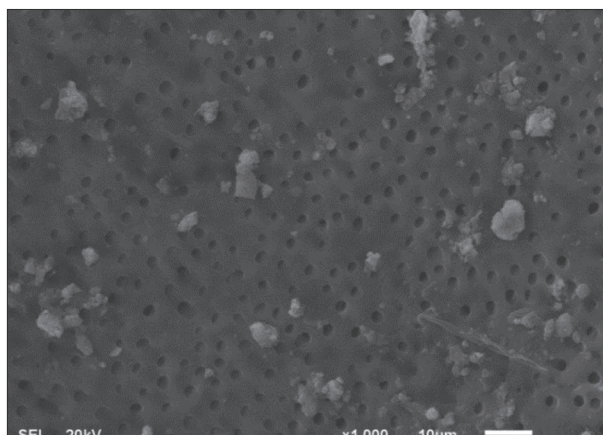


Figure 2. Representative microphotography of the middle third (NaOCl, intermittent protocol) (score 2) – scanning electron microscope, magnification $\times 1,000$

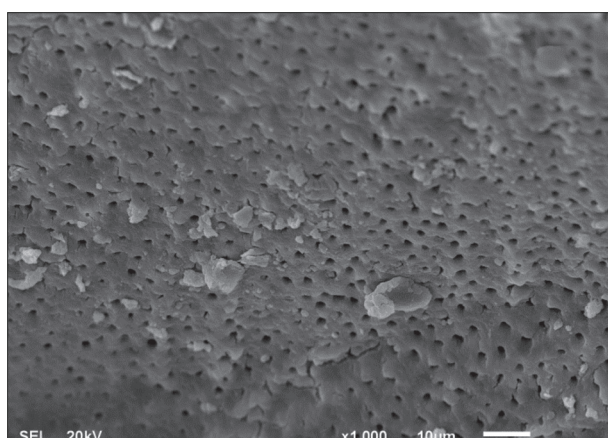


Figure 3. Representative microphotography of the apical third (citric acid, intermittent protocol) (score 2) – scanning electron microscope, magnification $\times 1,000$

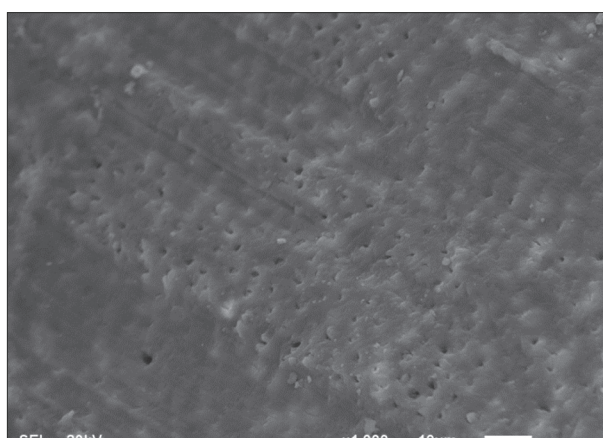


Figure 4. Representative microphotography of the apical third (chlorhexidine, intermittent protocol) (score 3) – scanning electron microscope, magnification $\times 1,000$

(1.54), followed by the middle one (1.66), and the highest value was in the apical third (2.06). When chlorhexidine was used as a final irrigant, the highest mean value was observed in the apical (2.11), slightly lower value was in the middle (1.66), and the lowest mean value was on the walls of the coronal third (1.62). The smallest amount of the residual smear layer was observed in the group with citric acid, the same average value was in the coronal and the middle third (1.52), and the weakest cleaning was in the apical third (1.64) (Table 1).

The analysis of the cleaning efficiency of root canal walls showed that each irrigant was more efficient with the protocol of intermittent final irrigation, with no statistically significant difference. After using NaOCl, 83% of clean walls in group 1 were detected, while 86% of clean walls were recorded in the second group. Less efficient cleaning was observed after the application of chlorhexidine, 80.3% of clean walls with continuous protocol, 83% of clean walls with the intermittent protocol. The most effective cleaning was observed after the final irrigation with citric acid using the intermittent irrigation protocol (90.7%), and slightly weaker in the group with continuous irrigation (85.3%) (Table 2).

The most effective cleaning of the root canal walls in both groups was observed after the application of citric acid with the intermittent final irrigation protocol (90.7% clean walls), while the final irrigation with chlorhexidine with continuous irrigation (80.3%) was the least effective.

The most efficient cleaning of root canal walls in the first group was observed in the coronal third (92%), followed by the middle third (87.3%), while on the walls of the apical third there was the largest amount of residual smear layer (69.3%) (Table 2).

By analyzing the effectiveness of wall cleaning in the second group, the largest amount of smear layer was observed on the walls of the apical third of the root (75% clean walls) (Figures 3 and 4), followed by the middle third (92%), while most of the dentinal tubules were open in the coronal thirds (92.7%) (Table 2).

DISCUSSION

Root canal instrumentation produces a smear layer on all instrumented surfaces of the root canal walls, while the uninstrumented areas of the canal system (isthmuses, lateral

canals, anastomoses between the canals, etc.) are usually occluded by debris. Although there are studies showing that the presence of the smear layer does not affect the outcome of endodontic treatment [16], most studies confirm that its presence prevents penetration of intracanal medications into the dentinal tubules and reduces the adhesion, so it is necessary to remove it before definitive obturation [1, 4, 17].

Earlier investigations used light microscopy to identify the smear layer on the canal walls, but today SEM analysis is the standard in the field of quantitative and qualitative estimation of the presence of the smear layer due to high resolution and high magnification [22–25].

One of the tasks of irrigation is to clean dentinal walls by removing the smear layer and debris and to reduce the number of microorganisms, i.e. to improve the adhesion of the sealer and thus minimize microleakage [6, 17]. The efficiency of irrigation depends on a number of factors, and above all on the type, quantity, concentration, time of exposure of the walls to the effect of irrigant and irrigation techniques [3, 7, 11, 12, 20, 22].

The complete instrumentation of the canal in this study was performed by one operator, on simple single root teeth, and all canals were instrumented in the same way with the same quantity of irrigant and the same total duration of irrigation, but with two different final irrigation protocols (continuous and intermittent irrigation) with three different irrigants.

The results of this study show that the mechanical instrumentation with rotating Ni-Ti files followed by extensive irrigation ensures efficient cleaning of the canal walls with a small amount of smear layer present on the walls.

Since no statistical significance was found, the hypothesis of this study is rejected, yet slightly better cleaning of the canal walls in all three thirds was observed after the intermittent final irrigation protocol in three steps in comparison with the convectional continuous irrigation. This is in accordance with the findings of other authors who have showed that increasing the number of irrigation cycles increases the cleaning capacity as the amount of fresh solution is restored, while in the case of continuous irrigation, the saturation of the solution occurs faster [7, 11, 25, 26]. Živković et al. [25] have determined that the protocol of the final irrigation in three cycles improves the efficacy of removing the smear layer in the apex segment of the root canal, and Macedo et al. [26] showed that the irrigation protocol in three cycles of fresh NaOCl solution increases its cumulative effect and thus the efficacy of cleaning root canal walls.

Such good results can be explained by the fact that instrumented canals were straight and simple, and adequate diameters of apical preparation (30/04) ensures that the tip of the irrigation needle will reach almost the working length of the instrumentation and in this way effectively clean the walls of the root canal. It also explains very good results for chlorhexidine, which, unlike NaOCl and citric acid, does not have the ability to dissolve tissues, but it is used because of a wide antibacterial spectrum (including

Enterococcus faecalis) and prolonged antimicrobial effect [8, 12, 13, 23].

Citric acid showed the best cleaning effects (in both groups). This chelating agent is equally effective in removing the smear layer as well as the EDTA according to the findings of Lenarda et al. [14]. This mineralolitic perfectly dissolves inorganic material and significantly affects the removal of the smear layer from root canal, although it does not have antibacterial properties [9, 15].

The worst cleaning of dentinal walls in both groups is observed in the apical third of the root canal, then in the middle, while the smallest amount of the smear layer is noticed in the coronal third of both groups, which is in compliance with the results of other studies confirming that the smear layer from the canal walls is more easily removed from the coronal and middle third [9, 10, 21, 26]. The cleansing problem is particularly emphasized in the region of the apical third due to anatomical specificity (isthmuses, ramification, additional canals), and due to the small diameter of the apical preparation, which makes the debridement of the canal more difficult [3, 5, 7, 25].

So far, research has shown that none of the irrigation protocols or tested solutions are able to completely clean root canal walls by removing the smear layer, and nowadays some kind of activation of the irrigation solution during the irrigation process is recommended [6].

Currently, passive ultrasonic irrigation (PUI) has an important role in the activation of irrigants, and its activity is based on cavitation and acoustic streaming of solutions during irrigation. Numerous studies have shown that PUI increases the effect of irrigation by removing more organic tissue, planktonic forms of bacteria, and debris from canal walls. [15, 18, 19, 20, 26].

Laser-activated irrigation is also very effective, but De Moor et al. [18] have found that PUI in three cycles is equally effective in the removal of debris as well as the laser-activated NaOCl solution.

Research has shown that XP-endo Finisher, which is used for the final debridement of the root canal, due to its specific design and extreme flexibility (it changes shape during instrumentation), can reach the inaccessible parts of the canal system [7, 20, 24].

Kato et al. [27] examined Easy Clean (Easy Dental Equipment, Belo Horizonte, MG, Brazil), new mechanical irrigant agitating device, powered by the reciprocating or continuous rotation, and indicated that Easy Clean in reciprocating motion is more efficient in cleaning the apical third of the curved canals compared to the PUI. Duque et al. [28] compared the effectiveness of Easy Clean in continuous and reciprocating motion, PUI, Endoactivator systems (Dentsply Maillefer, Ballaigues, Switzerland), and convectional irrigation for debris removal from the root canal and isthmus, and found that Easy Clean used in continuous rotation provides better cleaning of the canal and isthmus. They also concluded that protocol of three irrigating solution activations for 20 seconds ensures better cleaning.

CONCLUSION

The most efficient solution for final irrigation after root canal preparation with rotary iRaCe instruments, in this study was 10% citric acid, while the least effective one was chlorhexidine.

Under the conditions and limitations of this research, it can be concluded that root canal instrumentation by rotary

instruments followed by the final irrigation was efficient in smear layer removal from root canal walls. An intermittent irrigation protocol in three steps showed slightly more efficient cleaning of root canal walls compared to continuous irrigation.

Conflict of interest: None declared.

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Утицај протокола финалне иригације на ефикасност чишћења канала корена

Јелена Нешковић¹, Неда Нинковић¹, Вања Опачић-Галић¹, Милица Јовановић-Медојевић¹, Маријана Поповић-Бајић¹, Милош Максимовић², Славољуб Живковић¹

¹Универзитет у Београду, Стоматолошки факултет, Клиника за болести зуба и ендодонцију, Београд, Србија;

²Универзитет у Београду, Стоматолошки факултет, Клиника за стоматолошку протетику, Београд, Србија

САЖЕТАК

Увод/Циљ Иригација има важну улогу у чишћењу канала корена, а њена ефикасност зависи од врсте ириганса, количине, односно технике и протокола иригације.

Циљ овог рада био је да се анализом СЕМ процени ефикасност чишћења зидова канала после инструментације ротирајућим *NiTi* инструментима уз примену три различита раствора за иригацију и два протокола финалне иригације.

Методе Шездесет екстрахованих хуманих секутића је после машинске инструментације *iRaSe* инструментима подељено у две групе. У обе групе су коришћена по три раствора – 2% раствор натријум-хипохлорита, 2% раствор хлорхексидина и 10% раствор лимунске киселине, у истој количини (1,5 ml) и укупном времену финалне иригације (90 секунди). Финална иригација у првој групи је реализована техником континуиране, а у другој техником интермитентне иригације. Коренови су пресечени уздужно и анализирани по трећинама (крунична, средња и апикална) на скенирајућем

електронском микроскопу (*JSM 6460LV JEOL*, Токио, Јапан) на увећању од 1000х.

Резултати Најефикасније чишћење зидова канала корена у обе групе уочено је после примене лимунске киселине уз интермитентни протокол финалне иригације (90,7% чистих зидова), док је најмање ефикасна била финална иригација хлорхексидином уз континуирану иригацију (80,3%). Најефикасније чишћење зидова канала и у првој и у другој групи уочено је у круничној трећини, а највише размазног слоја у апикалној трећини.

Закључак Најефикасније чишћење канала остварено је применом лимунске киселине и интермитентног протокола финалне иригације. Код свих тестираних раствора интермитентни протокол иригације је био нешто ефикаснији од протокола континуиране иригације.

Кључне речи: протокол иригације; финална иригација; размазни слој

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prevalence of developmental dental anomalies in Serbian orthodontic patients

Evgenija Marković¹, Ana Vuković², Tamara Perić², Jovana Kuzmanović-Pfićer³, Bojan Petrović⁴¹University of Belgrade, School of Dental Medicine, Clinic of Orthodontics, Belgrade, Serbia;²University of Belgrade, School of Dental Medicine, Clinic for Pediatric and Preventive Dentistry, Belgrade, Serbia;³University of Belgrade, School of Dental Medicine, Department of Medical Statistics and Informatics, Belgrade, Serbia;⁴University of Novi Sad, Faculty of Medicine, Department of Pediatric and Preventive Dentistry, Novi Sad, Serbia**SUMMARY****Introduction/Objective** The aim of this study was to evaluate the prevalence of developmental dental anomalies (DDA) in Serbian orthodontic patients.**Methods** The sample was composed of 1,001 panoramic radiographs of orthodontic patients, older than seven years, taken as a part of the initial diagnostic procedure at the Clinic of Orthodontics, School of Dental medicine in Belgrade. The DDA that could be diagnosed accurately on panoramic X-rays were documented. Descriptive analysis was used to determine prevalence and sex distribution of DDA. The Pearson χ^2 test and Fisher's exact test were used to compare number of affected teeth in males and females (level of significance was 95%).**Results** The prevalence of DDA in Serbian orthodontic patients was 34.8% (15.5% males and 19.3% females). Impactions were present in 16.5%, hypodontia in 12.9%, hyperdontia in 4.4%, microdontia in 2.9%, macrodontia in 1.8% and transposition in 0.8% of patients. Maxillary canines were the most frequently impacted teeth. Maxillary second molars were more prone to impaction in females ($p < 0.05$). Impacted incisors were more prevalent in maxilla, premolars, and second molars in mandible. The most commonly missing teeth were upper left second premolars. Mesiodens was the most frequently found supernumerary tooth.**Conclusion** We reported a high a rate of DDA in Serbian orthodontic patients, more in females than males. The most frequently observed DDA were impaction, tooth agenesis, hyperdontia, microdontia, macrodontia, and transposition. All investigated DDA were more frequently present in females, except hyperdontia. Current findings could offer a foundation for epidemiological studies on DDA prevalence.**Keywords:** developmental dental anomalies; orthodontics; hypodontia**INTRODUCTION**

Developmental dental anomalies (DDA) occur during the period of teeth development. The etiology is complex and multifactorial. It involves genetic and environmental influences, as well as variation in sex distribution. DDA are presented as irregularities in tooth number, size, shape, and structure, and altered teeth eruption. The complexity of tooth development is influenced by over 300 genes, mutations, and/or localized or generalized insults (trauma, infection, therapeutic irradiation, low birth weight, vitamin D deficiency, metabolic and hormonal disturbances, as well as nutrition and available space in the dental arch). The outcome of these influences could be the presence of isolated or combined DDA in a person [1, 2]. Persons with DDA tend to have orthodontic, functional, and esthetic problems. The early discovery and information of prevalence and association of dental abnormalities with sex and type of teeth are important information for dental practitioners.

Epidemiological studies investigating the prevalence of DDA have been conducted all

over the world with variation in results [3, 4, 5]. Only a few recent studies, mostly on a particular type of DDA, were done in Serbia. Authors investigated the prevalence of hypodontia in Serbian schoolchildren [6, 7]. Two studies reported on the prevalence of structural dental anomalies (amelogenesis imperfecta and molar-incisor hypomineralization [8, 9]. To the best of our knowledge, any other studies investigating more types of DDA in Serbian population have not been conducted.

The aim of this study was to evaluate the prevalence and sex distribution of developmental dental anomalies in Serbian orthodontic patients.

METHODS**Sample**

This retrospective cross-sectional study was comprised of 1,324 panoramic radiographs of patients older than seven years of age referred to the Clinic of Orthodontics, School of Dental

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Clinic for Pediatric
and Preventive Dentistry
Dr Subotića 11
11000 Belgrade, Srbija
ana.vukovic@stomf.bg.ac.rs

Medicine, University of Belgrade from all over Serbia. Digital panoramic radiographs were taken as a part of the initial diagnostic examination in 2016. Only high-quality films of patients with no craniofacial abnormalities and syndromes associated with DDA (including cleft lip and palate), previously extracted permanent teeth, a trauma in the orofacial region, and previous orthodontic treatment with fixed appliances, were included in the sample. Consequently, a sample comprised of 1,001 panoramic radiographs (459 male and 542 female patients). Experienced orthodontist and pedodontist assessed the radiographs. Only tooth abnormalities that could be diagnosed precisely and solely on panoramic X-rays were documented. The DDA with a high probability of poor diagnosis without previous clinical examination and/or additional radiographs were excluded from the evaluation, such as:

- 1) Anomalies of tooth structure – hypomineralization, amelogenesis imperfecta, and molar-incisor hypomineralization (MIH);
- 2) Root deformation and number, concrescence and dilaceration;
- 3) Rotation.

Third molars were excluded from the evaluation due to the high incidence of variation in morphology, size, and position.

We evaluated panoramic radiographs for the following DDA:

- 1) Hypodontia – developmentally missing teeth (tooth agenesis) was diagnosed by counting present teeth when no sign of tooth formation existed. Oligodontia was defined when more than six teeth were missing;
- 2) Hyperdontia (supernumerary teeth) – additional teeth were present on the radiograph. They may be observed as teeth with normal size and shape, or with smaller size and atypical form;
- 3) Mesiodens – supernumerary tooth localized in the anterior region of maxilla;
- 4) Tooth transposition – two adjacent teeth changed their position partially or completely in dental arch [10];
- 5) Microdontia – teeth are smaller than average. Microdontia of maxillary lateral incisor was recorded when the maximum mesiodistal crown diameter was smaller compared to the same dimension of opposing mandibular lateral incisor in the same patient [11];
- 6) Macrodonia was referred to the tooth that was found to be immensely larger than the average one [12];
- 7) Impaction was defined in cases when physical barrier existed, and/or tooth had an orientation that prevented its emergence [13]. Canines were not evaluated for impaction in children younger than ten years of age due to the possibility of misdiagnosis.

Statistical analysis

The statistical analyses were performed using Statistical Package for Social Science, version 22.0 (IBM Corp., Armonk, NY, USA). The descriptive statistical analysis was used to evaluate the prevalence of DDA and sex distribution. Pearson's χ^2 test and Fisher's exact test were used to

compare number of teeth affected by anomalies in males and females. The level of significance was set at $p < 0.05$ with 95% confidence interval.

RESULTS

We analyzed panoramic radiographs and charts of 1,001 orthodontic patients (45.8% males and 54.2% females). At least one dental anomaly was found in 34.8% ($n = 348$) of patients. The distribution of dental anomalies by sex showed that females were more affected than males (19.3% vs. 15.5%). The prevalence of investigated developmental dental anomalies of number, size, and position is presented in Figure 1. The location, number of teeth affected by DDA in the upper and lower jaw and comparison between males and females are presented in Tables 1 and 2.

Abnormalities of tooth number

Tooth agenesis was the most frequent abnormality of tooth number presented in 12.9% ($n = 129$) of all patients (5.5% of males and 7.4% of females). Supernumerary teeth, including mesiodens, were observed in 4.4% ($n = 44$) of subjects (2.4% of males and 2% of females). A total of 2.5% ($n = 25$) patients had mesiodens (2.8% males and 2.2% females). And other kinds of supernumerary teeth were reported in 2.4% of patients. Prevalence of abnormalities of tooth number in male and female orthodontic patients is presented in Figure 2. The most commonly missing tooth was upper left second premolar ($n = 46$ teeth), followed

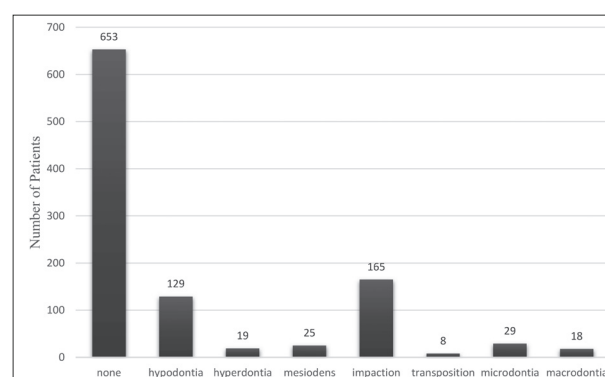


Figure 1. Prevalence of developmental dental anomalies in Serbian orthodontic patients

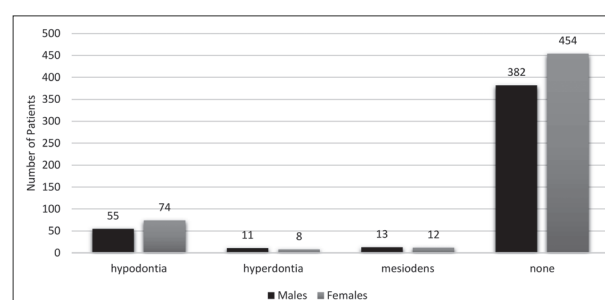


Figure 2. Number of male and female patients with anomalies of tooth number

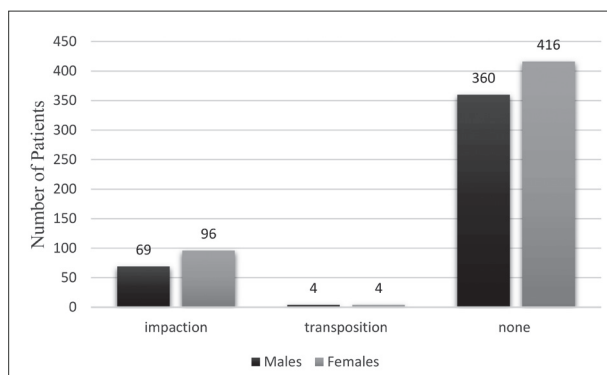


Figure 3. Number of male and female patients with anomalies of tooth position

by upper right and lower right second premolar (37 teeth in both right quadrants). In the anterior region of maxilla, lateral incisors showed the highest prevalence of agenesis ($n = 40$ teeth). We found 17 lateral incisors missing on the left side, and 23 on the right side of maxilla. In the anterior region of the lower jaw, agenesis of incisors was the most frequent finding (21 teeth). First molars were not affected by agenesis. More second molars were missing in the lower jaw compared to the upper jaw (22 vs. 15 teeth). Oligodontia was reported in one female patient (Table 1 and 2).

Abnormalities of tooth position

Tooth impaction was the most frequently found dental abnormality (16.5%). The number of male and female patients with anomalies of tooth position is presented in Figure 3. The high number of impacted canines in the upper arch is documented in current study (107 teeth). We found 49 impacted canines on the right side, and 58 on the left side. Bilaterally impacted canines were present in 24 patients. Only 11 mandibular canines were impacted (five on the right side and six on the left side). More impacted premolars were found in the lower jaw. The only statistically significant difference in the number of teeth affected by DDA between males and females was found in the number of impacted maxillary second molars ($p < 0.05$) (Tables 1 and 2).

Abnormalities of tooth size

The DDA affecting tooth size were present in 4.7% ($n = 47$) of all patients in the sample. Prevalence of microdontia and macrodontia in male and female orthodontic patients is presented in Figure 4. The location, prevalence, and sex distribution of teeth affected by an abnormality in size are presented in Tables 1 and 2.

DISCUSSION

The present study assessed sex distribution and prevalence of selected DDA in the sample of 1,001 orthodontic patients. Numerous studies presented epidemiological data

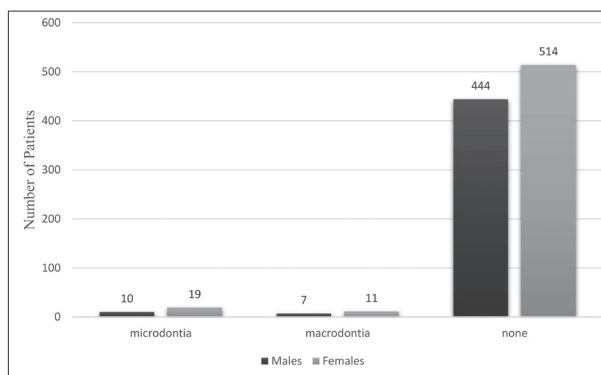


Figure 4. Number of male and female patients with anomalies of tooth size

and prevalence of DDA in either general population or pediatric and orthodontic patients. They vary in selection of methods, sample size, number of included anomalies, and results. The size of our sample was found to be either similar or larger in number of subjects, comparing to recently conducted investigations. Furthermore, the studies with the same purpose, conducted in different parts of the world, reported at least one dental anomaly in 5.4–45.7% of subjects [4, 14–17]. The prevalence of DDA in the present study was 34.8%, which may be because the sample consisted of patients referred to orthodontic treatment. Multifactorial etiology of dental anomalies, ethnical differences, and selection of DDA investigated in the study, inclusion and exclusion criteria contribute to the diversity of results.

Abnormalities of tooth number

Agenesis of one or more teeth could create malocclusions and esthetic and functional problems. Missing teeth were the most frequent abnormality of tooth number in the present sample of Serbian orthodontic patients (12.9%). The overall prevalence of missing teeth in recent studies was 0.027–21.6% [14, 16, 18–22]. Such considerable differences in results could be explained by variation in sample composition and size, ethnicity and methodology. In a systematic review of the literature, Rakhshan and Rakhshan [20] reported a significantly higher number of patients with tooth agenesis in the samples comprised of orthodontic patients, in comparison to the epidemiological samples and samples of dental patients. They argued higher prevalence of anomalies in patients seeking orthodontic treatment. The only two recent epidemiological studies in Serbia found a lower prevalence of missing teeth (6.28% and 5.34%, respectively) in comparison to our results [6, 7]. The high rate of hypodontia in Serbian orthodontic patients in a present study could be due to the nature of sample composition. Patients with the most challenging malocclusions, in need of potentially complicated and multidisciplinary treatment approach are almost automatically referred to the Clinic of Orthodontics. The present finding of more females than males with hypodontia (7.4% vs. 5.5%) supports the documented sex differences in the association between sex and hypodontia, microdontia,

Table 1. Location and prevalence of maxillary teeth affected by developmental dental anomalies. Comparison between males and females. χ^2 test and Fisher's exact test ($p < 0.05$)

Tooth	Sex	Hypodontia		Hyperdontia		p	Impaction		Transposition		p	Microdontia		Macrodontia		p
		n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
17	M	6	1.3	/		0.153	0	0	/		0.005*	/		/		/
	F	2	0.4				9	1.7								
16	M	/		/		/	/		/		/	/		/		/
	F															
15	M	21	4.6	3	0.7	0.332	6	1.6	/		0.796	/		/		/
	F	16	3	2	0.4		9	1.7								
14	M	1	0.2	/		0.382	/		1	0.2	1.000	/		/		/
	F	1	0.2						1	0.2						
13	M	1	0.2	/		1.000	25	5.5	1	0.2	0.658	/		/		/
	F	1	0.2				33	6.1	1	0.2						
12	M	8	1.7	3	0.7	0.549	1	0.2	/		1.000	6	1.3	1	0.2	0.873
	F	15	2.8	3	0.6		1	0.2				6	1.1	2	0.4	
11	M	0	0	/		1.000	10	2.2	/		0.477	/		2	0.4	0.120
	F	1	0.2				8	1.5						8	1.5	
21	M	0	0	/		0.256	6	1.3	/		0.526	/		4	0.9	0.761
	F	3	0.6				4	0.7						6	1.1	
22	M	7	1.5	3	0.7	0.468	2	0.4	/		0.209	7	1.5	1	0.2	0.310
	F	10	1.8	1	0.2		0	0				13	2.4	4	0.7	
23	M	3	0.7	/		1.000	22	4.8	2	0.4	0.894	/		/		/
	F	3	0.6				27	5	1	0.2						
24	M	1	0.2	/		1.000	/		2	0.4	1.000	/		/		/
	F	2	0.4						3	0.6						
25	M	19	4.1	1	0.2	0.571	6	1.3	/		1.000	/		/		/
	F	27	5	3	0.5		7	1.4								
26	M	/		/		/	/		/		1.000	/		/		/
	F															
27	M	5	1.1	/		0.257	0	0	/		0.256	/		/		/
	F	2	0.4				3	0.6								

M – males; F – females;

*statistically significant; ^a χ^2 test

hyperdontia and macrodontia. Females are more affected by tooth agenesis and microdontia, while more supernumerary and large teeth are expected to be found in men (1:1.5 ratio) [1, 23]. Previous studies in different world regions offered conflicting results regarding sex distribution of patients with missing teeth [15, 16, 19]. However, our findings are in agreement with the results of sex distribution in the Serbian population (5.34–6.28%) [6, 7]. In addition, the location of teeth agenesis is in relationship to teeth position in morphogenic field, i.e. to the most distal tooth in the group affecting second premolars and lateral incisors, as well as third molars [1]. Thus, these teeth are frequently affected by agenesis (4.28–7.52%) which is in accordance with our results [4–7, 18]. A rare occurrence of oligodontia was reported in the Italian population (0.08%) which is in agreement with our result (0.09%) [24].

Contrary to the high prevalence of hypodontia, supernumerary teeth are less frequently found in healthy individuals (0.5–3.8%). The prevalence of supernumerary teeth in our sample was 4.4%, slightly higher than in recent studies [24, 25, 26]. The etiological pattern of sex distribution in association with supernumerary teeth is the opposite of hypodontia [1]. Males are more prone to the formation of supernumerary teeth than females, which is in agreement with our findings [24, 27]. Mesiodens was the most frequently detected

supernumerary tooth on panoramic X-rays in the present study. The lower prevalence of mesiodens was reported in Italian non-orthodontic subjects and French orthodontic patients (0.05% and 0.66%) [15, 24].

Impaction

The prevalence of patients with tooth impactions in the current study was high (16.5%) in comparison to the results of recent studies (2.6–7.1%) [15, 16, 28]. The highest rate of tooth impaction was found in maxillary canines, followed by maxillary central incisors, mandibular premolars and second molar. In the present study, unerupted maxillary incisors were more frequently found in female subjects compared to males, which is not in agreement with the previous report [29]. The prevalence of patients with impacted canines was 10.7% in the present study, in comparison to findings in the general population ranging from 0.6–8.4% [4, 16, 24]. The higher rate of impaction in the current study is probably due to the composition of the sample comprised of persons referred to orthodontic treatment. Females were more affected by impacted maxillary canines compared to males (9.6% vs. 6.9%). Patients, especially females, perceive missing tooth in the anterior region of maxilla as an aesthetic problem, which motivates them to seek out orthodontic treatment.

Table 2. Location and prevalence of mandibular teeth affected by developmental dental anomalies. Comparison between males and females. χ^2 test and Fisher's exact test ($p < 0.05$)

Tooth	Sex	Hypodontia		Hyperdontia		p	Impaction		Transposition		p	Microdontia		Macrodontia		p
		n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
37	M	8	1.7	/	/	0.153	4	0.9	/	/	0.538	/	/	/	/	/
	F	4	0.7				7	1.3								
36	M	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	F															
35	M	21	4.6	3	0.7	0.332	6	1.3	/	/	0.796	/	/	/	/	/
	F	16	3	2	0.4		9	1.7								
34	M	/	/	/	/	/	/	/	1	0.2	0.457	/	/	/	/	/
	F								0	0						
33	M	/	/	/	/	/	4	0.9	1	0.2	0.517	/	/	/	/	/
	F						2	0.4	0	0						
32	M	2	0.4	/	/	0.596	/	/	/	/	1.000	6	1.3	1	0.2	0.873
	F	1	0.2									6	1.1	2	0.4	
31	M	6	1.3	0	0	0.297	/	/	/	/	/	0	0	/	/	1.000
	F	3	0.6	1	0.2							1	0.2			
41	M	2	0.4	1	0.2	0.539	/	/	/	/	/	0	0	/	/	1.000
	F	3	0.6	0	0							1	0.2			
42	M	3	0.7	0	0	0.330	/	/	/	/	/	/	/	/	/	/
	F	1	0.2	1	0.2											
43	M	/	/	/	/	/	2	0.4	/	/	0.535	/	/	/	/	/
	F						3	0.6								
44	M	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
	F															
45	M	18	3.9	1	0.2	0.268	6	1.3	/	/	1.000	/	/	/	/	/
	F	14	2.6	0	0		7	1.4								
46	M	/	/	/	/	/	/	/	/	/	1.000	/	/	/	/	/
	F															
47	M	6	1.3	/	/	0.536	5	1.1	/	/	1.000	/	/	/	/	/
	F	4	0.7				7	1.3								

M – males; F – females

Transposition

The maxillary canines and first premolars were found in complete transposition in four males and four females. Only a few recent studies reported a low prevalence of transposition (0.09%) which is in agreement with our findings (0.08%) [16, 30].

Microdontia and Macrodonia

Sogra et al. [16], found microdontia in 1.6% of Iranian orthodontic patients, while in a smaller sample, Baron et al. [15], reported 2.55%. Microdontia in Serbian patients was present in similar number of patients predominantly affecting maxillary lateral incisors. Low prevalence of macrodontia was reported in Iranian subjects (0.02%), which is in agreement with the results of our study (1.8%) [15].

Limitations

This study has a few limitations. Firstly, we assessed archived files of patients at the Clinic of orthodontics in 2016. The recruitment of patients could not be considered random since patients were already pre-selected from the general population and referred to orthodontic treatment.

Secondly, only charts and panoramic radiographs were used to evaluate DDA. That implied assessment of the sample for only selected DDA. In order to find the prevalence of all types of developmental dental anomalies, more extensive diagnostic methods should be included. Only DDA that can be observed with 100% accuracy on panoramic radiographs were reported making them more relevant than the findings of the rest. Third, DDA were reported in the sample of patients older than seven years of age. Dental abnormalities, such as impaction of canines and second molars, and agenesis of second premolars could not be observed in younger age groups. This could suggest a possible disparity in the diagnosis of DDA. Fourth, although, microdontia and macrodontia were evaluated by accepted reliable diagnostic method (visual examination and comparison), no additional confirmation was obtained from measurements on study models.

Despite the limitations, present findings could offer a foundation for much needed extensive epidemiological studies on DDA prevalence, sex distribution and association among different dental irregularities in the general population in Serbia and worldwide. Furthermore, this study provides information, which is of importance for dental practitioners.

CONCLUSIONS

The prevalence of developmental dental anomalies in Serbian orthodontic patients was 34.8%. At least one tooth anomaly was found in 15.5% of males, and 19.3% of females. The most frequently observed dental abnormality was tooth impaction, followed by tooth agenesis, hypodontia, and anomalies in tooth size and transposition. All investigated developmental dental anomalies, were more frequently present in females, except supernumerary teeth. The most commonly missing tooth was upper left premolar. The maxillary canines had the highest impaction rate. Mesiodens was the most frequently found supernumerary

tooth. The transposition of upper canine and first premolar was rare. The anomalies of tooth size predominantly affected incisors.

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Заступљеност развојних аномалија зуба код ортодонтских пацијената у Србији

Евгенија Марковић¹, Ана Вуковић², Тамара Перић², Јована Кузмановић-Пфићер³, Бојан Петровић⁴

¹Универзитет у Београду, Стоматолошки факултет, Клиника за ортопедију вилица, Београд, Србија;

²Универзитет у Београду, Стоматолошки факултет, Клиника за дечју и превентивну стоматологију, Београд, Србија;

³Универзитет у Београду, Стоматолошки факултет, Катедра за медицинску статистику и информатику, Београд, Србија;

⁴Универзитет у Новом Саду, Клиника за стоматологију Војводине, Одељење дечје и превентивне стоматологије, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Циљ овог истраживања је био да се испита заступљеност развојних аномалија зуба код ортодонтских пацијената у Србији.

Метод Узорак је чинио 1001 ортопантомографски снимак ортодонтских пацијената старијих од седам година са Клинике за ортопедију вилица Стоматолошког факултета у Београду. Бележено је присуство развојних аномалија за чију дијагностику је потребан само ортопантомографски снимак. За испитивање заступљености развојних аномалија зуба коришћена је дескриптивна статистичка анализа. χ^2 тест је коришћен ради поређења броја зуба са аномалијом између полова (степен значајности 95%).

Резултати Развојне аномалије зуба су биле заступљене код 34,8% ортодонтских пацијената (15,5% мушкараца и 19,3% жена). Импакције зуба су биле присутне код 16,5% пацијената, хиподонција код 12,9%, прекобројни зуби код 4,4%, микродонција код 2,9%, макродонција код 1,8% и транс-

позиција код 0,8% пацијената. Очњаци у горњој вилици су били најчешће импактирани зуби. Горњи други кутњаци су били склонији импакцији код жена ($p < 0,05$). Документовано је више импактираних секутића у горњој вилици, а преткутњака и других кутњака у доњој вилици. Најчешће су недостајали горњи леви преткутњаци. Од свих прекобројних зуба најчешће је био уочаван мезиоденс.

Закључак Приказали смо постојање високе учесталости развојних аномалија зуба код ортодонтских пацијената у Србији са већом израженошћу код особа женског пола. Најчешће аномалије биле су импакција, хиподонција, хипердонција, микродонција, макродонција и транспозиција. Све аномалије су биле учесталије код жена, осим у случају прекобројних зуба. Резултати садашње студије могу бити полазна тачка за епидемиолошке студије о учесталости развојних аномалија зуба.

Кључне речи: развојне аномалије зуба; ортодонција; хиподонција



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical efficiency of a sodium perborate – hydrogen peroxide mixture for intracoronal non-vital teeth bleaching

Tatjana Savić-Stanković, Branislav Karadžić, Marina Latković, Vesna Miletić

University of Belgrade, School of Dental Medicine, Department of Restorative Dentistry and Endodontics, Belgrade, Serbia

SUMMARY

Introduction/Objective The aim was to evaluate initial efficiency of sodium perborate (tetrahydrate) and 30% hydrogen peroxide mixture for intracoronal non-vital teeth bleaching ("walking bleach" technique).

Methods Forty patients with discolored teeth were included in the study. Based on their history and clinical examination, causes of discoloration were classified as necrotic pulp, "endo-sealer" or unknown. The "walking bleach" technique was performed by applying sodium perborate (tetrahydrate) and 30% hydrogen peroxide mixture intracoronally to cavity dentin walls. The mixture was renewed in seven-day intervals. Tooth color was assessed visually before, during, and after the procedure using the Vita Classical shade guide (Vita Zahnfabrik, Bad Säckingen, Germany). Numerical values or shade guide units (SGU) were assigned to Vita shade tabs on a bright-dark scale. Analysis of variance, t-test, correlation and regression analysis were used to analyze the data ($p < 0.05$).

Results On average, 26 ± 9 days or 3–4 appointments were required for intracoronal bleaching to achieve the desired or best possible shade. Better clinical efficiency was found in the necrotic pulp group (17 ± 6 days; 8 ± 3 SGU) than in the "endo-sealer" group (42 ± 13 days; 4 ± 2 SGU) ($p < 0.05$). Age significantly influenced bleaching efficiency ($p < 0.05$). There was no significant correlation between bleaching efficiency and initial shade ($p > 0.05$).

Conclusion Intracoronal, non-vital teeth bleaching ("walking bleach" technique) using sodium perborate (tetrahydrate) and 30% hydrogen peroxide mixture showed satisfactory clinical efficiency. Discoloration caused by pulp necrosis was treated more efficiently than that caused by endodontic sealers. Younger age had a positive effect and discoloration intensity had no effect on bleaching efficiency.

Keywords: walking bleach; intracoronal bleaching; non-vital teeth bleaching; tooth discoloration; sodium perborate; hydrogen peroxide

INTRODUCTION

Tooth color affects smile esthetics, which is among the first facial characteristics observed in a social interaction. Even mild tooth discoloration may reduce individual's self-esteem and quality of life [1]. A recent study showed that a single discolored tooth adversely affects patient's dental self-confidence as well as social and psychological aspects of one's well-being [2].

Non-vital teeth are discolored mainly due to trauma and intracoronal hemorrhage, proteolytic degradation, root canal sealers and cements [3]. Increasingly popular calcium-silicate cements, such as mineral trioxide aggregate (MTA) and Biodentine®, have recently shown to have tooth discoloration potential [4]. Higher discoloration potential has been reported for calcium-silicate-based cements containing bismuth oxide as the radio-pacifying agent and lesser for cements with zirconium oxide [4, 5].

A non-vital tooth bleaching is clinically performed by placing a bleaching agent intracoronally and sealing the crown temporarily. This so-called "walking bleach" technique may be performed in one or more consecutive visits

in intervals of three to seven days until the desired or maximum color change is achieved [3]. Regarding color assessment, it should be noted that visual shade matching using Vita shade guides is still most commonly used in daily practice [6].

Sodium perborate, hydrogen peroxide, and carbamide peroxide are commonly used bleaching agents for intracoronal bleaching using the "walking bleach" technique [7, 8]. The efficiency of the bleaching agent may be improved by additional activation with LED blue or laser infrared light or photon-initiated photoacoustic streaming [9, 10]. The mechanism of bleaching by all three agents is based on the release of nascent oxygen and hydrogen peroxide which forms free radicals in the alkaline solution, resulting in hydroperoxyl (HO_2) and hydroxyl ($\text{HO}\cdot$) ions capable of breaking longer-chained chromophores into shorter-chained colorless compounds [11].

In vitro studies of intracoronal bleaching focused on tooth fracture resistance, composition of calcium-silicate cements, their compressive strength, and bond strength to composite resin, adhesive bonding, orthodontic brackets

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Correspondence to:

Vesna MILETIĆ
School of Dental Medicine
Dept. of Restorative Dentistry
and Endodontics
Rankeova 4, 11000 Belgrade
Serbia
vesna.miletic@stomf.bg.ac.rs

bonding to enamel and marginal integrity of temporary and permanent restorative materials following various intracoronal bleaching protocols [12–16].

A similar number of recent clinical studies were found in the literature for in-office bleaching of vital teeth and intracoronal "walking bleach" approach, illustrating the relevance of tooth bleaching in current dental practice and research [1, 2, 7, 8, 9, 17–20]. Hydrogen peroxide, carbamide peroxide and sodium perborate were all-efficient in intracoronal bleaching, with stable effects up to six months or one-year post-bleaching [7, 19, 20]. Even after 25 years post-bleaching 85% of the endodontically treated teeth bleached with 10% carbamide peroxide retained tooth color within two color shades [8]. Multiple studies have confirmed a strong positive effect of both in-office and "walking bleach" procedures on patients' quality of life, psychosocial interaction, and esthetic self-perception [2, 21]. Regarding the "walking bleach" technique, no difference was found between carbamide and hydrogen peroxide bleaching agents in the context of patient's esthetic perception, self-confidence, and psychological and social impact [2].

The aim of this clinical study was to evaluate initial efficiency of the sodium perborate - 30% hydrogen peroxide mixture for intracoronal non-vital teeth bleaching ("walking bleach" technique). The null hypotheses were:

1. There is no difference in clinical efficiency of intracoronal bleaching between different causes of discoloration;
2. there is no relationship between clinical efficiency of intracoronal bleaching and patients' age;
3. there is no relationship between clinical efficiency of intracoronal bleaching and initial shade.

METHODS

Patient selection, examination, and endodontic treatment

The study was approved by the University of Belgrade, School of Dental Medicine Ethics Committee. Inclusion criteria were visibly discolored crown, non-vital or endodontically treated upper central and lateral incisors, previous endodontic treatment performed two or more years earlier. Exclusion criteria were caries on upper central and lateral incisors, inadequate fillings, and progressive periodontal disease.

Forty patients (25 female and 15 male) aged 18–58 years participated in the study. Patients' history was taken and clinical examination performed, including pulp sensitivity tests. Retroalveolar X-rays were taken to check the periapical status and, in cases of previous endodontic treatments, to check the quality of root canal obturation, by assessing the length, conicity and homogeneity of the root canal obturation material. The overall success of previous endodontic treatment was based on patients' history and clinical exam confirming no signs and symptoms of periapical disease. Based on patients' history and examination, potential causes of tooth discoloration were classified into three groups:

1. "Necrotic pulp" (teeth with necrotic pulp with or without patients' recollection of trauma);
2. "endo-sealer" (previously endodontically treated teeth with traces of endo-sealer on pulp chamber walls, patients' recollection that discoloration occurred post-treatment);
3. "unknown" (previously endodontically treated teeth with no traces of "endo-sealer" on pulp chamber walls, patient could not confirm whether discoloration occurred before or after endodontic treatment).

Initial endodontic treatment was performed in the "necrotic pulp" group. A re-treatment was performed in previously endodontically treated teeth with inadequate root canal obturation whereas in endodontically treated teeth with adequate root canal obturation the intracoronal bleaching was performed without prior endodontic re-treatment.

Access cavity was prepared and the working length determined using an apex locator (Root ZX, Morita Corp., Osaka, Japan). Root canal instrumentation was performed with Gates-Glidden and K-Flex hand files (Kerr, Orange CA, USA) following the crown-down and step-back technique with 1% sodium hypochlorite irrigation (Patenting, Belgrade, Serbia) Depending on the initial apical size, the master apical files were K#25-35, mostly K#30. Canals were dried with sterile paper points and obturated with gutta-percha (Spident, Incheon, Korea) and AH-Plus sealer (Dentsply DeTrey GmbH, Konstanz, Germany) using cold lateral compaction technique. Each tooth was prepared for bleaching by removing 1–2 mm of the obturation material at the canal orifice and sealing it with roughly two mm thick glass-ionomer cement (Vitrebond, 3M Corp., St. Paul, MN, USA).

Intracoronal bleaching procedure

Tooth color assessment was performed by shade matching with color tabs on the Vita Classical shade guide (Vita Zahnfabrik, Bad Säckingen, Germany). The procedure was performed by three specialists at daytime in a dental office with no extra dental unit light. Color assessment was determined by consensus agreement of at least two specialists.

A mixture of sodium perborate (tetrahydrate) and 30% hydrogen peroxide was prepared in the 1:2 ratio by measuring the appropriate quantities of each component on an analytical balance ($d = 0.1$ mg, Acculab, Sartorius, Goettingen, Germany) and mixing them with a metal spatula on a glass slab until the mixture was homogeneous. A portion of the mixture was applied intracoronaally as a thin layer and adapted to the entire cavity dentin using a dry, sterile cotton pellet. The cavity was then temporarily sealed with calcium-sulfate cement (Citodur, Dorigent, Wien, Austria). At a follow-up after seven days, color assessment was repeated. Temporary filling and the sodium perborate-hydrogen peroxide mixture were removed using an excavator and the cavity was thoroughly rinsed with air-water spray. Freshly prepared mixture was then applied to the inner cavity walls and the tooth was again temporarily restored.

The treatment ended when the desired color was achieved *i.e.* visually acceptable shade in relation to the adjacent teeth

Table 1. Bright–dark scale for numerical expression of the Vita Classical shade tabs as shade guide units

Vita tab	B1	A1	B2	D2	A2	C1	C2	D4	A3	D3	B3	A3.5	B4	C3	A4	C4
Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

or when the color remained unchanged at two consecutive visits. The final achieved shade on the Vita Classical shade guide was recorded as well as the number of required visits.

Following the bleaching procedure, a calcium hydroxide paste was applied to the cavity dentin walls to neutralize the pH. The final restoration was done after two weeks using a two-step total-etch adhesive (Optibond Solo Plus, Kerr, Scafati, Italy) and a micro-hybrid composite (XRV Herculite, Kerr, Scafati, Italy). The adhesive was light-cured for 20 s and composite for 40 s using a conventional LED light-curing unit (LEdition, Ivoclar Vivadent, Schaan, Liechtenstein).

All 16 Vita Classical shade tabs were converted to a numerical 1–16 scale, #1 corresponding to the brightest shade (B1) and #16 corresponding to the darkest shade (C4) (Table 1). For each patient, the start and end point were identified on the numerical scale as shade guide units. Intracoronary bleaching efficiency (BE) was expressed as the percentage of the bleached shade relative to the initial shade on the bright-dark scale.

$$BE (\%) = [(Initial\ shade - End\ shade) / Initial\ shade] \times 100$$

Statistical analysis

Data were statistically analyzed using analysis of variance, Student's t test, correlation and regression analyses at the level of significance $\alpha = 0.05$. Statistical analysis was performed in Minitab 16 (Minitab Inc., State College, PA, USA).

RESULTS

The age structure *i.e.* mean (standard deviation) of 15 male and 25 female patients involved in this study was comparable: 37 (10.4) years of male and 32.6 (10.6) years of female patients. Necrotic pulp was diagnosed in 16 patients, 14 patients were allocated to the “endo-sealer” group, and in 10 patients, the cause of discoloration was unknown. All data taken together, 26 ± 9 days or 3–4 appointments were required for the intracoronary bleaching procedure to achieve the desired or best possible shade.

Table 2 presents information on the treatment duration relative to the cause of discoloration. Significantly shorter treatment was required in the “necrotic pulp” group than in the “endo-sealer” group ($p < 0.05$). In addition to longer mean treatment time, the “endo-sealer” group showed larger variation in terms of minimum and maximum duration spanning to almost 50 days compared to the “necrotic pulp” group with only 18 days between the minimum and maximum treatment duration. No significant differences were found between the previous two groups and the “unknown group” ($p > 0.05$). The number of patients in each group indicates that all patients returned for follow-ups *i.e.* the recall rate was 100%.

All data taken together, color change of 7 ± 2 shade guide units could be achieved. Table 3 presents data relative to the cause of discoloration. There was a statistically significant difference between the number of shade guide units achieved by bleaching in the “necrotic pulp” than in the “endo-sealer” group ($p < 0.05$). The “unknown” group was comparable to both previous groups ($p > 0.05$). In all three groups, the minimum number of shade guide units was the same (3), but the “necrotic pulp” group exceeded the other two groups in the number of maximum achievable shade guide units during bleaching (14).

Table 2. Treatment duration in different etiological groups

Duration in days	Necrotic pulp	Endo-sealer	Unknown
Mean	17	42	29
Standard deviation	6	13	11
Minimum	3	21	14
Maximum	21	70	42
Number of patients	16	14	10

Table 3. Changes in shade guide units following intracoronary bleaching

Changes in shade units	Necrotic pulp	Endo-sealer	Unknown
Mean	8	4	6
Standard deviation	3	2	2
Minimum	3	3	3
Maximum	14	11	10
Number of patients	16	14	10

Figure 1 shows a significant relationship between BE and patients' age. Pearson correlation analysis showed negative correlation between BE and patients' age ($r = -0.4708$; $p = 0.002$), indicating that better clinical efficiency could be accomplished in younger patients. Correlation and regression analyses showed no significant relationship between BE and initial shade ($r = -0.2826$; $p = 0.077$) (Figure 2).

Figures 3 and 4 show a case of intracoronary bleaching of an upper right central incisor discolored by trauma. Figures 5 and 6 show a case of intracoronary bleaching of an upper left central incisor discolored by “endo-sealer”.

DISCUSSION

The first and second null hypotheses were rejected as different causes of tooth discoloration had a significant effect on intracoronary bleaching efficiency, which was more effective in younger patients. The third null hypothesis was upheld as no significant relationship was established between bleaching efficiency and initial shade.

This clinical study showed the potential of a sodium perborate (tetrahydrate) mixture with 30% of hydrogen peroxide to bleach discolored teeth. On average, the desired or maximum bleaching effect for this “walking bleach” technique required 3–4 appointments and 26 days. The

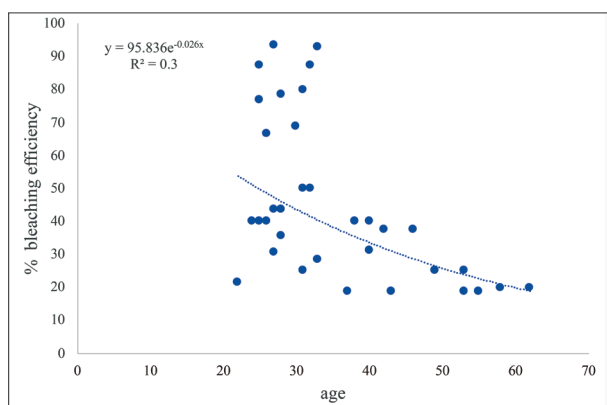


Figure 1. Regression analysis showing a significant relationship between bleaching efficiency and patients' age

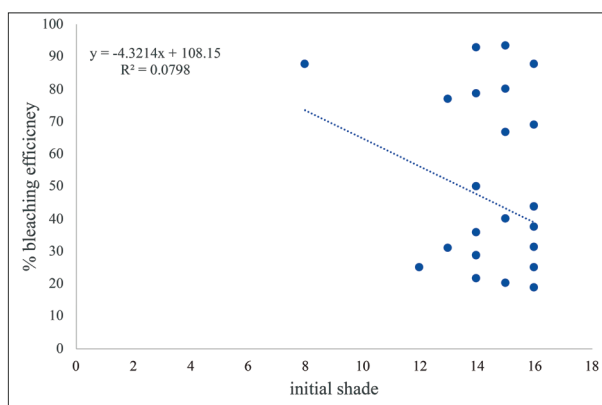


Figure 2. Regression analysis showing no significant relationship between bleaching efficiency and initial shade



Figure 3. An upper right central incisor discolored by trauma before intracoronary bleaching



Figure 4. The same upper right central incisors discolored by trauma after intracoronary bleaching



Figure 5. An upper left incisor discolored by endo-sealer before intracoronary bleaching



Figure 6. The same upper left incisor discolored by endo-sealer after intracoronary bleaching

present results are comparable to other recent clinical studies on the efficiency of the "walking bleach" technique. Pedrollo Lise et al. [7] used a mixture of sodium perborate (unspecified monohydrate, trihydrate, or tetrahydrate) and 20% hydrogen peroxide up to four weeks post-bleaching. Bersezio et al. [22] compared 35% hydrogen peroxide to 37% carbamide peroxide and Gupta et al. [20] used sodium perborate (tetrahydrate) alone for the same purpose. Both studies reported a similar number of required appointments for the most desirable outcome, 3–4 in Bersezio et al. [22] and three in Gupta et al. [20]. Given the fact that in all the studies, different mixtures were applied for intracoronary

bleaching, it may be concluded that similar treatment longevity *i.e.* the number of appointments is expected irrespective of the bleaching agent/agents.

The desired or maximum achievable effect of intracoronary bleaching in the present study was seven shades on average. This was fewer than 12 shades reported by Gupta et al. [20] or 15 shades achieved by Bersezio et al. [22]. The differences could be explained by the greater number of teeth discolored by "endo-sealer" reducing the number of achieved shades in the present study. Gupta et al. [20] treated 41 patients with discolored teeth due to trauma, but without previous endodontic treatment, meaning that

not a single “endo-sealer” case was included in their study. Nearly half of the 47 treated patients in Bersezio et al. [22] had discoloration due to trauma, whilst the other half of discolored teeth were previously endodontically treated but “endo-sealer” was not the stated cause of discoloration.

Generally, the “necrotic pulp” group showed a higher efficiency of intracoronary bleaching in the present study than the “endo-sealer” group both in terms of the required time/number of appointments and of the shade difference in bleached teeth. Despite the fact that the cause of discoloration was based on patients’ history and clinical examination and not confirmed by chemical testing, the necrotic pulp” and “endo-sealer” causes could be differentiated with high confidence. The same approach was followed in previously mentioned studies [7, 20, 22]. Furthermore, a distinct difference in the efficiency of bleaching confirms the correct diagnosis of the cause of discoloration. The “unknown” group showed the results between the other two groups indicating that it probably contained teeth with both causes of discoloration. The observed differences between the “necrotic pulp” and “endo-sealer” groups could be associated with the fact that pigments of natural origin (decomposition products of blood and pulp tissue components as well as pigments of microbial origin) are more susceptible to oxidation reactions that lead to chromophore cleavage and molecular conversion than endodontic sealers [23]. Endodontic sealers containing silver, bismuth, and resins cause not only discernible discoloration shortly after the placement but also show a significant degree of bleaching resistance [24]. Discoloration induced by endodontic sealers may be more bleaching-resistant than that induced by natural pigments due to the amount of excess sealer in the pulp chamber and complex interactions between sealer components and dentin tissue [25]. For example, it was recently explained that bismuth from MTA-based materials forms black precipitates upon interaction with dentin collagen in the presence of sodium hypochlorite, bismuth carbonate upon reaction with atmospheric carbon dioxide or breaks down to metallic bismuth and oxygen upon light irradiation in oxygen-free environment [26, 27].

Better treatment efficiency was associated with patients’ younger age and no direct relationship was found between bleaching efficiency and initial shade. These results are comparable to Gupta et al. [20] who also performed intracoronary non-vital teeth bleaching. Based on pooled data from 11 clinical trials, patients’ younger age was reported as a significant factor in clinical efficiency of vital teeth bleaching as well [28]. More efficient bleaching in younger patients and higher bleaching resistance in older patients may be associated with the diameter of dentinal tubules. In younger patients, wider dentinal tubules allow deeper penetration of hydroperoxyl (HO_2) and hydroxyl ($\text{HO}\cdot$) ions. Conversely, the results indicated that even a highly discolored tooth with necrotic pulp could be efficiently bleached, albeit taking more time and appointments, than a tooth mildly discolored by endodontic sealers. The cause was shown to have a more important effect on treatment efficiency than the intensity of initial discoloration.

It could be argued that in-office non-vital bleaching is faster than the “walking bleach” technique. Although this is true, the “walking bleach” technique is a more conservative approach that allows better control of the achieved result over a longer time. More aggressive in-office non-vital bleaching could lead to over-bleaching due to limited color control. Furthermore, studies indicate that the “walking bleach” technique results in a stable color over a period of months or even years [7, 8, 19]. The cost of commercial products for in-office bleaching often increases the cost of this treatment. Conversely, the low cost of sodium perborate powder and hydrogen peroxide used in the “walking bleach” technique makes this technique financially acceptable.

Despite advantages, biological risks of the “walking bleach” technique were recently investigated by Bersezio et al. [29]. They reported an increase in the production of IL-1 β and RANKL biomarkers in periodontal tissues by analyzing gingival crevicular fluid up to six months after intracoronary bleaching with either 35% hydrogen peroxide or 37% carbamide peroxide over four sessions. Increased production of these biomarkers may be associated with osteoclastic activity with a potential for root resorption as an adverse consequence of intracoronary bleaching [30, 31].

A limitation of this study is that the efficiency of intracoronary bleaching was assessed visually using a Vita Classical shade guide. However, the same approach was followed in other studies [8, 20, 22]. Though digital shade matching has proven more accurate and reliable than visual shade matching, experience and training may positively affect the accuracy of visual shade matching [32, 33]. Colorimeters and spectrophotometers have not been widely accepted probably due to their high costs. The fact that visual shade matching was performed in the present study ensures clinically relevant results as most dentists would likely resort to the same technique when assessing bleaching efficiency. Furthermore, the 50:50 perceptibility and acceptability thresholds in color observation in dentistry were found to be significantly lower for dentists (mean ΔE_{00} 0.62 and 1.79, respectively) than laypersons (mean ΔE_{00} 1.00 and 2.04, respectively) who largely constitute the patient group [33]. This indicates that dentists observe color differences better than patients do, likely due to training, ensuring better treatment results and patient satisfaction.

CONCLUSION

Intracoronary, non-vital teeth bleaching or the “walking bleach” technique using a mixture of sodium perborate tetrahydrate and 30% hydrogen peroxide showed satisfactory clinical efficiency. On average, 3–4 appointments were required for a desired or maximum possible outcome. The cause of discoloration affected treatment longevity and efficiency, in that discoloration due to pulp necrosis was resolved more efficiently than discoloration due to endodontic sealers. Younger patients had better results and discoloration intensity had no effect on bleaching efficiency.

Conflict of interest: None declared.

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Клиничка ефикасност микстуре натријум-пербората и водоник-пероксида за интракоронарно избељивање депулписаних зуба

Татјана Савић-Станковић, Бранислав Караџић, Марина Латковић, Весна Милетић
Универзитет у Београду, Стоматолошки факултет, Клиника за болести зуба, Београд, Србија

САЖЕТАК

Циљ Циљ овог рада је да испита иницијалну клиничку ефикасност микстуре натријум-пербората (тетрахидрата) и 30% водоник-пероксида за интракоронарно избељивање депулписаних зуба („шетајућа“ техника).

Методе У студију је било укључено 40 пацијената са пребојеним зубима. На бази анамнезе и клиничког прегледа, узроци дисколорације су класификовани као „некротична пулпа“, „ендо-силер“ или „непознат“. У интервалима од седам дана микстура натријум-пербората и 30% водоник-пероксида апликована је интракоронарно на дентинске зидове кавитета. Боја зуба је процењивана визуелном методом пре, током и после третмана применом кључа боја *Vita Classic* (*Vita Zahnfabrik*, Немачка). Нумеричка вредност (јединица нијансе) додељена је свакој нијанси кључа *Vita* помоћу светло-тамне скале. Анализа варијансе, *t*-тест, корелациона и регресиона анализа су коришћене за статистичку обраду података ($p < 0,05$).

Резултати Просечно 26 ± 9 дана или 3–4 посете су биле неопходне да се интракоронарним избељивањем постиг-

ну жељена или најсветлија могућа нијанса. Боља клиничка ефикасност избељивања забележена је у групи „некротична пулпа“ (17 ± 6 дана; 8 ± 3 нијанси) него у групи „ендо-силер“ (42 ± 13 дана; 4 ± 2 нијансе) ($p < 0,05$). Узраст пацијента је значајно утицао на ефикасност избељивања ($p < 0,05$). Није утврђена значајна повезаност између ефикасности избељивања и почетне нијансе ($p > 0,05$).

Закључак Интракоронарно избељивање депулписаних зуба односно „шетајућа“ техника избељивања применом микстуре натријум-пербората (тетрахидрата) и 30% водоник-пероксида показала је задовољавајућу клиничку ефикасност. Дисколорација услед некрозе пулпе је успешније избељена него дисколорација изазвана ендодонтским пастама. Ефикасније избељивање је забележено код млађих пацијената, док интензитет почетне дисколорације није значајно утицао на ефикасност избељивања.

Кључне речи: шетајућа техника; интракоронарно избељивање зуба; избељивање депулписаних зуба; дисколорација зуба; натријум-перборат; водоник-пероксид

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Upper and lower gastrointestinal endoscopy in patients with iron deficiency anemia

Dušan Đ. Popović^{1,2}, Simon Zec², Ivan V. Ranković¹, Tijana M. Glišić^{1,2}, Tamara M. Milovanović^{1,2}¹Clinical Centre of Serbia, Clinic for Gastroenterology and Hepatology, Belgrade, Serbia;²University of Belgrade, Faculty of Medicine, Belgrade, Serbia**SUMMARY****Introduction/Objective** The most common cause of iron deficiency anemia (IDA) in both men and postmenopausal women are gastrointestinal diseases.

This study aimed to determine the frequency of pathological and diagnostic findings observed on esophagogastroduodenoscopy (EGDS) and colonoscopy in IDA patients, and examine associations between demographic, anamnestic, and clinical features, with findings found on endoscopy.

Methods A retrospective cross section study of patients with IDA was conducted.**Results** Eighty-five patients with IDA were included, mean age of 60.3 ± 18.8 years, with 51.8% being women. Esophagogastroduodenoscopy, colonoscopy, or both was performed in 96.5%, 71.8%, and 70.6% of patients, respectively. The cause of IDA was established in 65.9% of cases. Diagnostic findings were observed in those who underwent EGDS, colonoscopy, or both in 43.9%, 47.5%, and 15.9% of patients, respectively. Diagnostic findings on EGDS were significantly more common in patients older than 50 years than in younger patients ($p = 0.031$). Patients with a diagnostic finding on colonoscopy more commonly reported weight loss ($p = 0.046$) and change in bowel habit ($p = 0.012$), alongside positive fecal occult blood test (FOBT; $p = 0.012$); they rarely had anemia previously ($p = 0.001$), rarely used iron supplements ($p = 0.022$), and were more likely to have malignancy in their past medical history ($p = 0.043$).**Conclusion** Diagnostic findings on EGDS were more commonly observed in older patients, while diagnostic findings on colonoscopy were more common in those with weight loss, change in bowel habit, positive FOBT, and prior malignancy. Colonoscopy was more often diagnostic in patients without anemia or iron supplementation in the past.**Keywords:** anemia; endoscopy; neoplasm; angiodysplasia**INTRODUCTION**

Iron deficiency anemia (IDA) is the most common type of anemia. It is estimated that its incidence in the general population is 12% and 23% in the population of hospitalized patients [1–4]. Approximately 1–5% of men, and 5–12% of women who are not pregnant have IDA [5, 6, 7]. In premenopausal women, the most common cause of IDA is menstrual bleeding, whereas in both men and postmenopausal women, the underlying cause is most often gastrointestinal blood loss [7, 8].

This study aimed to determine the frequency of pathological and diagnostic findings observed on esophagogastroduodenoscopy (EGDS) and colonoscopy in IDA patients, and examine associations between demographic, anamnestic and clinical features, with findings found on endoscopy.

METHODS

A retrospective cross section study was conducted for one year, from January 2014 to January 2015, at the Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia.

The inclusion criterion was IDA. Anemia was defined as a reduction in hemoglobin level below 130 g/L or hematocrit level below 0.40 for men, and hemoglobin level below 120 g/L or hematocrit level below 0.35 for women [2]. IDA was defined as an anemia with the following characteristics: reduced serum iron (men $< 11 \mu\text{mol/L}$; women $< 7 \mu\text{mol/L}$), decreased ferritin (men $< 20 \mu\text{g/L}$; women $< 10 \mu\text{g/L}$), transferrin saturation ($< 15\%$), elevated total iron binding capacity ($> 75.1 \mu\text{mol/L}$), elevated transferrin receptor ($> 1.76 \text{ mg/L}$) and/or reduced mean corpuscular volume ($< 80 \text{ fL}$). The exclusion criteria were the age < 18 years and the presence of another disease as the obvious cause of IDA. Patients with malignancy in the past medical history were only included if more than five years had passed since oncological treatment, and if they did not have a recurrence of the primary tumor.

A review of medical records was performed and the collected data included demographic, anamnestic and clinical data, as well as the results of endoscopic examination. Demographic data included sex and age. The anamnesis data included symptoms (including manifest bleeding), drug use, past medical history and comorbidities, and family history. Clinical data

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Clinical Center of Serbia
Clinic for Gastroenterology and
Hepatology
2 Dr. Koste Todorovica St.
Belgrade 11000
Serbia
tamara.alempijevic@med.bg.ac.rs

included physical examination of the abdomen, digital rectal examination, and laboratory analysis (complete blood count, serum iron, total iron binding capacity, ferritin, transfer saturation, soluble transfer receptors, and fecal occult bleed test). Laboratory analyzes were carried out at the Center for Medical Biochemistry, Clinical Center of Serbia.

The results of endoscopy were stratified into three groups: normal finding, pathological finding, and diagnostic finding.

Pathological finding was categorized as pathological changes which may or may not have been the underlying cause of IDA. Diagnostic findings were those which definitively established the cause of IDA. On EGDS diagnostic findings included severe esophagitis (grade 3 and 4 by Savary–Miller) with traces of blood/hematoma in the lumen of the gastrointestinal tract (GIT), esophageal varices with red spots, more serious form of erosive gastritis or duodenitis, ulcers (esophageal, gastric or duodenal), adenomatous polyps of at least 20 mm diameter, vascular ectasias, gluten-sensitive enteropathy and active inflammatory bowel disease (localized to esophagus, stomach, and duodenum) [7–10]. Based on data from previous studies, the findings of milder forms of esophagitis, hiatus hernia, esophageal varices without red spots, mild forms of erosive gastritis and duodenitis, and the presence of smaller polyps were classified as pathological rather than diagnostic findings on EGDS [7, 8, 11].

The diagnostic finding category on colonoscopy included: neoplasms (colon or terminal ileum), one or more polyps with a diameter > 15 mm, active colonic ulceration > 10 mm, vascular ectasias, inflammatory bowel disease, post radiation colitis and active colitis [7, 9, 12]. The findings of uncomplicated colonic diverticulosis, non-bleeding hemorrhoids, and small colonic polyps were classified into the pathological finding group, and were not diagnostic [7, 8].

Statistics

Descriptive and analytical statistics were used. Continuous variables were described as the average value \pm standard deviation, while frequency and proportions were utilized for discontinuous variables. The normality of the distribution for continuous variables was evaluated by the Kolmogorov–Smirnov test. To estimate the significance of the differences between continuous variables with a normal distribution, the t-test for independent samples was employed, while the Mann–Whitney U-test was used as a non-parametric alternative. Significance for categorical variables was assessed with the χ^2 test or, in the case of numerical constraints, the Fisher test. Significant difference was indicated as $p < 0.05$.

Ethics

The study was conducted according to the Declaration of Helsinki. The study was approved by the Collegium of the Clinic for Gastroenterology and Hepatology, Clinical Centre of Serbia, and the Council for Specialist Studies, Medical Faculty in Belgrade (04 Nr: 14-UGT-08, 23.12.2015).

RESULTS

Demographic data

The study included 85 patients with IDA. The average age of the patients was 60.3 ± 18.8 years (range 18–87 years). Of the total number of subjects, 51.8% ($n = 44$) were women.

Anamnestic data

The most commonly reported general symptoms were malaise and/or fatigue, as well as weight loss. The gastrointestinal-specific symptoms were present in 65.9% ($n = 56$) of the patients, the most common of which being abdominal pain and change in bowel habit. An active episode of GIT bleeding was evidenced in one third of the cases and included hematemesis in 3.5% ($n = 3$), melena in 24.7% ($n = 21$), and rectorrhagia in 22.4% ($n = 19$) of the patients. Of the comorbid diseases, most patients had arterial hypertension (44.7%), followed by diabetes mellitus (14.1%) and cardiac arrhythmia (12.9%). Of the concurrent GIT diseases, the most common was dyspepsia. One half of the patients had a prior history of anemia, for a period for 2–180 months. Regarding prior medication use, most patients reported taking iron preparations. The anamnestic data of the patients is shown in Table 1.

Table 1. Anamnestic data of the patients ($n = 85$)

Anamnestic data	%	n
Symptoms		
Malaise and/or fatigue	84.5	71
Abdominal pain	49.3	37
Weight loss	45.9	34
Irregular bowel emptying	43.2	32
Overt gastrointestinal bleeding	38.8	33
Dyspepsia	23.9	16
Heartburn	17.6	12
Tympanites	17.2	10
Vomiting	12.9	9
Loss of appetite	5.8	4
Syncope	2.9	2
Medication and alcohol consumption		
Iron preparations	27.1	23
Acetylsalicylic acid	22.4	19
Anticoagulants	16.5	14
Nonsteroidal anti-inflammatory drugs	11.8	10
Anti-platelet drugs	8.2	7
Alcohol consumption	4.7	4
Comorbidities		
Arterial hypertension	44.7	38
Diabetes mellitus	14.1	12
Arrhythmia	12.9	11
Cerebrovascular insult	9.4	8
Chronic obstructive pulmonary disease	3.5	3
Past medical history		
Dyspepsia	18.8	16
Ulcer disease	9.4	8
Gastroesophageal reflux disease	3.5	3
Overt gastrointestinal bleeding in past medical history	44.7	38
Malignancies	7.1	6
Anemia in past medical history	52.9	45
Family history		
Malignancies in family history	20	17

Clinical data

The majority of patients presented with abdominal tenderness and pallor. In a significantly lower percentage of patients, hepatomegaly, a palpable abdominal mass, and ascites were noted. None of the patients had splenomegaly. A pathological finding on digital rectal examination was present in slightly less than one half of the patients, with results of this examination not determined in 24.7% (n = 21) of the patients. A fecal occult blood test (FOBT) was performed in 56.5% (n = 48) of the patients, with a positive finding in 23.5% (n = 20) of the cases. The clinical data of the patients is shown in Table 2.

Table 2. The clinical data of the patients (n = 85*)

Signs	%	n
Pallor	51.8	44
Abdominal tenderness	65.9	56
Hepatomegaly	7.1	6
Abdominal mass	3.5	3
Ascites	2.4	2
Pathological finding of digital rectal examination	43.8	28
Melena	34.3	22
Rectorrhagia	3.1	2
Palpable mass of the rectum	3.1	2
Palpable internal hemorrhoids	3.1	2

*For digital rectal examination n = 64

Endoscopy

EGDS was performed in 96.5% (n = 82) of the subjects, and colonoscopy in 71.8% (n = 61). Both procedures were performed in 70.6% (n = 60) of the patients. Using these modalities, the cause of IDA was established in 65.9% (n = 56) of the cases. A pathological finding on EGDS was present in 93.9% (n = 77) of those included in the study.

A diagnostic finding on EGDS was present in 43.9% (n = 36) of the patients. The highest percentage of patients had angiodysplasia of the stomach and/or duodenum, gastric ulcer, stomach neoplasm, and duodenal ulcer. Detailed data of the diagnostic and pathological findings of EGDS is shown in Table 3. The selected diagnostic findings of EGDS is shown in Figure 1.

Table 3. Pathological and diagnostic finding of esophagogastroduodenoscopy (n = 82)

Finding	%	n
Gastroesophageal reflux disease*	8.5	7
Esophageal varices	1.2	1
Hiatus hernia*	6	5
Chronic gastritis/gastroduodenitis**	37.8	31
Gastric and/or duodenal angiodysplasia	14.6	12
Gastric ulcer	6	5
Gastric neoplasm	6	5
Duodenal ulcer	4.8	4
Duodenal neoplasm	1.2	1
Polyps	2.4	2
Mb. Crohn	2.4	2
Gluten sensitive enteropathy	1.2	1
Gastrointestinal stromal tumor	1.2	1

Bold – pathological and diagnostic finding;

*diagnostic finding in 2.4% (n = 2) of the patients;

**diagnostic finding in 10.9% (n = 9) of the patients

The pathological finding on colonoscopy was seen in 78.6% (n = 48) of the patients, 47.5% (n = 29) had a diagnostic finding. The most common were colonic neoplasms and inflammatory bowel disease. Diagnostic and pathological findings of colonoscopy are shown in Table 4.

In 15% (n = 9) of the patients, there was a positive finding on both EGDS and colonoscopy. The most common diagnostic finding in the upper and lower parts of the GIT is angiodysplasia, which was present in 4.7% (n = 4) patients.

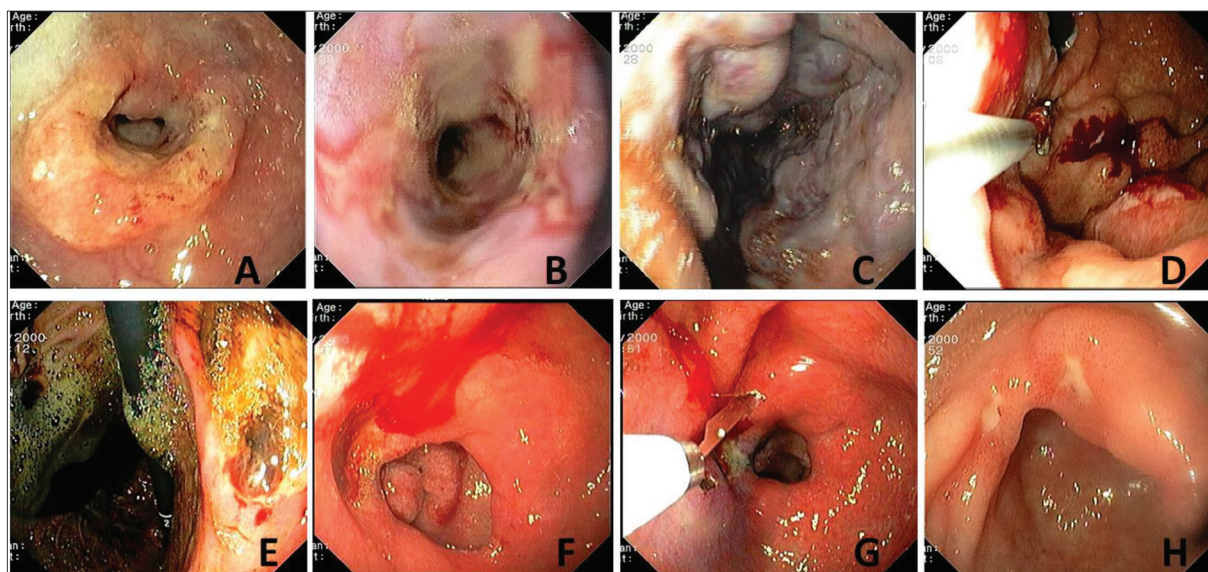


Figure 1. The selected diagnostic finding of esophagogastroduodenoscopy; A) esophageal carcinoma; B) gastro-esophageal reflux disease with stenosis after extraction of the foreign body; C) esophageal varices; D) gastric lymphoma infiltration; E) gastric ulcer, Forrest Ib; F) and G) bleeding gastric ulcer, Forrest Ib, during hemostasis; H) two ulcers of the antral region

Factors associated with diagnostic finding on endoscopy

A positive diagnostic finding on EGDS was significantly more common in patients older than 50 years compared to younger patients. For other socio-demographic, anamnestic, and clinical data there was no significant difference (Table 5). Patients with diagnostic findings on colonoscopy more commonly reported symptoms of weight loss, and change in bowel habit; they rarely had anemia prior, and rarely used iron supplements, and often had malignancy in their past medical history. Patients with diagnostic findings on colonoscopy often have a positive FOBT. For other assessed variables, no significant difference was found (Table 5).

Table 4. Pathological and diagnostic finding of colonoscopy (n = 61)

Finding	%	n
Colon neoplasm	19.6	12
Inflammatory bowel disease	14.7	9
Hemorrhoids*	9.8	6
Colonic polyps*	9.8	6
Diverticulosis*	8.1	5
Angiodysplasia	6.5	4
Post radiation colitis	4.9	3
Resected colon*	3.2	2
Colonic ulcer	1.6	1

Bold – pathological and diagnostic finding;

*pathological but not diagnostic finding for iron deficiency anemia

DISCUSSION

Gastroenterological and endoscopic examinations are a necessity in the workup of patients with IDA; in fact, 7.6% to 13% of patients are referred to the gastroenterologist because of IDA [13, 14].

In our study, the frequency of diagnostic findings on EGDS and colonoscopy was in line with previously published results, indicating that the incidence of positive endoscopic findings in IDA patients is in the range of 30–85% [8, 9, 15–19].

A high percentage of pathological findings but not diagnostic findings were observed for EGDS in our study, which can be explained by the subjective assessment of the endoscopist regarding the existence of gastritis/gastroduodenitis (the most common overall pathological finding). Another reason may be the fact that, in our study, we described uncomplicated hiatus hernia as a pathological finding. The impact of hiatus hernia on the development of IDA is a matter of some debate. In some studies, hiatus hernia was considered a normal finding [11]. The exception is a large hernia (hernia \geq 4 cm, measured by EGDS), as well as hernia with Cameron erosion [18, 20, 21, 22]. Large hiatal hernias are responsible for IDA in 9.2% of patients, with Cameron's erosion present in one third of patients [23]. In our study, hiatus hernia was a diagnostic finding only if it was \geq 4 cm with Cameron erosion, which was present in 2.4% of the patients.

A study by Majid et al. [24] found that the most common causes of IDA in the upper part of the GIT were erosive

Table 5. Diagnostic finding of esophagogastroduodenoscopy and colonoscopy in relation to patient characteristics

Variable	EGDS diagnostic finding			Colonoscopy diagnostic finding		
	%	n	p	%	n	p
Age 50 years	13.9	5	0.031	37.9	11	0.243
Female sex	52.8	19	0.957	48.3	14	0.622
Malaise and/or fatigue	88.6	31	0.454	82.8	24	0.693
Syncope	3.8	1	0.644	0	0	0.279
Weight loss	46.4	13	0.853	58.6	17	0.046
Loss of appetite	7.7	2	0.517	7.4	2	0.205
Abdominal pain	56.7	17	0.339	55.2	16	0.256
Dyspepsia	24	6	0.932	17.2	5	0.313
Heartburn	12	3	0.288	17.2	5	0.865
Tympanites	10	2	0.335	13	3	0.434
Vomiting	7.7	2	0.273	17.2	5	0.298
Irregular bowel emptying	34.5	10	0.271	59.3	16	0.012
Active overt gastrointestinal bleeding	47.2	17	0.120	37.9	11	0.082
Arterial hypertension	44.4	16	0.842	39.3	11	0.154
Diabetes mellitus	6.2	2	0.062	17.2	5	0.415
Arrhythmia	14.3	5	0.902	14.3	4	0.260
Cerebrovascular insult	9.4	3	0.572	3.4	1	0.074
Gastritis	12.5	4	0.144	24.1	7	0.992
Ulcer disease	15.6	5	0.192	6.9	2	0.270
GERD	6.3	2	0.365	3.4	1	0.721
Malignancies*	6.3	2	0.522	13.8	4	0.043
Overt gastrointestinal bleeding in past medical history	69.6	16	0.404	71.4	10	0.652
Iron preparations	27.8	10	0.961	20.7	6	0.022
Acetylsalicylic acid	27.6	8	0.805	17.2	5	0.313
Nonsteroidal anti-inflammatory drugs	20	6	0.191	13.8	4	0.289
Anti-platelet drugs	21.2	7	0.582	10.3	3	0.289
Alcohol consumption	6.7	2	0.577	3.4	1	0.357
Anemia in past medical history	80	20	0.198	47.8	11	0.001
Malignancies in family history	15.4	4	0.208	26.9	7	0.827
Pallor	52.8	19	0.803	48.3	14	0.482
Abdominal tenderness	33.3	12	0.945	34.5	10	0.877
Hepatomegaly	8.3	3	0.384	10.3	3	0.259
Ascites	2.8	1	0.688	0	0	0.178
Pathological finding of digital rectal examination	40	10	0.502	31.8	7	0.367
FOBT positive	36.8	7	0.866	66.7	12	0.012

Bold – p < 0.05; EGDS – esophagogastroduodenoscopy;

GERD – gastroesophageal reflux disease; FOBT – fecal occult blood test;

EGDS – esophagogastroduodenoscopy;

*malignancies in past medical history

gastritis (8.4%), erosive esophagitis (6.3%), gastric (5.3%), and duodenal ulcer (5.3%). In the same study, the most common causes in the lower part of the GIT were colonic ulcers (4.3%), colonic mass (2.1%), and colonic polyps (2.1%) [24].

Rockey et al. [9] found that the causes of IDA in the upper part of the GIT were duodenal ulcer (11%), esophagitis (6%), gastritis (6%), gastric ulcer (5%), vascular ectasia (3%), anastomosis ulcer (3%), gastric cancer (1%), and other causes (2%) [9]. Furthermore, they found that the most common cause of IDA in the lower part of the GIT was colon cancer (11%), polyps (5%), vascular ectasias

(5%), colitis (2%), cecum ulcer (2%), and parasite infestation (1.05%). In contrast to these studies, we found that the most common lesion underlying IDA in the upper GIT was gastric and/or duodenal angiodysplasia. The explanation for these results is multifactorial. We collected data on patients who were examined at a tertiary care institution, to where patients are generally referred when diagnosis and/or treatment cannot be carried out at the primary or the secondary level. Our sample included patients with an average age of about 60 years, and angiodysplasias are more common in the older population [25]. The average age of subjects in the study by Rockey et al. [9] was 60 ± 14 years, which is very similar to our sample; however, that study was conducted in the 1990–1992 period.

One third of our patients had a non-diagnostic finding of endoscopy. Based on recent literature data, 10–41% of IDA patients have a negative finding of endoscopy [26, 27]. The cause of the negative finding is also multifactorial; namely, anemia can be caused by a lack of iron in the diet, other organ and systemic diseases, significant lesions overlooked during endoscopy, and/or lesions unavailable to endoscopy (especially lesions in the small intestine). Exploration of the small bowel is indicated in patients who are transfusion-dependent or have persistent symptoms [28].

Our research concluded that the diagnostic finding on EGDS was significantly more frequent in patients older than 50 years, which is in line with previously published results [8, 13, 19, 24]. These results can be explained by the fact that GIT disorders, which cause chronic bleeding, are more common in the older population.

More than one half of our patients had symptoms specific to the digestive system, supporting previously published results [8]. By analyzing the effects of individual symptoms on a positive endoscopic finding, we concluded that weight loss and irregular bowel emptying were more frequent in patients with a diagnostic finding on colonoscopy. This is a logical conclusion considering that the highest percentage of our patients with a positive colonoscopy finding had colonic carcinoma or inflammatory bowel disease, and that weight loss and irregular bowel emptying form the basis of the clinical presentation of these conditions. Literature on abdominal symptoms and diagnostic endoscopic findings are contradictory. Rockey et al. [9] concluded that abdominal symptoms are associated with a pathological finding, adding that, symptoms “specific to the side” were specific for a positive finding of endoscopy of that respective side, whereas the absence of such symptoms did not exclude pathological changes on that side. Supporting the

predictive significance of abdominal symptoms in the diagnosis found on endoscopy are the results of Nahon et al. [8] and of Carter et al. [15]. In contrast, however, Fireman et al. [12] found no significant correlation between abdominal symptoms and endoscopic findings.

The use of alcohol as well as non-steroidal anti-inflammatory drugs were not associated with a higher incidence of EGDS and colonoscopy diagnostic findings amongst our patients, which is consistent with the results of other studies [9]. Furthermore, the use of other investigational drugs did not indicate a significant association. The exception was the use of iron preparations; namely, we found that patients who used iron supplementation, alongside those with anemia in their history, had a significantly lower occurrence of diagnostic findings on colonoscopy.

We concluded that a positive personal history of malignancy was associated with a higher incidence of a diagnostic finding of colonoscopy.

Our study had limitations. We did not have information about the patient's *H. pylori* status, and *H. pylori* infection can play an important role in IDA [29, 30]. The study included patients who were examined in a tertiary institution, so selection bias cannot be excluded.

CONCLUSION

Diagnostic findings on EGDS in patients with IDA was more common in older patients, while a diagnostic finding on colonoscopy was more frequent in those with presenting symptoms of weight loss, change in bowel habit, positive FOBT and malignancy in their personal history. Patients who had no history of anemia, and did not consume iron preparations previously, were more likely to show diagnostic findings on lower endoscopy.

NOTE

This manuscript was partially presented as an abstract “Endoscopy in patients with iron deficiency anemia,” ESGE Days 2018, April 19–21, 2018, Budapest (Endoscopy 2018; 50(04): S159). The manuscript is part of the postgraduate (subspecialist) thesis titled “Esophagogastroduodenoscopy and colonoscopy in patients with anemia due to iron deficiency,” which was finished in 2016.

Conflict of interest: None declared.

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Горња и доња гастроинтестинална ендоскопија код болесника са анемијом услед недостатка гвожђа

Душан Ђ. Поповић^{1,2}, Симон Зеџ², Иван В. Ранковић¹, Тијана М. Глишић^{1,2}, Тамара М. Миловановић^{1,2}

¹Клинички центар Србије, Клиника за гастроентерологију и хепатологију, Београд, Србија;

²Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод/Циљ Најчешћи узрок сидеропенијске анемије (СА) код мушкараца и жена у постменопаузи су гастроинтестиналне болести.

Циљ ове студије је одређивање учесталости патолошких и дијагностичких промена приликом езофагогастродуоденоскопије (ЕГДС) и колоноскопије код болесника са СА, као и испитивање повезаности демографских, анамnestичких и клиничких карактеристика болесника са налазом ендоскопије.

Метод Сprovedена је ретроспективна студија у коју су били укључени болесници са СА.

Резултати У студију је укључено 85 болесника са СА, просечне старости 60,3 ± 18,8 година. Од укупног броја болесника 51,8% су жене. ЕГДС је спроведена код 96,5% болесника, колоноскопија код 71,8%, док су обе ендоскопске процедуре спроведене код 70,6% болесника. Узрок СА је утврђен код 65,9% болесника. Дијагностички налаз ЕГДС је био присутан код 43,9% болесника, колоноскопије код

47,5%, док је дијагностички налаз обе ендоскопске методе био присутан код 15,9% болесника. Дијагностички налаз ЕГДС је значајно чешћи код болесника старијих од 50 година него код млађих ($p = 0,031$). Болесници са дијагностичким налазом колоноскопије чешће имају губитак на тежини ($p = 0,046$), промене у цревном пражњењу ($p = 0,012$), позитиван тест на окултно крварење у столицу ($p = 0,012$), ређе имају анемију у личној анамнези ($p = 0,001$), ређе користе препарате гвожђа ($p = 0,022$) и чешће имају малигнитет у личној анамнези ($p = 0,043$).

Закључак Дијагностички налаз ЕГДС је чешћи код старијих болесника, док је дијагностички налаз колоноскопије чешћи код болесника који имају губитак телесне тежине, нередовно цревно пражњење, позитиван тест на окултно крварење и малигнитете у личној анамнези. Болесници који немају анемију у личној анамнези, као и они који не користе препарате гвожђа, чешће имају дијагностички налаз колоноскопије.

Кључне речи: анемија; ендоскопија; неоплазма; ангиодисплазија

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Unilateral external fixation of the tibial shaft malunion

Saša S. Milenković^{1,2}, Milan M. Mitković^{1,2}, Milorad B. Mitković²¹Clinical Center of Niš, Clinic for Orthopaedics and Traumatology, Niš, Serbia;²University of Niš, Faculty of Medicine, Niš, Serbia**SUMMARY**

Introduction/Objective Fracture malunion is still a major problem in orthopaedic practice. The external fixation of tibial fracture malunion has become popular in recent years. The objective of this work was to evaluate clinical results in tibial shaft malunion treatment based on unilateral external fixation method.

Methods The patients with tibial shaft malunion have surgically been treated by unilateral Mitković external fixation system. Malunion deformities were corrected by "one stage" technique, using Mitković-CD type external fixator, or gradually, using Mitković-V type external fixator. This retrospective study included 15 patients with tibial shaft angular malunion. The main type of malunion was valgus deformity, in 10 patients, and varus deformity, in five patients.

Results The mean healing time was 89.66 days (range 50–125). There were no complications in the present study. The follow-up time after surgery was three years. Final functional results were excellent in 13 cases and good in two cases.

Conclusion This unilateral external fixator system was successfully used in the treatment of tibial shaft malunion, with good results and low complications rate.

Keywords: external fixation; tibial shaft; malunion

INTRODUCTION

Delayed union, nonunion and malunion are relatively frequent complications of tibial shaft fractures [1]. According to Nicoll, the important factors in prognosis are the amount of initial displacement, the degree of comminution, the presence or absence of infection and the severity of the soft tissue injury excluding infection [2]. What had to be taken into consideration were the clinical presence, age, level of activity and general health status of the patients. Rosemeyer and Pörringer [3] consider surgery indicated if valgus deformity exceeds 12°, varus deformity exceeds 6°, external rotational deformity exceeds 15° or internal rotational exceeds 10°. Commonly accepted indications for surgical management of tibial shaft malunion include 10° of varus, 15° of valgus or 20 mm of medial shift of the mechanical axis. Other indications include inability to place the foot in a plantigrade position and limb-length discrepancy greater than 20 mm [4]. Treatment of tibial shaft malunion is a challenge for the surgeon and requires extensive experience. Abnormal joint loading induced by the deformity may result in early osteoarthritis. Angulation may usually be corrected by corticotomy. Satisfactory alignment after corticotomy or hemi-corticotomy is difficult to maintain unless some type of internal fixation (compression plate, intramedullary nail, etc.) or external fixation is used [5–9]. External fixation techniques for the management of tibial malunion has become popular in recent years [10–16].

The objective of this study was to evaluate the clinical results for tibial shaft malunion treated with the unilateral external fixation method.

METHODS

The patients with tibial shaft angular malunion have primary been non-operatively treated, by plaster cast immobilisation, or surgically, by an open reduction and internal fixation or by an external fixation method. All these malunions have been secondary treated by tibial corticotomy or hemi-corticotomy followed by external fixation. Tibial corticotomy was performed in patients with angular deformity of 10°–15° and was followed by "one stage" correction technique using Mitković-CD type external fixator. Tibial hemi-corticotomy was performed in patients with angular deformity > 15° and was followed by gradual correction technique, using Mitković-V type external fixator. One patient with valgus/anteversion deformity and with delayed union had been treated by gradual correction technique without previous tibial hemi-corticotomy. Malunion correction process was begun in the first postoperative day at the rate of 1 mm/day until good alignment was achieved. Fibular osteotomy was performed in 14 cases.

RESULTS

This retrospective study includes 15 patients with tibial shaft angular malunion (Figure 1

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Correspondence to:

Milan MITKOVIĆ
Romanijska 19/52
18000 Niš
milanmitkovic@hotmail.com

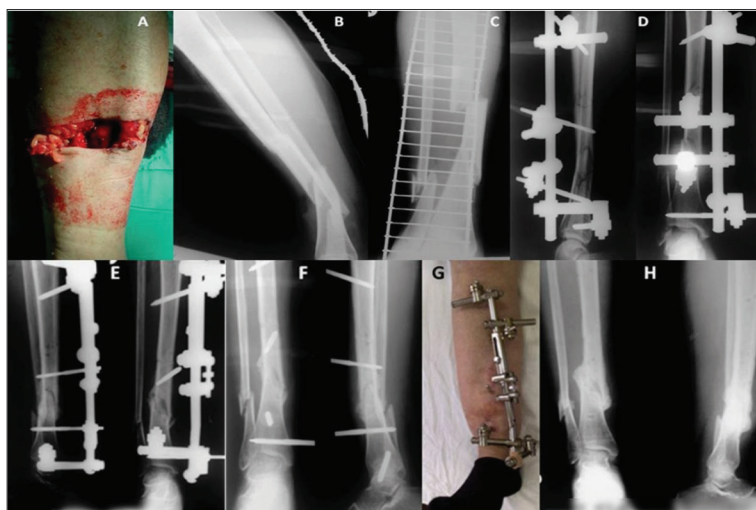


Figure 1. Open segmental tibial shaft fracture treated by external fixation method. A – Injured leg of the 27-year-old patient, injured in a traffic accident as a passenger on the motorcycle; B – X-ray after the injury (lateral view); C – X-ray after the injury (anteroposterior view); D – X-ray (lateral and anteroposterior view) after the external fixation; E – X-ray (lateral and anteroposterior view), four months after the injury; F – X-ray (anteroposterior and lateral view) varus and antecurvatum deformity was observed two weeks after the fixator frame removal; G – External fixator with V frame is installed for gradual angular deformity correction; H – X-ray (anteroposterior and lateral view) after deformity correction and after fixator removal, eight months after the injury [20]

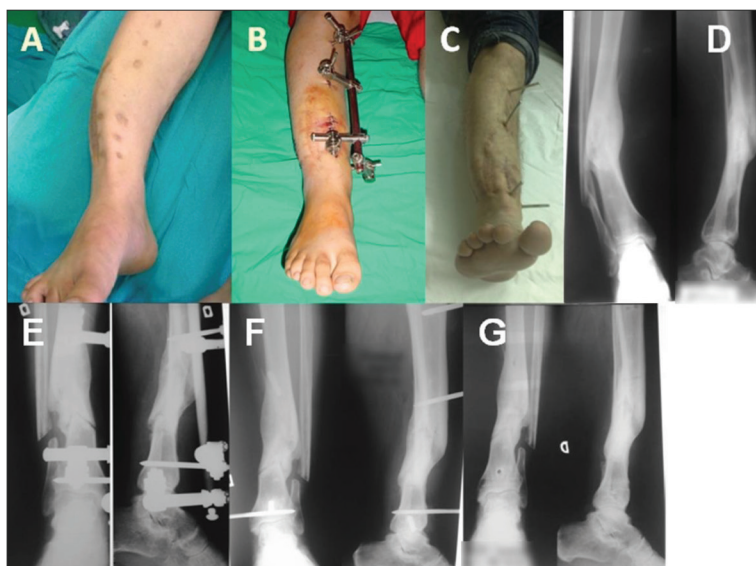


Figure 2. A – Leg of the 29-year-old male patient with posttraumatic varus malunion, before correction; B – The same patient after correction using Mitkovic type external fixator; C – External fixator was removed 100 days after the correction surgery; D – X-rays (anteroposterior and lateral view) of varus (26°) and antecurvatum malunion, 20 months after injury; E – X-rays (anteroposterior and lateral view) one month after tibial and fibular corticotomy, correction of the deformity and application of the Mitkovic type external fixator; F – X-rays (lateral and anteroposterior view) three months after corticotomy and external fixation; G – X-rays (lateral and anteroposterior view) 100 days after correction of the malunion

and 2). The average age was 34.93 years (range 24–49). Ten were male and five were female. The mean healing time was 89.66 (50–125) days. There were two (13.33%) superficial pin tract infections, with good response to local pin care and oral antibiotics. There were no cases of deep infection or nonunion. There were no serious complications such as deep vein thrombosis, deep infection, iatrogenic neurovascular injuries and no instrumentation failure in the present

study. Ten patients suffered from malunion valgus deformity and five patients suffered from a varus deformity. Postoperatively, all patients were encouraged to walk using crutches with 50% weight bearing, gradually increasing until full weight bearing. Generally, full weight bearing was allowed 6–8 weeks after operation. In nine cases, tibial hemi-corticotomy was performed, followed by application of Mitković-V type external fixator, and gradual correction afterwards. In six cases, correction was realized intraoperatively, as “one stage” technique, followed by application of Mitković-CD type external fixator. The follow-up time after surgery was three years. Final functional results were excellent in 13 cases and good in two cases. Poor results were not perceived.

DISCUSSION

Deformities are described in terms of abnormalities of length, angulation, rotation, and translation. The malunion was defined by the location, range, and direction of the deformity. Proper evaluation allows the surgeon to determine an effective plan of deformity correction treatment. Surgical intervention is primarily indicated in symptomatic patients or those with relatively severe deformity. Abnormal joint loading, induced by the deformity, may result in early osteoarthritis. They are generally accepted by the surgical community as being predictive in preventing posttraumatic arthritis of the knee and ankle joints. Once the deformity has been corrected by a corticotomy, the bone requires stabilization to maintain the correction. Internal fixation with plates and screws provides compression across the osteotomy. Intramedullary fixation stabilizes osteotomies and allows early weight bearing. Intramedullary fixation can be technically difficult due to changes in the alignment of the intramedullary canal because of the osteotomy [5]. Gradual correction of a malunion can be performed using Ilizarov external fixator. This device uses distraction osteogenesis by slowly stretching the soft callus at the corticotomy site. The advantage of

this technique is that multiple complex corrections can be performed at one time to include angular, translational, and rotational deformities and length discrepancy [17, 18].

Unilateral Mitkovic external fixators give the possibility of post-traumatic malunion deformities correction using the same biomechanical principle as the Ilizarov fixation method. Mitković-CD type external fixator is suitable for “one stage” correction of tibial shaft malunion. Preferred

location of the corticotomy in this technique is proximal tibial metaphysis. The pins are set proximally (two pins) and distally (two pins) to the corticotomy level before the corticotomy, procedure starts. After corticotomy procedure has been finished, the “one-stage” correction of the deformity is being performed. The final step is the attachment of Mitković-CD type external fixator frame for previously set pins. Mitković-CD type external fixator can also be used in correction of rotational deformities.

Other device, Mitković-V type external fixator, gives the possibility for gradual correction after hemi-corticotomy procedure. This treatment is based on gradual opening wedge technique, after hemi-corticotomy. Hemi-corticotomy can be performed on the same side as external fixation frame is or on opposite side [19]. If hemi-corticotomy is on the same side then opening wedge is performed by distraction of the telescoping unit in the external fixator frame. If hemi-corticotomy is on opposite side, then opening wedge is realized by compression of telescopic unit in the frame. Mitković-V type external fixator also allows corrections of antecurvatum or recurvatum combined with varus or valgus deformities [20]. The fixator-articulating unit has to be set as more as near to the hemi-corticotomy level. Thus, undesirable excess tension between external fixator components is being minimized during the compression or distraction maneuvers in the dynamic unit of the device. As hinge articulating unit is in the bar component of the device, plane of correction can be easily defined by proper rotation of the bar. This rotation can be completed intraoperatively or even postoperatively, within several first postoperative days, during temporary unlocking of the clamps. This procedure requires surgeon's extensive previous experience.

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- Mitković external fixators are unilateral devices and its application is very simple. The most common complication of the present study was pin tract infection, but all of these cases had had good response to local pin care and to oral antibiotics therapy. If over-correction happened during the correction process, it would be easy to perform the correction, by the change of performance direction.

CONCLUSION

Mitković unilateral external fixator system has been proved as successful method in the tibial shaft malunion correction, with good clinical results and with low complications rate. After pins insertion and corticotomy or hemi-corticotomy has been performed, the frame of the device is relatively easy to be set. These external fixation devices and techniques are suitable for minimally invasive surgery.

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Conflict of interest: Saša Milenković and Milan Mitković declare no conflict of interest. Milorad Mitkovic has at this moment agreement with Ortokon, producer of the external fixator, on temporary assignment to the use of patent.

Једностранна спољашња фиксација лоше сраслих прелома дијафизе тибије

Саша С. Миленковић^{1,2}, Милан М. Митковић^{1,2}, Милорад Б. Митковић²

¹Клинички центар Ниш, Клиника за ортопедију и трауматологију, Ниш, Србија;

²Универзитет у Нишу, Медицински факултет, Ниш, Србија

САЖЕТАК

Увод/Циљ Лоше срасли преломи су још увек велики проблем у ортопедској пракси. Спољашња фиксација у лечењу лоше сраслих прелома тибије је последњих година све популарнија.

Циљ рада је евалуација клиничких резултата у третману лоше сраслих прелома дијафизе тибије методом једностранне спољашње фиксације.

Метод У овом раду су анализирани болесници са лоше сраслим преломом дијафизе тибије, који су хируршки лечени методом једностране спољашње фиксације апаратом по Митковићу. Деформитети су кориговани у једној фази спољним фиксатором Митковић-CD или постепено спољним фиксатором Митковић-V. Ова ретроспективна студија

обухвата 15 болесника са лоше сраслим преломом дијафизе тибије. Код 10 болесника су преломи лоше срасли у положају валгус, а код пет болесника у положају варус.

Резултати Просечно време зарастања је било 89,66 дана (50–125 дана). У испитиваној серији није било компликација. Просечно време праћења је било три године. Крајњи функционални резултат је био одличан код 13 и добар код два болесника.

Закључак Метод једностране спољашње фиксације апаратом по Митковићу обезбеђује успешну корекцију лоше сраслих прелома дијафизе тибије, са dobrим резултатима и ниском стопом компликација.

Кључне речи: спољашња фиксација; дијафиза тибије; лоше срастање

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Estimation of risk factors of early postoperative mortality in elderly patients who are subjected to emergency operations of the gastrointestinal tract

Ivan Pešić, Milan Radojković, Milica Nestorović, Vanja Pečić

University of Niš, Faculty of Medicine, Niš Clinical Center, Clinic for Digestive Surgery, Niš, Serbia

**SUMMARY****Introduction/Objective** The elderly (age ≥ 65 years) comprise an increasing proportion of patients undergoing emergency general surgery (EGS) procedures nowadays.

The objective of the paper was to determine the intra-hospital mortality rate in elderly patients undergoing emergency gastrointestinal surgical procedures.

Methods 914 elderly patients (> 65 years old) were examined, divided into two groups: emergency and elective surgery patients, treated for diseases (benign and malignant) of the stomach, duodenum, small intestine and colon. The patients were divided into four age groups and five American Society of Anesthesiologists (ASA) groups, taking into account the presence of chronic diseases, the values of some laboratory parameters, administering transfusion, and the occurrence of surgical complications during hospitalization.**Results** The mortality rate among elderly patients was 17.8%. The univariate analysis in EGS patients revealed that gastro-duodenal surgical interventions ($p < 0.001$), ASA ≥ 3 score ($p < 0.001$), heart, lung, kidney diseases, and postoperative complications ($p < 0.001$), as well as the white cell count $> 10,000/\text{mm}^3$ ($p = 0.043$) were independent risk factors for mortality. In the multivariate analysis, in EGS patients, the significant risk factors for mortality were gastric surgical interventions ($p = 0.001$), ASA score of 4 ($p < 0.001$), heart and kidney disease ($p \leq 0.001$), and white cell count $> 10,000/\text{mm}^3$ ($p = 0.039$).**Conclusion** The characterization of independent validated risk indicators for mortality in those patients is essential and may lead to an efficient specific workup, which constitutes a necessary step towards developing a dedicated score for elderly patients.**Keywords:** elderly; gastrointestinal surgery; mortality**INTRODUCTION**

Increase in the very number of people in the elderly population in developed societies, as well as the use of screening programs, increases the number of requests for surgical procedures in this group of patients. In people aged 65 or older, the patient's risk of requiring surgical procedures is three times higher than in the younger population, especially in the case of emergency conditions [1, 2, 3].

Surgeons are still generally reluctant to treat elderly patients, considering them more sensitive to surgical treatments due to lower physiological reserves, as well as more concealed diseases. The published data that indicate the poor outcome of surgical procedures in the elderly corroborate these facts [2, 3, 4].

Some studies suggest that surgery should often not be postponed in elderly patients. They conclude that the rate of mortality in the elderly can be reduced by performing elective surgical procedures, by carefully "selecting" patients with emergency conditions, thereby excluding the possibility of having inoperable patients, as well as by the participation of a large number of surgeons of various subspecialties during surgery [5].

The objective of the research was to determine the total rate of early postoperative mortality of elderly patients undergoing emergency surgical interventions on the gastrointestinal tract, with an overview of the impact of the American Society of Anesthesiologists (ASA) score, malignant diseases, septic conditions, associated chronic diseases, and the localization of a pathological process to the occurrence of the mentioned.

METHODS

The study, done in accord with standards of the institutional committee on ethics, included the examination of 914 elderly patients (65 years of age and those older than 65) in the period from January 1, 2013 to December 31, 2014 at the Clinic for General Surgery of the Clinical Center in Niš, divided into two groups: emergency and elective surgical care. Patients included in the study were surgically treated for diseases (benign and malignant) of the gastrointestinal tract, and were divided into the following groups: patients with gastric surgical diseases; patients with diseases which required duodenal surgery; patients with diseases which

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Rajićeva 30A/26
18000 Niš
Serbia
sicpeni1977@yahoo.com

required small intestinal surgery; patients with diseases which required colon surgery. Owing to the increased incidence of patients with appendicitis, this group of patients was also isolated. During the research, the sex and age of the patients were also monitored, (four age groups of patients were examined): the first group of patients was 65–69 years of age; the second group of patients was 70–75 years old; the third group of patients was 76–80 years old; the fourth group of patients was over 80 years old. Particular attention was paid to the nature of the underlying disease (benign or malignant), associated chronic diseases (heart diseases, pulmonary function disorder, neurological diseases of the central nervous system, diabetes). In the study, the patients were also included in the ASA classification, and divided into five categories.

The study also included monitoring some laboratory parameters with their measurement on two occasions during patient hospitalization: before the surgery itself, and just before the end of the clinical treatment or before the fatal outcome. The tables show the average values of the tested parameters. The following values were monitored: serum creatinine, serum albumin, total proteins of the serum, erythrocyte values, leukocytes, serum hemoglobin, serum sodium and potassium values, serum parameters that indicate infection (C-reactive protein – CRP, procalcitonin – PCT), glycemic level.

Surgical treatment of the examined patients included surgery of the stomach, duodenum, small intestine and colon, appendectomy.

In the immediate postoperative period, the appearance of surgical complications was observed: laparotomy dehiscence, dehiscence of the primarily performed intestinal/gastro-intestinal anastomosis, postoperative bleeding.

Since surgical treatment, as well as the nature of the underlying disease, is accompanied by blood loss, a decrease in the blood cell count, a decrease in the serum levels of hemoglobin, albumin, and total proteins, the number of received transfusion units was also monitored in the examined patients.

Statistical data processing

The data are presented in the form of an arithmetic mean and a standard deviation, or in the form of absolute and relative numbers. Frequency comparisons were done with the χ^2 test. The comparison of the continuous variables was done with the Mann–Whitney test. The correlation of potential risk factors with mortality was investigated with a univariate and multivariate (backward: Wald method) logistic regression analysis. The calibration ability of the model was tested with the Hosmer–Lemeshow test. The discriminatory ability of the multivariate model was tested on the basis of the receiver operating characteristic curve. The hypothesis was tested with a significance threshold of $p < 0.05$. The data analysis was performed with the SPSS version 16.0 software package (SPSS Inc., Chicago, IL, USA).

Table 1. Demographic and clinical characteristics of the examined population related to the type of operation

Risk factors	Emergency n = 458		Elective n = 456		p [†]
	n	%	n	%	
Patient characteristics					
Age					
65–69	208	45.4	71	15.6	< 0.001
70–74	101	22.1	117	25.6	
75–79	100	21.8	140	30.7	
80+	49	10.7	128	28.1	
Sex of the patients					
Male	417	91	155	34	< 0.001
Female	41	9	301	66	
Clinical characteristics					
Localization					
Stomach	44	9.6	64	14	0.049
Duodenum	53	11.6	5	1.1	< 0.001
Small intestine	176	38.4	2	0.4	< 0.001
Appendix	41	0	0	0	< 0.001
Colon	144	31.4	385	84.4	< 0.001
Type of surgical disease					
Malignant	99	21.6	397	87.1	< 0.001
Benign	359	78.4	59	12.9	
ASA					
1	21	4.6	0	0	< 0.001
2	207	45.2	329	72.1	< 0.001
3	139	30.3	114	25	0.083
4	76	16.6	13	2.9	< 0.001
5	15	3.3	0	0	< 0.001
Heart diseases	375	81.9	328	71.9	< 0.001
Respiratory diseases	52	11.4	61	13.4	0.407
Renal diseases	43	9.4	4	0.9	< 0.001
Neurological disorders	47	10.3	3	0.7	< 0.001
Diabetes mellitus	11	2.4	13	2.9	0.828
Transfusion	230	50.2	242	53.1	0.324
Surgical complications ¹	18	3.9	11	2.4	0.262
Mortality	129	28.2	34	7.5	< 0.001

ASA – American Society of Anesthesiologists scoring;

[†] χ^2 test;

[‡]laparotomy dehiscence, anastomose dehiscence, postoperative bleeding

Table 2. Biochemical parameters with regard to the type of surgery

Biochemical marker [†]	Emergency	Elective	p [‡]
Serum creatinine	160.67 ± 86.59	106.54 ± 37.77	< 0.001
Total proteins	61.42 ± 14.22	66.76 ± 8.28	< 0.001
Serum albumin	34.84 ± 10.67	40.45 ± 7.17	< 0.001
Erythrocyte count	4.22 ± 1.04	4.11 ± 0.46	0.003
Leukocyte count	11.57 ± 6.75	8.68 ± 3.16	< 0.001
Serum hemoglobin	125.25 ± 30.68	122.8 ± 16.66	0.003*
Serum sodium	133.95 ± 5.35	137.14 ± 3.04	< 0.001
Serum potassium	4.32 ± 0.71	4.37 ± 0.57	0.061
CRP	133.41 ± 93.23	82.46 ± 68.4	< 0.001
PCT	1.41 ± 9.02	0.27 ± 3.72	< 0.001
Glycaemia	18.36 ± 4.13	4.79 ± 6.08	< 0.001

CRP – C-reactive protein; PCT – procalcitonin;

[†]mean ± SD;

[‡]Mann–Whitney test;

*t-test

Table 3. Risk factors of a fatal outcome with regard to the type of surgery (univariate logistic regression analysis)

Risk factors	Emergency procedure				Elective procedure			
	Death yes/no	OR	95% CI	p	Death Yes/no	OR	95% CI	p
Female	41/41	-		< 0.001	27/301	2.083	0.886–4.899	0.127
Male	88/417				7/155	Reference group		
Age								
65–69	28/208	Reference group			7/71	Reference group		
70–74	28/101	2.465	1.367–4.449	0.004	10/117	0.948	0.349–2.606	0.917
75–79	24/100	2.031	1.106–3.727	0.032	17/140	1.402	0.554–3.543	0.623
80+	49/49	-	-	-	0/128	-	-	-
Localization of surg. dis.								
Stomach	24/44	3.531	1.874–6.653	< 0.001	7/64	1.660	0.691–3.990	0.257
Duodenum	23/53	2.163	1.203–3.888	0.010	0/5	-	-	-
Small intestine	46/176	0.848	0.556–1.295	0.446	0/2			
Colon	36/144	0.792	0.506–1.240	0.308	27/385	0.690	0.288–1.651	0.404
Appendix	0/41	-			0/0			
ASA								
1	0/21				0/0			
2	4/207				11/329	Reference group		
3	41/139	21.232	7.395–60.955	< 0.001	10/114	2.780	1.148–6.732	0.023
4	69/76	500.250	142.112–1760.932	< 0.001	13/13	-	-	-
5	15/15	-	-		0/0	-	-	-
Heart diseases	114/375	1.980	1.086–3.611	0.026	33/328	14.207	1.922–105.00	0.009
Respiratory diseases	32/52	5.097	2.788–9.319	< 0.001	13/61	4.823	2.269–10.254	< 0.001
Renal diseases	32/43	9.537	4.634–19.628	< 0.001	4/4	-	-	-
Neurological disorders	13/47	0.972	0.495–1.908	0.935	3/3	-	-	-
Diabetes mellitus	11/11				3/13	3.987	1.043–15.240	0.043
Transfusion	114/230	13.955	7.783–25.022	< 0.001	31/242	10.333	3.111–34.320	< 0.001
Surgical complications ¹	15/18	13.965	3.970–49.117	< 0.001	5/11	12.012	3.458–41.790	< 0.001
Malignant surg. diseases	24/99	1.292	0.774–2.157	0.328	32/397	2.499	0.583–10.711	0.218
Leukocytes > 10,000	92/118	4.246	1.199–15.032	0.043	25/78	3.655	1.389–9.619	0.014

OR – odds ratio; CI – confidence interval; ASA – American Society of Anesthesiologists scoring;

¹laparotomy dehiscence, anastomose dehiscence, postoperative bleeding**Table 4.** Risk factors for a fatal outcome with regard to the type of procedure (multivariate logistic regression analysis)

Risk factors	Emergency procedure			Elective procedure		
	OR	95% CI	p	OR	95% CI	p
Sur. diseases on the stomach	4.028	1.742–9.311	0.001			
ASA 3				1.899	0.757–4.762	0.171
ASA 4	65.896	26.913–161.343	< 0.001			
Heart diseases	5.032	1.928–13.138	0.001	8.029	1.055–61.085	0.044
Respiratory diseases				6.453	2.635–15.801	< 0.001
Renal diseases	27.714	10.110–75.977	< 0.001			
Malignant sur. diseases				0.177	0.032–0.974	0.047
Leukocytes > 10,000	2.781	1.596–36.097	0.039			
Hosmer–Lemeshow test	p = 0.633			p = 0.123		
C index	0.852, p < 0.001			0.863, p < 0.001		

OR – odds ratio; CI – confidence interval; ASA – American Society of Anesthesiologists scoring

RESULTS

It was determined that there is a statistically significant difference between emergency and elective procedures in the age categories ($p < 0.001$). Elective surgical procedures are statistically significantly more common in female patients (66% vs. 9%, $p < 0.001$). ASA score 2 is dominant in elective surgical procedures ($p < 0.001$). The elective surgical procedures are dominant in patients with diseases requiring colon surgery (84.4% vs. 31.4%, $p < 0.001$). Small intestine

surgery was statistically significantly more commonly performed in emergency surgical procedures (38.4% vs. 0.4%, $p < 0.001$). The incidence of heart disease, kidney disease, and neurological disorders is statistically significantly higher in patients undergoing emergency surgical procedures ($p < 0.001$). Malignant surgical diseases are statistically significantly more commonly treated as elective surgical procedures ($p < 0.001$). The death outcome was statistically significantly more common in emergency surgical procedures ($p = 0.021$). Surgical complications

were equal between emergency and elective surgical procedures ($p = 0.262$).

In emergency surgical procedures, the following values were statistically more significant: serum creatinine ($p < 0.001$), erythrocyte count ($p < 0.001$), leukocyte count ($p < 0.001$), hemoglobin ($p < 0.001$), CRP ($p < 0.001$), PCT ($p < 0.001$), and glycaemia ($p < 0.001$). In patients with performed elective surgery, statistically significant values were the following: total serum proteins ($p < 0.001$), serum albumin ($p < 0.001$), and serum sodium ($p < 0.001$).

In emergency surgical procedures, in the univariate model, the statistically significant risk factors for fatal outcome were the following: age, surgical interventions on the stomach and duodenum, ASA 3 and ASA 4 score, comorbidity on the heart, lungs, kidneys, surgical complications, transfusion, and the value of leukocytes above 10,000 units/ml. In elective surgical procedures, in the univariate model, statistically significant risk factors for fatal outcome were the following: ASA 3 score, comorbidity on the heart, lungs, diabetes, surgical complications, malignant type of surgical disease, receiving transfusion, leukocyte value over 10,000 units/ml.

For emergency surgical procedures, in the multivariate model, the following were statistically significant risk factors, corrected for the other parameters in the model: surgical gastrointestinal diseases, ASA 4 score, heart and renal disease, and leukocyte level above 10,000 units/ml. For elective surgical procedures, in the multivariate model, the following were statistically significant risk factors for fatal outcome, corrected for the other parameters in the model: the ASA 3 score, heart and respiratory diseases, and malignant surgical diseases.

The patients who underwent emergency surgery had statistically significantly lower survival compared to patients treated with elective surgery ($p < 0.001$) (Figure 1). The shortest survival was exhibited by patients with duodenal surgery, followed by surgery of the small intestine,

while the patients with surgical diseases of the stomach and colon had the longest survival. It has been established that there is a statistically significant difference in the length of intra-hospital survival compared to the localization of the surgical disease itself ($p < 0.001$) (Figure 2). The patients with malignancies had statistically significantly shorter survival compared to the patients with benign diseases ($p < 0.001$) (Figure 3).

DISCUSSION

In people aged 65 years and older, the risk of death to the patient from the required surgical procedures is three times higher than to the younger population, especially in the

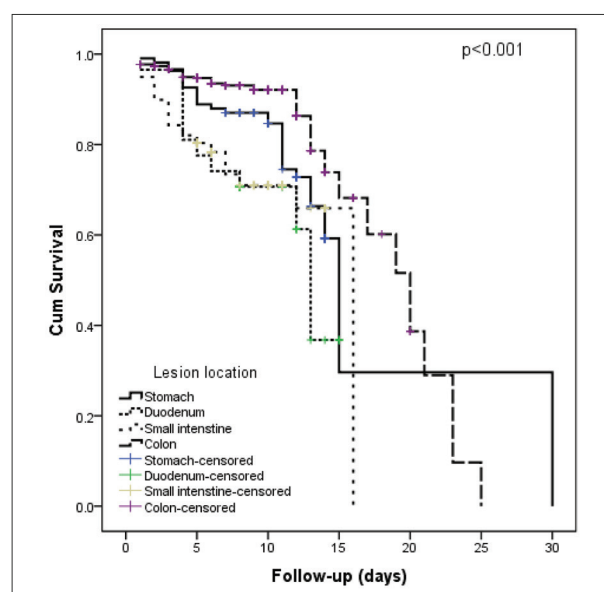


Figure 2. The Kaplan–Meier curve of intra-hospital survival with regard to the localization of the surgical disease in the whole population

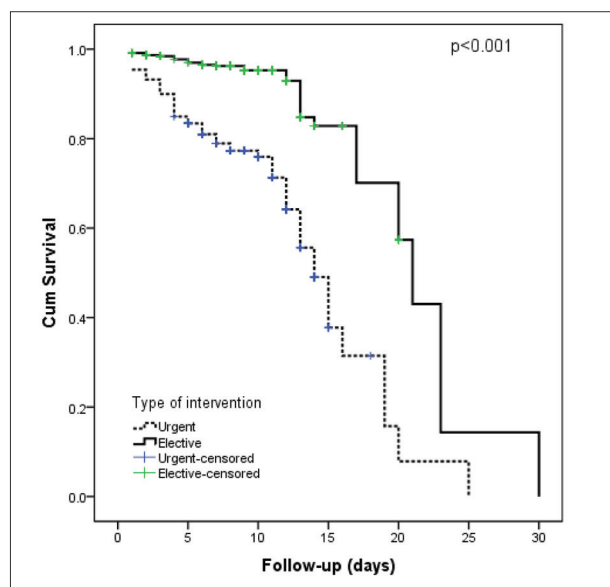


Figure 1. The Kaplan–Meier curve of intra-hospital survival with regard to the type of surgery in the whole population

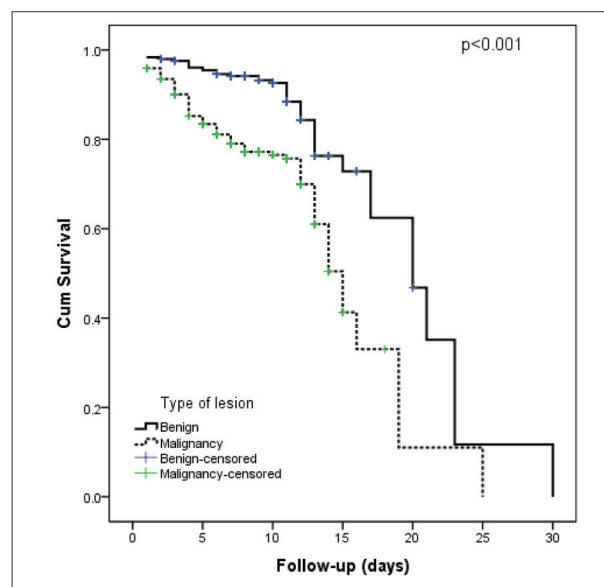


Figure 3. The Kaplan–Meier curve of intra-hospital survival with regard to the type of lesion in the whole population

case of emergency conditions [5]. Ozturk and Yilmazlar [6] did not show a statistically significant correlation between age and mortality of elderly patients undergoing gastrointestinal tract surgery, while in other authors' studies, the "age of the patients," as an independent risk factor of direct postoperative mortality, was statistically significant [7]. According to our data, it was found that the largest number of patients who underwent surgical care was 65–69 years of age. In addition, there is a statistically significant difference in age in relation to the fatal outcome, so in the group of emergency surgically treated patients, the group of 70–74-year-olds had an almost 2.5 times greater chance of a fatal outcome (OR 2.465) compared to the reference group (65–69), while in the group of elective surgically treated patients, the group of 75–79-year-olds had a 1.5% greater chance of a death outcome (OR 1.402) than the reference group (65–69).

Emergency surgery is a well-known risk factor [8–12]. It increases the operative mortality rate from three to as many as 10 times [10]. Ozturk and Yilmazlar [6] state that about 70% of the non-surviving patients were subjected to emergency surgery. Some authors indicate a better outcome in elderly patients who underwent elective surgery, compared to emergency surgical care patients [12]. Our data suggest that the fatal outcome was statistically significantly more common in emergency procedures ($p = 0.021$).

The data obtained in our study show that elective surgical procedures were statistically significantly more frequent in female patients (66% vs. 9%, $p < 0.001$). In the group of elective patients, female patients had a two times greater chance of death outcome (OR 2.083), compared to male patients, which was in correlation with some other studies [13].

Patients with a higher ASA score have a higher chance of fatal outcome [14]. In elective care patients, with an increase in the ASA score by 1, the chance of fatal outcome increases by almost three times (OR 2.780), while the chance is far greater in emergency care patients.

Some studies indicate that the primary preoperative factor for a poor surgical outcome in the elderly was the comorbidity itself rather than age [15]. Electively treated patients with respiratory diseases had an almost five times greater chance of fatal outcome (OR 4.823), while emergency care patients with respiratory and renal diseases had an almost five and nine times greater chance of fatal outcome, respectively (OR 5.097; OR 9.537).

In the category of "laboratory values," Visser et al. [13] reveal three statistically significant morbidity and mortality factors: an elevated level of serum creatinine, reduced preoperative albumin level and elevated leukocyte levels. In our study, serum creatinine values were statistically significantly higher in emergency procedures ($p < 0.001$).

Hypoalbuminemia is a common laboratory abnormality in the elderly, which can lead to high morbidity and mortality [16]. In patients who underwent elective surgical procedures, the statistically significantly higher values were total serum proteins ($p < 0.001$) and serum albumin ($p < 0.001$).

In sepsis, the underlying problem is the high rate of mortality, which is even higher than in patients at the mo-

ment of myocardial infarction [17]. According to our data, the CRP values were statistically significantly higher in emergency procedures ($p < 0.001$).

Neumayer et al. [18] report that the leukocyte value above 10,000 units/ml was statistically significant for the development of a serious infectious process, while, according to Davenport et al. [19], the value of leukocytes above 10,000 units/ml was statistically significant for the development of heart complications. Our data indicate that leukocyte values were statistically significantly higher in emergency surgically treated patients. Emergency surgically treated patients with values of leukocytes above 10,000 units/ml have a 2–4 times greater chance of fatal outcome (OR 2.781; OR 4.246), compared to patients of the same examined group without leukocytosis, while in cases of patients with elective surgical treatment, with leukocyte values above 10,000 units/ml, the chance of fatal outcome was 3.5 times higher (OR 3.655).

The serum hemoglobin concentration was higher in patients with emergency surgical treatment, compared to the elective ones, but not at the level of statistical significance, which was in correlation with previous studies [16].

Surgery of the upper part of the digestive tract increases the risk of heart and respiratory complication occurrence [20]. Our research has established that there is a statistically significant difference in the localization of the disease itself compared to fatal outcomes, so gastric surgical diseases were at the level of statistical significance ($p < 0.001$). The shortest survival was exhibited in patients with duodenal diseases, followed by the ones with diseases of the small intestine, while the patients with stomach and colon diseases had the longest survival.

Many patients who develop surgical anemia receive a transfusion. The outcome of such patients is poor, and it is not clear whether this is due to bleeding, anemia, or the transfusion itself [21]. In our study, both in emergency and in elective surgical procedures, in the univariate model, the transmission of transfusion was also considered a statistically significant risk factor for fatal outcome. Patients receiving transfusion had a 14 times (OR 13.955) greater chance of fatal outcome in emergency cases and a 10 times (OR 10.333) greater chance of fatal outcome in elective care patients, compared to non-transfusion patients.

Duron et al. [22] indicate that the presence of a malignant surgical disease as a risk factor for immediate postoperative mortality is at the level of statistical significance. Malignant changes are statistically significantly more commonly operated on in the form of elective surgical procedures ($p < 0.001$). Elective surgery-treated oncology patients have a three times greater chance of a fatal outcome, compared to non-oncology patients of the same group (OR 2.499).

Wound dehiscence is one of the most common early postoperative complications with a frequency of approximately 2% [23]. There is no unique cause that leads to laparotomy dehiscence, and, as a rule, there is a combination of several factors, such as old age, anemia, jaundice, uremia, diabetes, hypoalbuminemia, COPD, malignancy, steroid use, obesity, wound infection, intra-abdominal sepsis,

emergency surgery [24]. Among the postoperative complications, anastomosis dehiscence leads to greater pain and distress of the patient than any other surgical complication [25]. The percentage of anastomosis dehiscence depends on the location of occurrence: stomach 1–9%, small intestine 1–3%, colon 3–29%, and rectum 8–41% [26–30]. Owing to surgical complications, re-intervention was performed in 15 deceased emergency surgery-treated patients and in five deceased elective surgery-treated patients. Emergency surgery-treated patients with surgical complications had a 14 times greater chance of fatal outcome (OR 13.965), while in elective surgery-treated patients with surgical complications, this chance was 12 times higher (OR 12.012).

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CONCLUSION

Our research suggests that fatal outcome was statistically significantly more common in emergency surgical procedures. Premorbid factors, characteristics of the disease, the preoperative condition of patients, and operative factors predict a poor surgical outcome.

The characterization of independent validated risk indicators for mortality in those patients is essential and may lead to an efficient specific workup, which constitutes a necessary step towards developing a dedicated score for elderly patients.

Conflict of interest: None declared.

Процена фактора ризика ране постоперативне смртности болесника старијег животног доба подвргнутих хитним хируршким операцијама на гастроинтестиналном тракту

Иван Пешић, Милан Радојковић, Милица Несторовић, Вања Пецић

Универзитет у Нишу, Медицински факултет, Клинички центар Ниш, Клиника за дигестивну хирургију, Ниш, Србија

САЖЕТАК

Увод/Циљ Болесници старијег животног доба (≥ 65 година) узимају све више удела као хитно хируршки збринуте болесници.

Циљ студије је био одредити стопу интрахоспиталне смртности болесника старијег животног доба, подвргнутих хитним гастроинтестиналним хируршким интервенцијама.

Методе Испитивано је 914 болесника старијег животног доба (> 65 година) подељених у две групе – ургентно и елективно хируршки збринуте, а због болести (бенигних и малигних) на желуцу, дуоденуму, танком и дебелом цреву. Болесници су били подељени и у четири старосне групе и пет група које је дефинисало Америчко удружење анестезиолога (*American Society of Anesthesiologists – ASA*) уз осврт на присуство хроничних обољења, вредности неких лабораторијских параметара, давање трансфузије и појаву хируршких компликација током хоспитализације.

Резултати Укупна стопа смртности у испитиваној популацији била је 17,8%. Униваријантна регресиона анализа код

ових болесника открива да су гастродуоденалне хируршке интервенције ($p < 0,001$), $ASA \geq 3$ скор ($p < 0,001$), срчана, респираторна, бубрежна обољења, постоперативне компликације ($p < 0,001$), као и вредност леукоцита $> 10.000/mm^3$ ($p = 0,043$), представљали независне факторе ризика од смртности. У мултиваријантној анализи исте групе болесника статистички значајни фактори смртности били су: гастричне хируршке интервенције ($p = 0,001$), $ASA 4$ скор ($p < 0,001$), респираторна и срчана обољења ($p \leq 0,001$), вредност леукоцита $> 10.000/mm^3$ ($p = 0,039$).

Закључак Карактеризација независних прогностичких фактора ризика ове групе болесника је од суштинског значаја и може довести до ефикаснијег лечења, што представља неопходан корак у изради наменског бодовног система ових болесника.

Кључне речи: старија животна доб; гастроинтестинална хирургија; смртност



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Benign transient hyperphosphatasemia in children

Nedeljko Radlović¹, Zoran Leković^{2,3}, Vladimir Radlović², Siniša Dučić^{2,3}, Zoran Golubović^{2,3}, Marija Mladenović⁴, Meho Mahmutović⁵, Polina Pavićević^{2,3}, Goran Đuričić², Snežana Petrović-Tepić⁶

¹Serbian Medical Society, Academy of Medical Sciences, Belgrade, Serbia;

²University Children's Hospital, Belgrade, Serbia;

³University of Belgrade, Faculty of Medicine, Belgrade, Serbia;

⁴Valjevo Medical Centre, Valjevo, Serbia;

⁵Novi Pazar General Hospital, Novi Pazar, Serbia;

⁶University of Banja Luka, Faculty of Medicine, Republic of Srpska, Bosnia and Herzegovina

SUMMARY

Introduction/Objective Benign transient hyperphosphatasemia (BTH) is a pathogenetic insufficiently clear clinical entity that is mostly seen in infants and young children.

The objective of this paper is to present our experience regarding the age of occurrence, the conditions of the discovery, and the length of duration of BTH in children.

Methods The study was realized on a sample of 18 children, nine boys and nine girls, aged 10–42 (21.06 ± 9.35) months with BTH. The diagnosis of BTH is based on the absence of bone and hepatobiliary diseases, and its spontaneous disappearance over the course of several months.

Results One patient was in the first year, 13 in the second, three in the third, and one in the fourth. Isolated high activity of serum alkaline phosphatase, which was 2.04–21.9 (8.05 ± 5.31) times above the upper reference value for the corresponding age, in 14 cases it was found during the acute diarrhea, and in four with acute rhinopharyngitis, of which in two complicated with otitis media. The cause of diarrhea in six cases was rotavirus, in two *Campylobacter*, and in one adenovirus, and otitis media in one case was caused by *Streptococcus pneumoniae*, while in others, etiologic factors of infection were not identified. Spontaneous normalization of serum alkaline phosphatase activity was recorded between one and three months after the onset.

Conclusion BTH is a harmless biochemical disorder that spontaneously subsides within three months after initial observation. It is found randomly as a routine laboratory finding most often within the treatment of acute gastrointestinal and respiratory infections.

Keywords: benign transient hyperphosphatasemia; diagnostics; children

INTRODUCTION

Benign transient hyperphosphatasemia (BTH) is a complex and pathogenetically vague clinical entity expressed by transiently increased serum activity of alkaline phosphatase (ALP) [1–7]. It occurs in the absence of skeletal, liver, and other diseases characterized by the increase in ALP [2, 3, 5–9]. It is detected by accident either during routine health check or by examining one of the diseases [2, 3, 5–10]. It is most commonly found in children under five years of age, especially in infants, and rarely later [2–12]. Although seldom, BTH also occurs in adults [13]. Return to normal ALP levels usually occurs within four months, and sometimes a little later [4, 9–12]. The most common circumstance of its occurrence are various infections, usually viral, and rarely other pathological conditions [1, 3, 10, 14]. Bearing in mind the absence of any negative consequences, BTH is considered a benign biochemical disorder and does not require extensive investigations nor the use of vitamin D or other therapeutic procedures [3, 4, 8].

We present our experience regarding the age of occurrence, detection conditions, diagnostic mode, and duration of BTH in children.

METHODS

The study included a sample of 18 children, nine boys and nine girls, aged 10–42 (21.06 ± 9.35) months with BTH. The diagnosis of BTH is based on the absence of bone and hepatobiliary diseases, and its spontaneous disappearance over the next few months. The study protocol was approved by the local ethics committee.

Apart from current infections in which isolated elevated serum ALP levels were identified, medical history, clinical findings, and routine laboratory analyzes indicated that the patients were healthy, optimally developed and adequately nourished children.

Bearing in mind the fact that skeletal and hepatobiliary diseases are the most frequent cause of increased serum activity of ALP, initial diagnostic procedures have been primarily targeted in this direction. In this sense, ultrasonographic examination of the abdomen and radiography of the wrist was done in all the patients. A key laboratory parameter for the absence of a hepatobiliary disease as the cause of hyperphosphatemia was the normal serum activity of gamma glutamyl transferase, while the elimination of bone disease was based on

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Correspondence to:

Nedeljko RADLOVIĆ
Serbian Medical Society
Džordža Vašingtona 19
11000 Belgrade, Serbia
n.radlovic@botel.net

the values of several laboratory parameters, such as normal serum calcium, phosphorus, 25(OH)D, parathyroid hormone, creatinine, as well as blood acid-base status and urinary calcium/creatinine ratio. After skeletal and hepatobiliary disorders were excluded, the follow-up of the patients included a checkup of ALP every two to four weeks, until the normalization of the values.

RESULTS

One patient was in the first year, 13 in the second, three in the third, and one in the fourth.

In all the patients, BTH was detected accidentally within a routine laboratory blood test, in 14 with acute diarrhea and in four with acute rhinopharyngitis, two of which complicated by otitis media. The cause of diarrhea in six cases was rotavirus, in two it was *Campylobacter*, and in one adenovirus, and otitis media in one case was caused by *Streptococcus pneumoniae*, while in other etiologic factors of infection it was not identified.

The initial value of serum ALP was 2.04–21.9 (8.05 ± 5.31) times above the upper reference value for the corresponding age, while its spontaneous normalization was registered approximately after one to three months of follow-up – in 10 patients within one month, in four within five months, and in four within three months.

DISCUSSION

ALP is an omnipresent cell membranous zinc-containing metalloenzyme that catalyzes the hydrolysis of phosphate monoesters at basic pH values [15, 16]. According to the origin, human APHs are divided into four isozymes – intestinal, placental, germ cell, and tissue nonspecific or liver/bone/kidney [2, 15, 16]. Except for the bone ALP, which has a role in skeletal mineralization, the exact physiological function of other isoenzymes both in the physiological and pathological conditions is not clear [16–19]. In circulation it is an inactive enzyme. The half-life of the liver isoenzyme in the blood is three days, and of the bone isoenzyme it is one to two days [20, 21]. The serum level of ALP in children is normally two to three times higher than in adults due to physiologically higher osteoblast activity [2]. For the same reason, bone isoenzyme in healthy children contributes by 85% to ALP activity, and liver isoenzyme contributes by only 15% [2]. Due to placental isoenzyme, the serum ALP level is physiologically elevated during pregnancy, while in all other conditions, with the exception of BTH, it represents a significant marker of the presence of various diseases, primarily skeletal and hepatobiliary [3].

BTH represents a harmless biochemical abnormality that spontaneously disappears within a few months [1–9]. It is most commonly found in children under five years of age, usually as an incidental finding during laboratory testing in routine health care, or as part of an evaluation for a specific complaint [2, 3, 5, 10]. When it comes to children, the most common illnesses accompanied by BTH are various infections, usually viral, and rarely other pathological conditions [1–5, 10, 11, 14, 22, 23, 24]. Also, BTH occurs as part of the use of some drugs, such as sulfamethoxazole/trimethoprim, cyclosporine, methotrexate and 6-mercaptopurine, as well as after renal and liver transplantation [25–28]. There are descriptions of rare cases of benign familial hyperphosphatasemia [29, 30].

Our patients demonstrate the classic features of children with BTH. Apart from current infections in which isolated elevation of serum ALP levels were identified, all were healthy, optimally developed and adequately nourished children. They all belonged to the children of the youngest age, of whom 13 were in the second and third year, one in the first, and one in the fourth. Similar to most authors, BTH was found in our patients as an incidental finding during routine laboratory testing as part of an evaluation of intercurrent infections. In 14 of our patients, BTH was identified during acute infectious diarrhea, and in four during acute upper respiratory infection, two of which were complicated by otitis media. The cause of diarrhea in six patients was rotavirus, *Campylobacter* was the cause in two, and adenovirus in one, while *Streptococcus pneumoniae* was the cause of otitis media in one patient; in other patients, etiologic factors of infection were not identified. The period of spontaneous normalization of serum ALP activity occurred after 1–3 months, so none of them, except initial exclusion of bone and hepatobiliary disease, required additional examination.

CONCLUSION

BTH represents a harmless biochemical disorder. Its diagnosis is based on the absence of bone and hepatobiliary diseases, and its spontaneous disappearance over the next few months. According to our findings, it occurs in children within the first four years of life as a random finding during a routine laboratory testing as part of evaluation of intercurrent gastrointestinal and respiratory infections. If bone and hepatobiliary disorders are excluded and thereafter a spontaneous fall in the serum ALP activity takes place, no additional examination is required.

Conflict of interest: None declared.

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Бенигна пролазна хиперфосфатаземија код деце

Недељко Радловић¹, Зоран Лековић^{2,3}, Владимир Радловић², Синиша Дучић^{2,3}, Зоран Голубовић^{2,3}, Марија Младеновић⁴, Мехо Махмутовић⁵, Полина Павићевић^{2,3}, Горан Ђуричић², Снежана Петровић-Тепић⁶

¹Српско лекарско друштво, Академија медицинских наука, Београд, Србија;

²Универзитетска дечја клиника, Београд, Србија;

³Универзитет у Београду, Медицински факултет, Београд, Србија;

⁴Медицински центар „Ваљево“, Ваљево, Србија;

⁵Општа болница „Нови Пазар“, Нови Пазар, Србија;

⁶Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина

САЖЕТАК

Увод/Циљ Бенигна пролазна хиперфосфатаземија (БПХФ) представља патогенетски недовољно јасан клинички ентитет, који се претежно виђа код одојчади и мале деце.

Циљ рада је да се изнесу наша искуства везана за узраст јављања, околности откривања и дужину трајања БПХФ код деце.

Методе Рад је реализован на узорку од 18 деце – девет дечака и девет девојчица, узраста 10–42 ($21,06 \pm 9,35$) месеца са БПХФ. Дијагноза БПХФ је базирана на одсуству коштаних и хепатобилијарних обољења, као и њеном спонтаном ишчезавању током неколико наредних месеци.

Резултати Једно дете је било у првој години, 13 у другој, три у трећој и једно у четвртој. Изолована висока активност серумске алкалне фосфатазе, која је била $2,04\text{--}21,9$ ($8,05 \pm 5,31$) пута изнад горње референтне вредности за одговарајућу старост, код 14 случајева је нађена у оквиру акутне дија-

реје и код четири случаја са акутним ринофарингитисом, од чега код два са компликованим отитисним медијем. Узрок дијареје у шест случајева био је ротавирус, у два случаја кампилобактерија и у једном случају аденовирус, а узрок отитисног медија у једном случају биле су стрептококе пнеумоније, док код осталих етиолошки чинилац инфекције није идентификован. Спонтана нормализација серумске активности алкалне фосфатазе регистрована је између једног и три месеца.

Закључак БПХФ представља безазлен биохемијски поремећај који се спонтано повлачи унутар три месеца после иницијалне опсервације. Открива се случајно као рутински лабораторијски налаз најчешће у склопу третмана акутних гастроинтестиналних и респираторних инфекција.

Кључне речи: бенигна пролазна хиперфосфатаземија; дијагностика; деца



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Incidence of bronchopulmonary dysplasia and mortality of very low birth weight infants in Vojvodina

Gordana Vilotijević-Dautović^{1,2}, Aleksandra Doronjski^{1,2}, Gordana Vijatov-Đurić^{1,2}, Milena Bjelica^{1,2}¹Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia;²University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia**SUMMARY**

Introduction/Objective The incidence of bronchopulmonary dysplasia (BPD) varies depending on the prematurity rate, definition, and therapy that are applied at a certain center. The average incidence of BPD for very low birth weight infants (VLBW) in developed countries ranges 4–53%. The mortality of VLBW infants is high and represents 50% of the total neonatal and infant mortality. In recent years, the survival limits are shifted towards lower gestations. The aim of our study was to determine the incidence and severity of BPD in VLBW infants in Vojvodina and the overall mortality.

Methods This retrospective study was conducted from January 2006 to December 2011 and included 504 infants with birth weight < 1,500 g.

Results In the total premature infants' population, 82.3% survived by the gestational age of 36 weeks. According to the original definition of BPD, as supplemental oxygen use at 28 days of life, BPD had 45.4% of infants. According to the severity based definition 19.4% had mild BPD, 19.8% moderate BPD and 6.5% severe BPD. If BPD is observed as supplemental oxygen use at 36 weeks postmenstrual age, BPD had 26% of infants.

Conclusion The overall mortality and incidence of BPD in our study are comparable to those in some developed countries and lower compared to underdeveloped countries.

Keywords: bronchopulmonary dysplasia; mortality; incidence; infant, very low birth weight

INTRODUCTION

When Northway described bronchopulmonary dysplasia (BPD), the gestational age (GA) of infants who had BPD was around 34 weeks and the average birth weight (BW) was 2,200 g. The mortality rate of those children was 59% [1]. Today, BPD rarely occurs in infants with BW over 1,500 g and GA over 32 weeks [2]. Since then, new preventive and therapeutic methods were introduced, the most important being: prenatal application of corticosteroids in cases of a premature labor risk, as well as the surfactant usage and noninvasive ventilation, which enhanced the survival of very low birth weight (VLBW) infants, who are at the greatest risk of having BPD [2, 3, 4]. For this reason, the incidence of BPD in VLBW infants in recent years mainly stagnates [5].

According to the literature, the incidence of BPD differs in accordance to the rate of prematurity, definition, and therapy that are applied at a certain center [2, 6]. The incidence varies depending on whether BPD is defined according to the original definition – as dependence on oxygen therapy at the age of 28 days, according to clinical definition – as dependence on oxygen therapy at the postmenstrual age (PMA) of 36 weeks, or by physiological definition. Differences in incidence also exist depending on which group of infants is taken into account,

i.e. which is the upper limit of GA or BW, and whether all infants or only surviving ones are considered. Taking into account the differences, the overall average incidence of BPD for VLBW infants in different countries ranges 4–53% [3, 7–11].

According to the data of the neonatal research network of the National Institute for Child Health and Human Development (NICHD) from 1997 to 2002 in VLBW infants at 28 days the BPD incidence ranged 11–41% (on average 25%), at 36 weeks PMA it varied 10–50% (on average 22%) [7]. According to the NICHD's data from 2003 to 2007 in infants with BW ≤ 1,500 g and GA < 29 weeks the average incidence of BPD according to the severity based BPD definition (Jobe and Bancalari, 2001) was 68% (27% mild, 23% moderate and 18% severe BPD) [5, 12]. Taking into account the clinical definition (at 36 weeks of PMA), the average incidence was 42% (20–89%), and if surviving infants were considered only, it was 43%. According to the physiological definition, the average incidence was 40% (15–82%) [5].

The Vermont Oxford Network published that from 2000 to 2009 the incidence of BPD in surviving VLBW infants at 36 weeks PMA recorded a statistically significant decrease (from 27.7 to 26.3%) [3].

The incidence of BPD in our community has not been determined so far. There are major

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Correspondence to:

Gordana VILOTIJEVIĆ-DAUTOVIĆ
Institute of Child and Youth
Health Care of Vojvodina
Hajduk Veljkova 10
21000 Novi Sad, Serbia
gordana.vilotijevic-dautovic@mf.uns.ac.rs

Table 1. Birth weight of infants

Birth weight	≤ 500 g	501–700 g	700–1,000 g	1,001–1,250 g	1,251–1,499 g	< 1,500 g
Number of patients (%)	9 (2)	39 (8)	109 (22)	158 (31)	189 (37)	504 (100)

Table 2. Gestational age of infants

Gestational age (weeks)	21–22	23–24	25–26	27–28	29–30	31–32	33–34	35–36	< 36
Number of patients (%)	4 (1)	33 (7)	65 (13)	118 (23)	139 (28)	108 (21)	28 (6)	9 (2)	504 (100)

variations in different regions in the incidence of BPD in VLBW infants, that indicate that organizational, preventive, and therapeutic differences may affect the incidence of BPD, such as: prenatal use of corticosteroids and antibiotics in case of a risk of premature delivery, tocolysis for the purpose of delaying premature labor, application of surfactant, non-invasive mechanical ventilation and other measures [2, 7, 9]. Considering that, in a survey involving infants with GA < 32 weeks from 10 European countries in 2003, the incidence of BPD at 36 weeks PMA ranged 10.2–24.8% [13]. The biggest difference between neonatal care centers was reported in South Korea where the incidence of BPD in infants with BW < 1,500 g ranged 5–50% [14].

The mortality of VLBW infants is high and represents 50% of the total neonatal and infant mortality. The high mortality rate of VLBW infants is due to immaturity of organs and reduced adaptability to extrauterine life [3, 6, 15]. In recent years, after new preventive and therapy strategies were applied, the survival limits are shifted towards lower gestations. The NICHD's data show that the mortality of VLBW infants from 1988 to 1996 was reduced 26–16%. After 1996, mortality rate was decreasing slowly, but the survival rate of the infants with the lowest GAs significantly increased, indicating further progress in perinatal health care [4, 7]. The Vermont Oxford Network's survey showed that from 2000 to 2009 there was a mortality decline from 14% to 12.4%. The highest drop in mortality was found in the group of infants with the lowest BWs (501–750 g), from 41.8% to 36.6%, while in the groups of infants with BW 1,001 to 1,250 g, and 1,251 to 1,500 g it was constant – about 6% and 3.5%, respectively [3].

METHODS

The retrospective study was conducted in the six-year-long period, from January 2006 to December 2011. This study was done in accordance with the standards of the institutional Committee on Ethics. The population in study was composed of 504 premature infants with BW < 1,500g who were hospitalized in a tertiary Center for newborn and neonatal intensive care at the Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia. In this period, there were 530 VLBW infants. Newborns with congenital heart defects, congenital genetic, metabolic diseases and chromosomopathies, who died after 12 hours of life or who did not have all the data needed to be included in the study, were not included. The incidence and severity of BPD in all live-born and in survived VLBW infants was determined, as well as the overall mortality.

RESULTS

Gestational age and birth weight of infants

The average birth weight was $1,125.6 \pm 280.9$ g. Out of the total number of infants ($n = 504$), 32% ($n = 157$) had BW ≤ 1,000 g and 68% ($n = 347$) had BW > 1,000 g (Table 1).

The average GA was 28.78 ± 3.01 weeks. Analyzing by subgroups, the highest number of infants was born at GA ≤ 32 weeks, 92.7% ($n = 467$), the remaining 7.3% ($n = 37$) was born at GA 33–36 weeks (Table 2).

Incidence of bronchopulmonary dysplasia

According to the definition that takes into account the severity of BPD (15), 45.4% ($n = 229$) had BPD, 19.4% had mild BPD, 19.8% moderate BPD, and 6.5% severe BPD (Table 3).

Table 3. Incidence and severity of BPD (severity based definition)

Outcome	Number of patients	%
No BPD	186	36.9
Mild BPD	98	19.4
Moderate BPD	100	19.8
Severe BPD	31	6.1
Died	89	17.6
All	504	100.0

BPD – bronchopulmonary dysplasia;

*total BPD = 45.4%

According to the same definition, if only infants who survived by PMA of 36 weeks are considered results are different (Table 4). Incidences of BPD according to the traditional clinical definition and according to the original definition are shown in Table 4.

Table 4. Incidence of BPD at 28 days of life and at 36 weeks PMA in all studied infants and in surviving ones

Outcome	Number of patients	%
BPD at 28 days	229/504*	45.4
BPD at 36 weeks PMA	131/504*	26
BPD in survivors at 28 days	229/422†	54.3
BPD at 36 weeks PMA in survivors to 36 weeks PMA	131/415‡	31.6
BPD at 28 days in survivors to 36 weeks PMA	229/415‡	55.2
Died	89/504	17.7

BPD – bronchopulmonary dysplasia; PMA – postmenstrual age;

*all infants;

†out of the whole number of infants at 28 days of age there were 422 alive (82 infants died);

‡out of the whole number of infants at 36 weeks PMA there were 415 alive (89 infants died)

All infants with BPD had GA \leq 32 weeks. All survived infants with GA \leq 24 weeks had BPD. Among the survivors with GA \leq 28 weeks, 84% had BPD. All infants with GA $<$ 23 weeks died before the BPD was diagnosed. Moderate BPD most often occurred in all survived GAs, the frequency of mild BPD was gradually increasing with the rise of GA, while the incidence of severe BPD was more frequent in lower GAs (Table 5).

Out of the total number of infants with BW \leq 1,000 g ($n = 157$), 45.2% (71/157) had BPD at 28 days. Out of the total number of survivors with BW \leq 1,000 g ($n = 89$), 80% (71/89) had BPD. In infants with BW $>$ 1,000 g ($n = 347$) 45.5% (158/347) had BPD at 28 days and 48.5% (158/326) of surviving ones (Table 6). Out of the total number of infants with BW \leq 1,000 g 30.6% had BPD at 36 weeks PMA, in case of BW $>$ 1,000 g incidence of BPD was 23.9%.

Mortality

In the total population of premature VLBW infants ($n = 504$) 415 (82.3%) survived by GA of 36 weeks. Out of the total number of deaths ($n = 89$), most occurred during the first week of life ($n = 59$, 66.4%). By the age of 28 days, 82 infants died (92.1%), from 28 days to 36 weeks PMA, the remaining eight (8.9%) died. Out of the total number of deaths ($n = 89$), 89% ($n = 79$) occurred in infants with GA \leq 28 weeks. All infants GA $<$ 23 weeks died (100%). Out of the total number of infants with GA \leq 28 weeks ($n = 220$), 35.9% ($n = 79$) died as well as 83.78% ($n = 31$) of infants with GA \leq 24 weeks. No newborn with GA over 33 weeks died (Table 5).

Among infants with BW $>$ 1,000 g the mortality rate was low, 6% died. Out of the total number of infants with BW \leq 1,000 g 43% died, with BW 700–1,000 g 30% died and among those with BW \leq 700 g 73% died (Table 6).

DISCUSSION

Incidence of bronchopulmonary dysplasia

The results obtained by our study are the first results on the incidence of bronchopulmonary dysplasia in Vojvodina, Serbia, on a representative sample of 504 VLBW infants. Since different definitions of BPD are applied in different neonatal centers and published studies, for the purpose of easier comparison, our results concerning incidence are presented in relation to two definitions:

a) According to definition that takes into account the severity of the disease (supplemental oxygen use at 28 days of age, assessment of severity at 36 weeks PMA)

b) According to the original definition of BPD (supplemental oxygen use at 28 days of age) [2, 10, 12]. These results are shown in Tables 3 and 4.

According to the literature, the incidence of BPD is variable, but similar in tertiary and secondary health care institutions in countries of the Western Europe and the United States [2, 6].

Our results were first compared to those studies in which the same group of infants was included (BW under 1,500 g). When we observed the latest results of large studies in developed countries, the incidence of BPD in VLBW infants, according to the definition at 36 weeks PMA, in this study is comparable with the results of some centers, while the incidence of BPD, according to the definition at 28 days, is higher in our study. According to the NICHD's study, the incidence of BPD at 28 days varied 11–41% (on average 25%), which is slightly lower than in our study where the incidence was 45.4%. If a definition at 36 weeks PMA was used incidence ranged 10–50% (on average 22%), in our research it was 26% [7]. According to the Vermont Oxford Network's data, using definition of BPD at 36 weeks PMA, the incidence of BPD in surviving VLBW infants

Table 5. Relationship between gestational age in weeks and the outcome in absolute numbers

Outcome	GA 21–22	GA 23–24	GA 25–26	GA 27–28	GA 29–30	GA 31–32	GA 33–34	GA 35–36	GA $<$ 36
No BPD	0 (0)	0 (0)	2 (3)	21 (17)	54 (39)	73 (67)	27 (96)	9 (100)	186
BPD	0 (0)	6 (18)	36 (55)	76 (65)	81 (58)	30 (28)	0 (0)	0 (0)	229
Mild BPD	0 (0)	1 (17)	11 (28)	30 (30)	44 (32)	12 (11)	0 (0)	0 (0)	98
Moderate BPD	0 (0)	4 (66)	15 (39)	32 (33)	32 (23)	17 (16)	0 (0)	0 (0)	100
Severe BPD	0 (0)	1 (16)	10 (26)	14 (14)	5 (4)	1 (1)	0 (0)	0 (0)	31
Death	4 (100)	27 (82)	27 (42)	21 (17)	4 (3)	5 (5)	1 (4)	0 (0)	89
All	4	33	65	118	139	108	28	9	504

BPD – bronchopulmonary dysplasia; GA – gestation age;
*percentages are given in the brackets

Table 6. Relationship between birth weight and the outcome in absolute numbers

Outcome	\leq 500 g	501–700 g	701–1,000 g	1,001–1,250 g	1,251–1,499 g	$<$ 1,500 g
No BPD	1 (11)	1 (3)	16 (15)	55 (35)	113 (60)	186 (37)
BPD	2 (22)	9 (23)	60 (55)	91 (58)	67 (35)	229 (45)
Mild BPD	1 (11)	2 (5)	20 (18)	33 (21)	42 (22)	98 (19)
Moderate BPD	1 (11)	4 (10)	30 (28)	44 (28)	21 (11)	100 (20)
Severe BPD	0 (0)	3 (8)	10 (9)	14 (9)	4 (2)	31 (6)
Died	6 (67)	29 (74)	33 (30)	12 (7)	9 (5)	89 (18)
All	9	39	109	158	189	504

BPD – bronchopulmonary dysplasia;
*percentages are given in the brackets

was 26.2–30.4% [3]. In our study, the incidence of BPD in surviving VLBW infants at 36 weeks PMA was 31.6%, which is slightly higher. Kusuda et al. [16] reported that in Japan the incidence of BPD in VLBW infants at 36 weeks PMA was 28%, which is 3% more than in our study.

In comparison with some developed countries, our study showed that the incidence of BPD in VLBW infants is higher. Klinger et al. [17] reported that the incidence of BPD in surviving VLBW infants in Israel was 13.7% observed at 36 weeks PMA. Defining BPD in the same way, but taking into account all live born VLBW infants, Isayama et al. [8] published that in Canada the incidence was 12.3% and in Japan 14.6%. Compared to the above-mentioned studies, the incidence of BPD in our study is higher by about 17%. Ali et al. [18] published that according to the severity based definition incidence of BPD in surviving VLBW infants in Denmark was 18%, which is 36% lower than in our study.

Demirel et al. [19] reported that the incidence of BPD at 28 days in Turkey in surviving VLBW was 52.8%. Kiciński et al. [20] published that in Poland the incidence of BPD at 28 days in surviving VLBW infants with GA < 32 weeks was 52.7%, which is in both cases comparable to our research where the incidence of BPD in surviving infants at 28 days was 54.3%. Fernández et al. [21] reported that in South America (16 centers from Argentina, Chile, Paraguay, Peru, and Uruguay) the incidence of BPD in VLBW infants at 36 weeks PMA is 25%, which corresponds with our study. Yen et al. [22] published that in Taiwan in surviving VLBW infants at 36 weeks PMA the incidence of BPD was 34.9%, higher than in our study. Data on the incidence of BPD in some studies are presented in relation to GAs, BWs or both.

Incidence of bronchopulmonary dysplasia in relation to gestation age

By reducing GA, the incidence of BPD in survived infant increases (Table 5). The results of our study show that BPD occurs in newborns GA < 32 weeks. Taking into account the definition at 36 weeks PMA in the subgroup of newborns with GA ≤ 32 weeks BPD had 28%, and in subgroup with GA of ≤ 28 weeks 34.5% of newborns. According to the severity based definition in infants with GA ≤ 32 weeks BPD had 49%, and in infants with GA ≤ 28 weeks 53.6% (19.1% mild, 23.18% moderate, and 11.36% severe). Presented results match the literature's data, which shows that BPD rarely occurs in infants with GA over 32 weeks [2]. In the NICHD's study, the incidence of BPD is estimated in VLBW infants with GA < 29 weeks and according to the severity based BPD definition it was 68%, while according to the BPD definition at 36 weeks PMA it was 41% [5]. The incidence of severity based BPD in infants with GA ≤ 28 weeks in our study is lower by 15%. The differences in incidence exist also in the subgroup of infants with GA ≤ 24 weeks. Results in our study show that all surviving infants with GA ≤ 24 weeks had BPD observed at 28 days and 83% at 36 weeks PMA, while all newborns with GA < 23 week died before defining BPD. In the NICHD's study,

half of newborns with GA ≤ 24 weeks survived, 70–80% had BPD at 36 weeks PMA [5]. Handerson Smart et al. [23] wrote that the incidence of BPD at 36 weeks PMA in New Zealand and Australia in surviving infants with GA < 32 week was 22–25%. In our study, it was higher (34.6%).

Incidence of bronchopulmonary dysplasia in relation to birth weight

Our study shows that the lower the BW was, the higher was the frequency of BPD in survived VLBW infants. In our study in infants with BW ≤ 1,000 g the incidence of BPD at 28 days and at 36 weeks PMA was 45.2% and 30.6% respectively. In infants with BW > 1,000 g the incidence was 45.5% and 23.9%. Botet et al. [24] published that the incidence of BPD at 36 weeks PMA in Spain in infants with BW < 1,000 g from 1997–2009 increased from 18% to 24%, which is significantly lower than in our study. In our study the incidence of BPD in infants who survived at 28 days and at 36 weeks PMA was: for BW ≤ 1,000 g 80% and 54%, for BW > 1,000 g 48% and 25.5%. In study of Botet et al. [24], the incidence of BPD at 36 weeks PMA in surviving infants with BW < 1,000 g ranged from 28% to 31%. Klinger et al. [25] reported that in Israel it was 31%. Latini et al. [26] published that in Italy the incidence of BPD at 28 days in surviving infants with BW < 1,000 g increased from 1986 to 2012 for 9% (from 30.5% to 39.3%), while at 36 weeks PMA it increased from 5.5% to 13.1%. These studies reported a lower incidence than in our study. Farstad et al. [27] published results from Norway, where the incidence of BPD at 28 days in surviving infants with BW < 1,000 g or GA < 28 weeks was 86% and at 36 weeks PMA 45%. Tømmiska et al. [28] reported that in Finland it was 49%. In both studies, the incidence of BPD is higher than in study we carried out. According to the NICHD, the incidence of BPD in infants with BW ≤ 750 g was 66% at 28 days and 36% at 36 weeks PMA, taking into account that in this study half of infants with BW ≤ 750 g survived [7]. In our study, the incidence of BPD in infants with BW ≤ 700 g is low (23%), caused by the high mortality rate before making the diagnosis of BPD (73% of infants died), but in survivors with BW ≤ 700 g the incidence was high – 85% (at 28 days) and 62% (at 36 weeks PMA).

Mortality

In our study, the mortality rate for different BWs and GAs is shown. The survival rate of VLBW infants, as well as subgroups with BW > 1,000 g, it is comparable to survival rate in developed countries and higher than survival rate in underdeveloped countries. In contrast to that the survival rate of infants with the lowest BWs and GAs in our study, it is not as high as in developed countries.

The average BW of patients who died in our study was 831 ± 260. The mortality rate of premature infants with BW < 1,500 g was 17.7%; the survival rate was 82.3%. The NICHD published that the average survival rate of infants with BW ≤ 1,500 g in the US was 85% (ranging 79–93%), which is slightly more than in our study [7]. Ballot et al. [29] reported that in South Africa survival rate of infants

with BW < 1,500 g was 70.5% which is significantly lower than in our study.

The survival rate according to the GA and BW categories is shown in Tables 5 and 6.

Mortality in relation to gestation age

According to data from various European regions, the survival rate of infants with GA < 32 weeks in 2003 was 89.5%, ranging 74.8–93.2% [13]. In our study, for infants with GA < 32 weeks it was 81.1%. According to Fellman et al. [30] in Sweden the survival rate of infants with GA < 27 weeks was 70% (9.8% for GA 22 weeks to 85% for GA 26 weeks), which is 43% higher than in our study. According to Isayama et al. [8] survival rate of infants with GA < 25 weeks in Canada was 47.7% and in Japan was 72.9%, while in our study it is significantly lower – 16.3%.

Mortality in relation to birth weight

Latini et al. [26] reported that the survival rate of infants in Italy with BW < 1,000 g in the period from 1986 to 2012 rose from 42.3% to 72.6%, which is comparable to our research (56.7%). According to NICHD the survival rate of infants with BW 1,000–1,250 g was 94% and BW 1,250–1,500 g was 96%, which is almost identical to the survival rate of the same groups of infants in our study (93% and 95%). In the study we carried out, the survival rate of infants with BW 751–1,000 g was 87%, BW 501–750 g was 55%, i.e. survival rate in these categories of BWs was higher than in our study [7]. Ballot et al. [29] reported that in South Africa, survival rate of infants with BW of 1,001–1,500 g was 85.8% and BW < 1,000 g was 34.9%, which is lower than in our study.

CONCLUSION

The overall mortality and incidence of BPD in VLBW newborns our study are comparable to those in some developed countries and lower compared to underdeveloped countries. However, the incidence of BPD and mortality rate in VLBW newborns in our study is higher in the population of the most immature infants, especially those with BW < 700 g and GA < 25 weeks, compared with the results from developed countries. These differences can be explained by variations in implementation of available preventive prenatal and therapeutic postnatal measures (prenatal use of corticosteroids and antibiotics in case of a risk of premature delivery, application of surfactant, non-invasive mechanical ventilation), along with the incidence of respiratory distress syndrome, neonatal sepsis and other postnatal risk factors that can influence the outcome, especially the incidence of BPD. Prenatal factors are in close relation with the obstetric practice while all named postnatal factors can be closely influenced by technical possibilities of neonatal intensive care units, which are better equipped in developed countries.

NOTE

This paper is a part of the doctoral thesis of dr Gordana Vilotijević-Dautović entitled “Predictive model for bronchopulmonary dysplasia in very low birth weight infants,” defended in 2015, at the Faculty of Medicine of Novi Sad.

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Учесталост бронхопулмоналне дисплазије и смртност новорођенчади веома мале порођајне масе у Војводини

Гордана Вилотијевић-Даутовић^{1,2}, Александра Дороски^{1,2}, Гордана Вијатов-Ђурић^{1,2}, Милена Бјелица¹

¹Институт за здравствену заштиту деце и омладине Војводине, Нови Сад, Србија;

²Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Учесталост бронхопулмоналне дисплазије (БПД) разликује се у односу на стопу недонесености, као и дефиницију и терапију које се примењују у различитим неонаталним центрима. У различитим земљама учесталост БПД за новорођенчад порођајне масе (ПМ) испод 1500 g варира између 4 и 53%. Смртност новорођенчади ПМ < 1500 g има удео од 50% у укупној смртности новорођенчади и одојчади. Границе преживљавања се последњих година померају према нижим гестацијама.

Циљ нашег истраживања је утврђивање учесталости и степена тежине БПД, као и смртности новорођенчади ПМ < 1500 g у Војводини.

Метод Ретроспективно истраживање је спроведено у периоду од јануара 2006. до децембра 2011. године и обухватило је 504 превремено рођена новорођенчета ПМ < 1500 g.

Резултати Од укупног броја превремено рођене новорођенчади ПМ < 1500 g преживело је 82,3% до 36. недеље кориговане гестацијске старости. Посматрајући БПД према оригиналној дефиницији, што представља оксигенотерапију 28. дана живота, БПД је имало 45,4% новорођенчади. Узимајући у обзир дефиницију која одређује степене тежине, БПД у благом облику имало је 19,44%, средње тежак облик 19,84%, а тежак облик 6,15% новорођенчади. Уколико се БПД посматра као зависност од оксигенотерапије 36. недеље кориговане гестацијске старости, БПД је имало 25,99% новорођенчади.

Закључак Смртност превремено рођене новорођенчади ПМ < 1500 g и учесталост БПД у истраживању које смо спровели су упоредиви са подацима из појединих развијених земаља, а нижи су у поређењу са појединим неразвијеним земљама.

Кључне речи: бронхопулмонална дисплазија; смртност; учесталост; новорођенче веома мале порођајне масе



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Short-term outcome in preterm infants depending on whether they were born from singleton, twin, or triplet pregnancy – data from a tertiary care hospital in Serbia

Gordana Velisavljev-Filipović^{1,2}, Aleksandra Matić^{1,2}, Marina Dragičević^{1,3}, Divna Damjanovski⁴

¹University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;

²Institute for Child and Youth Health Care of Vojvodina, Pediatric Clinic, Novi Sad, Serbia;

³Clinical center of Vojvodina, Department of hematology, Novi Sad, Serbia;

⁴Clinical center of Vojvodina, Department of Obstetrics and Gynecology, Novi Sad, Serbia

SUMMARY

Introduction/Objective After the introduction of the national program of fertility treatment, increased frequency of multiple pregnancies was noted. The literature has shown controversies regarding the higher risk of morbidity and mortality of the preterm newborns from multiple pregnancies.

Methods Preterm singletons, twins and triplets born within a two-year study period were included in the analysis. Data about preterm twins were extracted first. For each pair of twins, two singletons of the same gestation age were chosen. The set of the examinees was completed by including the triplets born during the same period. The short-term outcomes were compared between these three groups.

Results A total of 210 preterm infants were included in the study, out of which 84 singletons, 84 twins and 42 triplets. Statistical analysis showed significant difference between the three groups regarding type of conception ($p < 0.0001$), mode of delivery ($p < 0.001$) and birth weight ($p = 0.005$). Short-term mortality and morbidity (neonatal death, the need for intubation at birth, respiratory support, surfactant therapy, and intracranial hemorrhage) were significantly increased in triplets comparing to singletons and twins.

Conclusion Preterm triplets have an increased risk for adverse short-term outcomes comparing to singletons and twins of the similar gestation age in our study sample.

Keywords: premature baby; single pregnancy; twins; triplets; morbidity

INTRODUCTION

In Serbia, and especially in the Autonomous Province of Vojvodina, increasing number of infertile couples is one of the biggest health issues, while birthrate is in constant decline. One third of all the couples in Serbia are childless, while half of them are not able to have children. Since 2006, the national program for infertility treatment has been active. Within this program, the biomedical procedures of assisted reproductive technologies or in vitro fertilization (IVF) are used, hence the initial program title *One free attempt of IVF for 1,000 couples*. [1] After the introduction of this program, an increased number of multiple pregnancies that often end up in premature labor have been observed. A similar expansion of assisted reproductive techniques accompanied by increased frequency of multiple pregnancies has also been noted in the developed countries 10 years prior to the introduction of our national program. [2, 3]

The recent literature findings are controversial with respect to the risk of the increased morbidity and mortality of preterm singletons compared to twins and preterm triplets [4–8]

To the best of our knowledge, no studies have compared outcome between these groups

of preterm infants in Serbia. Clarifying the consequences of multiple premature births on a local level can be helpful in the planning of local perinatal health resources as well as closer surveillance of high-risk infants. In this way, an improvement of the perinatal protection could be achieved, with an impact on the decline in adverse short-term outcome of the premature infants, regardless of whether they are from singleton, twin, or triplet pregnancies.

METHODS

This retrospective case-control study was carried out at the Institute for child and youth health care of Vojvodina, Novi Sad, Serbia, a part of which is regional tertiary-level and university pediatric clinic with level III neonatal intensive care unit (NICU). The study was done in accord with standards of the institutional Committee on Ethics. A total of 210 preterm infants were included, who were hospitalized at the Institute during the two-year study period. Although neonatal service of our clinic performs neonatal transport from six remote maternity hospitals in Vojvodina province, only preterm infants born in Novi Sad were included in the study, in order

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Correspondence to:

Gordana VELISAVLJEV-FILOPOVIĆ
Institute for Child and Youth
Health Care of Vojvodina
Pediatric Clinic
Hajduk Veljkova 10, Novi Sad,
Serbia
gordana.velisavljev-filipovic@mf.uns.ac.rs

to exclude impact of the transport and local protocol differences in the primary newborn care on the overall outcome.

Our study sample was created in the way that we first identified and retrieved medical records of every preterm twin hospitalized during two-year period. Then, for every twin we found singleton of a matched gestation (\pm two days) born within the same two years. Finally, the set of the examinees was completed by the triplets who were born and hospitalized during the study period.

Stillborn twins and triplets were excluded from the study. Furthermore, twins and triplets from pregnancies that were affected by the embryo reduction were also excluded from the study. Only preterm infants from the twin and triple pregnancies, which all completed with all live-born fetuses, were included in the study sample.

When we completed our study sample, we wanted to check whether the study sample size was of sufficient to meet the research goal. Having in mind the average annual number of live births with approximate percentage of premature births in maternity hospital in Novi Sad, with the margin of error of 5% and the confidence level of 95%, the study sample should have at least 205 examinees. This calculation shows that our study sample of 210 examinees is appropriately sized.

The short-term outcomes of these three groups, singles, twins and triplets, were compared in the study. Collected prenatal and perinatal data refers to the conception type, antenatal steroids, mode of delivery, birth weight (BW), gestational age (GA), sex and Apgar score in the first and the fifth minute.

The data about neonatal outcomes that have been gathered were: respiratory distress syndrome (RDS), based on the need for supplemental oxygen as well as on the lung X-ray; need for intubation at birth; respiratory support applied (which was defined as the need for assisted ventilation with continuous positive pressure or mechanical ventilation); surfactant therapy, chronic lung disease (CLD) defined as continuing need for oxygen therapy at 36 weeks corrected GA with abnormal X-ray; intracranial hemorrhage based on ultrasound examination of the brain; retinopathy of prematurity (ROP) based on ophthalmologic examination, according to the International Classification for ROP.

The SPSS software version 21.0 (IBM Corp. Armonk, NY, USA) was used for the statistical data analysis. Categorical variables were compared between groups. All

categorical variables are presented as frequencies and percentages. All continuous variables are presented as mean \pm standard deviation (SD). The significance in differences in perinatal data between three study groups was tested. For quantitative variables, one-way ANOVA was used. Frequencies were tested using Fisher's exact test or Pearson χ^2 test. Multivariable logistic regression was used to assess the differences in mortality and morbidities between the groups with adjustment for perinatal data, which showed significance at the level $p < 0.1$ on univariate analysis. Statistical significance was set at $p < 0.05$ for all tests. Results of the generalized logistic regression are presented as adjusted odds ratios (OR) with the appropriate 95% confidence intervals (CI).

RESULTS

Our study sample included 210 preterm infants, of which 84 singletons, 84 twins and 42 triplets. Examinees had a mean GA of $31.1 (\pm 0.29)$ weeks (range: 26–35 weeks), with 32.14 ± 2.51 in singletons, 32.12 ± 2.51 in twins and 31.14 ± 1.907 in triplets. The difference in mean GA between the groups was not statistically significant, but with the p value of 0.061 had a tendency toward significance. Since this p value is less than 0.1, we included GA in confounding factors when performing multivariate statistical analysis. Mean BW in singletons was 1,788 (± 68.50) grams, in twins 1,681 (± 41.15) grams and in triplets 1,476 (± 68.79) grams (Table 1).

Among singletons, there were only 2.38% IVF pregnancies, while it was the case with 50% studied twins and 92.85% triplets. This difference in the way of conception between singleton and multiple pregnancies is certainly statistically significant ($p < 0.0001$). Caesarean section births were noted significantly more frequent in triplets compared to singletons and twins ($p < 0.001$) (Table 1).

There was no significant difference regarding sex, antenatal steroids, and Apgar score in the first and fifth minute between the studied singleton, twin and triplet group (Table 1).

Neonatal death during primary hospitalization was significantly more often recorded in triplets compared to singletons ($p = 0.046$) as well as to twins ($p = 0.44$), even after adjustment for gestation, BW and caesarean delivery (Table 2).

Table 1. Comparison of prenatal and perinatal characteristics of studied preterm singletons, twins and triplets.

Characteristics	Singletons (n = 84) n (%) or mean \pm SD (min–max)	Twins (n = 84) n (%) or mean \pm SD (min–max)	Triplets (n = 42) n (%) or mean \pm SD (min–max)	p
Gesational age (weeks)	32.14 ± 2.51 (26–35)	32.12 ± 2.51 (26–35)	31.14 ± 1.907 (27–34)	0.061
Birth weight (grams)	$1,787.61 \pm 627.77$ (850–2,910)	$1,680.71 \pm 377.12$ (890–2,500)	$1,476.19 \pm 448.53$ (610–2,650)	0.005
Male sex	35 (41.66%)	44 (52.38%)	22 (52.38%)	0.31
Antenatal steroids	7 (8.33%)	6 (7.14%)	3 (7.14%)	0.95
Cesarean delivery	47 (55.95%)	48 (57.14%)	39 (92.85%)	< 0.001
Apgar score in 1st minute	6.29 ± 2.08 (1–9)	6.107 ± 2.17 (1–9)	6.76 ± 1.24 (3–9)	0.17
Apgar score in 5th minute	7.66 ± 1.54 (2–10)	7.53 ± 1.44 (2–10)	7.97 ± 0.84 (6–10)	0.247
In vitro fertilization	2 (2.38%)	42 (50%)	39 (92.85%)	< 0.0001

SD – standard deviation

Table 2. Neonatal outcomes in studied preterm singletons, twins and triplets and their comparison between the groups using multivariate logistic regression

Parameters	Singletons (n = 84)	Twins (n = 84)	Triplets (n = 42)	Singletons vs. twins		Singletons vs. triplets		Twins vs. triplets	
				p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)
Death	1 (1.19%)	1 (1.19%)	6 (14.28%)	1.00	/	0.046	16.36 (1.05–253.46)	0.044	14.65 (1.07–100.67)
RDS (any degree)	69 (82.14%)	67 (79.76%)	38 (90.47%)	0.844	1.16 (0.54–2.52)	0.174	0.36 (0.09–1.33)	0.073	0.31 (0.08–1.13)
Endotracheal intubation	30 (35.71%)	24 (28.57%)	24 (57.14%)	0.408	1.39 (0.72–2.66)	0.035	0.41 (0.19–0.88)	0.003	0.30 (0.13–0.65)
Respiratory support	37 (44.04%)	33 (39.28%)	27 (64.28%)	0.532	1.27 (0.69–2.35)	0.038	0.43 (0.20–0.93)	0.013	0.35 (0.16–0.37)
Surfactant	14 (16.66%)	19 (22.62%)	19 (45.23%)	0.437	0.68 (0.31–1.47)	0.001	0.24 (0.10–0.55)	0.013	0.35 (0.16–0.78)
CLD	8 (9.52%)	5 (5.95%)	5 (11.9%)	0.565	1.66 (0.52–5.31)	0.758	0.77 (0.23–2.54)	0.299	0.46 (0.12–1.71)
Intracranial hemorrhage	16 (19.04%)	17 (20.24%)	17 (38.09%)	1.00	0.95 (0.47–2.12)	0.057	2.83 (0.97–8.26)	0.027	0.40 (0.17–0.90)
ROP	15 (17.85%)	10 (11.9%)	4 (9.52%)	0.386	1.61 (0.67–3.82)	0.294	2.06 (0.63–6.66)	0.772	1.28 (0.37–4.36)

RDS – respiratory distress syndrome; CLD – chronic lung disease; ROP – retinopathy of prematurity; aOR – adjusted odds ratio (adjusted for gestation, birth weight and caesarean delivery); 95% CI – 95% confidence interval

Triplets had a greater need for endotracheal intubation at birth compared to singletons as well as compared to twins, even with the adjustment for difference in GA, BW, and mode of delivery. The results of the analysis indicate that there was no statistically significant difference in relation to the need for endotracheal intubation between singletons and twins. More than half of the triplets (64.28%) received surfactant therapy, which was significantly more often than in twins or in singletons. There was no difference between singletons and twins in relation to the frequency of the use of surfactant. The same stands for need for respiratory support, which was also most common in triplets. Altogether, early respiratory morbidity was significantly increased in triplets compared to singletons and twins, even after adjustment for differences in perinatal data. The data on the incidence of RDS and early respiratory morbidity indicators in singletons, twins, and triplets, as well as the results of comparison according to these criteria among groups of examinees are shown in Table 2.

In relation to the frequency of CLD, no statistically significant difference was found between the studied groups of preterm infants (Table 2).

Intracranial hemorrhage was most commonly diagnosed in triplets compared to twins and, in lesser extent, to singletons. ROP did not show statistically significant difference in frequency between the groups (Table 2).

DISCUSSION

Studies that investigated the impact of multiple births on the incidence of RDS, intracranial hemorrhage, and overall morbidity, as well as on mortality, gave conflicting data [9, 10, 11]. In a study given by Israel database, the authors analyzed preterm infants from singleton and multiple pregnancies with BW below 1,500 g and GA from 24–34 weeks. They found an increased mortality in preterm triplets compared to preterm singletons and twins. These results are

in consistency with the findings in our study. However, they also found that triplets and twins had more frequent RDS than singletons of the similar gestation. In accordance with our results, they also did not find a difference in the frequency of chronic lung disease between the studied groups [12]. Ziadeh et al. [13] found a significantly higher mortality rate in triplets compared to twins, while they did not find differences regarding the incidence of RDS and intracranial hemorrhage between twins and triplets. Contrary to the results of the above-mentioned studies, Russell et al. [14] found that mortality of premature infants from multiple pregnancies was lower than of those from singleton pregnancies, when it was adjusted to BW.

Obeichina et al. [15] analyzed perinatal data from 3351 deliveries completed in term as well as preterm at the University Hospital in Southeast Nigeria. The authors found that there was a significantly increased mortality in twins compared to singletons. Mathews et al. [16] in their report of infant mortality statistics from the 2013 have also found increased mortality in triplets than in singletons and twins. However, no differences in mortality between preterm singletons and twins have been found.

Data from a large study regarding rate of multiple births in European countries showed that median rate of triplet pregnancies in Europe in 2010 was 0.3 per 1,000 deliveries, regardless of the presence of stillbirths [17]. Overall, the frequency of triplets was similar in European countries included in the analysis. Results from the same study showed that multiple pregnancies had a nine-fold relative risk of preterm delivery compared to singletons. Furthermore, the median neonatal mortality rate among multiples was considerably higher than in singletons [17].

The study dealing with outcomes of multiple births in Korea found that neonatal mortality rate was higher in the triplets compared to singletons in a group of infants born with less than 28 weeks of gestation, while this difference was lost for gestations over 28 weeks. An interesting finding in the same study is that survival rate was higher

in triplets than in twins for gestations of 32 weeks and above [9].

Donovan et al. [18] in their analysis of outcomes of a very low BW twins cared for in the National Institute of Child Health and Human Development Neonatal Research Network's intensive care units found no differences in frequency of CLD, grade 3/4 intraventricular hemorrhage and in death rate between the very low BW singletons and twins. Wolf et al. [19] did not find differences in morbidity and mortality between a very low BW twins and singletons. These results are in consistency with the results of this study, since we did not find differences in short-term outcomes between singletons and twins either. A recent study comparing the neonatal outcome of late-preterm twins and late-preterm singletons at the university clinic in Toronto found that the risk of RDS in singletons was like that of twins. However, antenatal corticosteroids were administered significantly more frequently in pregnant women with twin pregnancy [20]. The level of respiratory morbidity was the same between the twins and the singles when adjustment for the mode of delivery and exposure to antenatal steroids was made. Contrary to above mentioned studies, opposite results can be found in contemporary literature. Comparing singletons, twins, and triplets of similar GA, Kaufman et al. [21] did not find a significant difference in morbidity and mortality between them. However, this study included only 55 sets of triplets.

In their retrospective study, Spasojevic et al. [22] analyzed the morbidity of preterm twins from IVF pregnancies who were treated in the NICU. They found that the signs of RDS were present in all of them, making RDS the main reason for addition to NICU in this group of infants.

Regarding antenatal steroids administration, we did not find a statistically significant difference between singleton, twin, and triplet pregnancies. In addition, the frequency of RDS of any degree was not different between the studied groups. However, a statistically significant difference in the need for endotracheal intubation and the need for the administration of surfactant in triplets compared to singletons and twins was found. As it was expected, the triplets required significantly more frequent respiratory support compared to singletons and twins, too. These data support the higher incidence of severe early respiratory morbidity in triplets than in singletons and twins in our study sample. However, one should not ignore the possibly that surfactant was sometimes given as a preventative or over-therapy in triplets.

In the study conducted in Japan, the authors have found that the incidence of RDS was significantly lower in preterm twins than in singletons [23]. The other study from Japanese authors showed that the frequency of RDS decreased significantly in twins born with 34 weeks, and at 36 weeks, the twins had a frequency of RDS as singletons at 38 weeks [10]. The authors concluded that lungs matured

much faster in twins than in singletons. It is possible that intrauterine stress or fetal growth restriction accelerates lung maturation or leads to abnormal development of the pulmonary vascular bed [23].

In a multicentric study of maternal and neonatal outcomes in 15,194 pregnancies from 15 hospitals in Beijing, the results show that infants from multiple pregnancies had significantly higher admission to NICU compared to infants from single pregnancies. There was a significant association of adverse maternal and neonatal outcomes and multiple pregnancies [24]. In a multicentric, randomized, controlled study conducted in the US, Refuerzo et al. [25] also found an increased risk of admission to NICU of infants from multiple pregnancies. The recent study that analyzed the neonatal outcome of the late-preterm twins and late-preterm singletons found that twins often required resuscitation at birth and were more often admitted to NICU [26]. However, there was no difference between singletons and twins in terms of non-respiratory morbidity, that is, the frequency of ROP and intracranial hemorrhage [4].

The plurality and length of gestation are in inverse correlation, as confirmed by several studies. Assisted reproductive techniques are one of the main reasons for the increase in incidence of multiple births worldwide, and especially in developing countries [6, 7, 27, 28].

Twin and triple pregnancies in low- and middle-income countries give an inherent risk to adverse outcomes at both maternal and neonatal levels [28].

The limitation of our study is a relatively small study sample from just one tertiary-care center. Furthermore, chronic pregnancy-related diseases and socioeconomic status of the mothers, as factors of significant impact on perinatal outcome, were not considered in our study. On the other hand, given the growing problem of infertility and increasing implementation of assisted reproductive techniques with consequent rise in multiple births in Serbia and in Vojvodina in particular, this is the health problem of great local significance.

Large, population-based studies comparing the outcome of preterm singletons, twins, and triplets, as well as higher-order multiples would be of great importance for the improvement of perinatal care [15, 29, 30, 31].

CONCLUSION

The findings of our study suggest that preterm triples have an increased risk of neonatal death, early respiratory morbidity, and intracranial hemorrhage compared to singleton and twin premature infants.

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Краткорочни исход превремено рођене деце у зависности од тога да ли су рођена из једноструких, близаначких или тригемеларних трудноћа – подаци из терцијарне здравствене установе у Србији

Гордана Велисављевић-Филиповић^{1,2}, Александра Матић^{1,2}, Марина Драгићевић^{1,3}, Дивна Дамјановски⁴

¹Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;

²Институт за здравствену заштиту деце и омладине Војводине, Клиника за педијатрију, Нови Сад, Србија;

³Клинички центар Војводине, Клиника за хематологију, Нови Сад, Србија;

⁴Клинички центар Војводине, Клиника за гинекологију и акушерство, Нови Сад, Србија

САЖЕТАК

Увод После увођења националног програма лечења неплодности запажен је повећан број вишеплодних трудноћа. Налази из литературе су спорни у погледу постојања повећаног ризика морбидитета и mortalитета код превремено рођене новорођенчади из вишеплодних трудноћа.

Методе У студију су укључена превремено рођена новорођенчад из једноплодних, близаначких и тригемеларних трудноћа, рођена током двогодишњег периода трајања студије. Најпре су пронађени подаци о свим превремено рођеним близанцима. За сваки пар близанаца одабрано је двоје превремено рођене новорођенчади из једноплодних трудноћа, рођених после истог трајања гестације. Сет испитаника је употпуњен укључивањем све превремено рођене деце из тригемеларних трудноћа. Поређени су краткорочни исходи ове три групе – сингли, близанци и тројке.

Резултати У студију је укључено укупно 210 превремено рођене деце, од којих 84 из једноплодних трудноћа, 84 близанца и 42 тројке. Статистичка анализа је показала значајну разлику међу групама у погледу начина зачећа ($p > 0,0001$), начина порођаја ($p < 0,001$) и телесне масе на рођењу ($p = 0,005$). Краткорочни mortalитет и морбидитет (смрт у новорођеначком узрасту, потреба за интубацијом на рођењу, респираторном потпором и терапијом сурфактантом, интракранијално крварење) били су знатно чешћи код тројки у поређењу са синглима и близанцима.

Закључак Превремено рођене тројке имају већи ризик за неповољни краткорочни исход у поређењу са синглима и близанцима приближне гестације у нашем узорку испитаника.

Кључне речи: превремено рођена деца; једнострука трудноћа; близанци; тројке; морбидитет; mortalитет



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Selective fetal termination in monochorionic twin pregnancies – pregnancy outcome after bipolar cord coagulation and interstitial laser coagulation

Vesna Mandić-Marković^{1,2}, Željko Miković^{1,2}, Dejan Filimonović^{1,2}

¹University of Belgrade, Faculty of Medicine, Belgrade, Serbia;

²Narodni Front University Clinic for Gynecology and Obstetrics, Belgrade, Serbia

SUMMARY

Introduction/Objective In this paper we present the perinatal outcome after selective fetal termination (SFT) in monochorionic (MH) twins done by bipolar cord coagulation (BCC) and interstitial laser coagulation (ILC).

Methods During a five-year period, SFT was done in 22 MH twins. BCC was done in 15 and ILC in seven cases. We registered the indication for SFT, gestational age at SFT, immediate postoperative death and late death of the co-twin, PPROM (preterm pre-labor rupture of membranes), gestational age at delivery/abortion, procedure-to-delivery interval, mode of delivery, neonatal body weight and 5-minute Apgar score.

Results Live birth was significantly higher after BCC than after ILC (86.7:57.1%). Gestational age at intervention was higher in BCC (20.2 ± 1.8 : 16.5 ± 1.7 weeks). Gestational age at delivery/abortion was lower for ILC (32.5 ± 4.8 : 27.5 ± 9.5 weeks); however, there was no difference when comparing live births only (33.8 ± 3.7 : 34.7 ± 4.5 weeks). There was no difference between procedure-to-delivery/abortion interval (86.7 ± 33.7 : 77.1 ± 73 days); however, the interval was significantly higher after ILC when comparing live births only (93.3 ± 33 : 133 ± 30.9 days). There was no difference in PPROM (26.7:14.3%); preterm delivery (69.2:50%); Cesarean section rate (84.6:75%); neonatal body weight (2174 ± 82.4 : 2475 ± 823 g); or Apgar score (7.7 ± 1.9 : 9.2 ± 1).

Conclusion There is no ideal method of SFT in MH twins. Success of each SFT method depends upon the correctly set indication, gestational age at the procedure, and the SFT technique. The risk of co-twin death is lower after BCC than after ILC. As in Narodni Front University Clinic for Gynecology and Obstetrics better results were achieved after BCC, this method became a standard for SFT in MH twins, except in cases of twin reversed arterial perfusion sequence before 16 weeks.

Keywords: selective fetal termination; monochorionic twins; bipolar cord coagulation; interstitial laser coagulation

INTRODUCTION

Monochorionic (MC) twin pregnancies present challenge to the obstetricians due to the placental anastomoses between the twins. About one half of those pregnancies are uneventful, but the other half may be complicated by twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin reversed arterial perfusion (TRAP) sequence or discordance for fetal abnormality (DFA). In the most severe forms of those complications, when one fetus is severely anomalous, or is suffering severe distress, particularly if the condition is compromising the non-affected fetus, selective fetal termination (SFT) may be the best option, as in the case of single intrauterine death of one fetus, profound consequences for the surviving twin are reported, including a 15–25% risk of death or neurological damage [1–4].

SFT in MC pregnancies is difficult because conventional feticide techniques with intracardiac injection of potassium chloride are not an option, as the substance could embolize to the non-affected twin through the

placental vascular anastomoses [1, 2, 5]. Complete separation of the twin's blood flow is the only option for successful SFT. In cases of incomplete separation, the other twin may die as the consequence of acute agonal interfetal hemorrhage through placental anastomoses [2, 5]. Therefore, complete and permanent occlusion of the affected twin's umbilical cord flow is recommended to protect the surviving twin. Umbilical cord occlusion may be done by several methods, such as fetoscopic cord ligation, interstitial laser coagulation, monopolar coagulation, radiofrequency ablation or ultrasound-guided bipolar cord coagulation [5–9].

The objective of this study is to present pregnancy outcome after SFT in MC pregnancies done by ultrasound-guided bipolar cord coagulation and interstitial laser coagulation in a single tertiary center.

METHODS

A retrospective observational study included all MC pregnancies in which SFT was performed

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Correspondence to:

Vesna MANDIĆ-MARKOVIĆ
Mihaila Bulgakova 7/8
11160 Belgrade
vesna.m.mandic@gmail.com

by bipolar cord coagulation (BCC) or interstitial laser coagulation (ILC) at the Narodni front University Clinic for Gynecology and Obstetrics during a five-year period. Indications for SFT were severe forms of TTTS, Quintero stage III and IV [10]; sFGR with worsening fetal Doppler velocity suggesting high risk of intrauterine death in the non-viable fetus [11]; TRAP sequence in cases when abdominal circumference ratio between the acardiac fetus and the donor is over 50% or with the signs of congestive heart failure in the donor; or DFA. In each case, after extended counseling about the risk of selective feticide vs. expectant management, the patients opted for the SFT. After the Ethics Committee had approved SFT, written consent for the procedure was obtained.

BCC was done in the operating room under general anesthesia, complete aseptic procedures, and prophylactic measures – intravenous antibiotics (ceftriaxone) and acute tocolysis for 48 hours. After skin disinfection, under the ultrasound guidance, a 3.3-mm trocar was introduced into the targeted fetus amniotic cavity avoiding transplacental approach, if possible 5–10 cm from the chosen coagulation site. Then 3 mm bipolar forceps were passed down the trocar, directed towards the cord of the terminating twin, which was grasped with the forceps. Coagulation started at the power of 26 W for 15 seconds. The effect of the coagulation was monitored by the appearance of turbulence and steam bubbles caused by the local heating of tissue between the blades of the forceps. If necessary, bipolar energy was increased by 5 W for 15 seconds, to a maximum 45 W. The procedure was considered successful when echogenic bubbles were seen coming from the cord and the cord itself appeared hyperechogenic. The procedure was repeated in two other sites for safety. Confirmation of occlusion was also provided by the absence of detectable color Doppler flow in the distal part of the cord, with at least 2 minutes of persistent asystole. If necessary, interventions that enable easier BCC performance (amniocentesis, amnioreduction, septostomy) had been done previously.

ILC was done under ultrasound guidance by introducing an 18-gauge needle next to abdominal cord insertion of the targeted twin near the confluence of vitelline arteries and intrahepatic veins. Then, a laser fiber 400 m was introduced through the needle 4 mm outside the top of the needle, and coagulation started with the power of 20 W for 10–15 seconds. If necessary, coagulation was repeated with power higher by 5–10 W up until the maximum of 50 W. The procedure was considered successful if the hyperechogenic area was visualized peripherally and cessation of circulation was visualized by Doppler. Prophylactic measures included intravenous antibiotics (ceftriaxone) and acute tocolysis for 48 hours.

Cardiac activity of the co-twin was monitored during the entire procedure and immediately afterwards, and peak systolic velocity in the middle cerebral artery was measured after 2 hours and after 24 hours to detect acute fetal anemia. Fetal heart rate monitoring or tocogram was done after 1 hour, 24 hours, and 48 hours. Patients were discharged after at least 48 hours. CNS ultrasound was done after 7–14 days, and CNS MRI after 3–8 weeks.

Monitoring continued in two-week intervals by measuring biometry, blood pressure, and Doppler. Delivery was conducted near term. Mode of delivery was according to obstetrical indications. After birth, chorionicity was confirmed by the pathologist.

We registered maternal age and parity, indication for SFT, gestational age at SFT, operating time for BCC (defined as skin-to-skin time), early complications (postoperative uterine activity, amniotic fluid leakage), immediate postoperative death within 24 hours of the co-twin, late death of the co-twin, preterm pre-labor rupture of membranes (PPROM), gestational age at delivery, procedure-to-delivery interval, mode of delivery, neonatal body weight, and 5-minute Apgar score.

Statistical analysis included calculating means and standard deviations, frequencies, Student's t-test and χ^2 test (IBM SPSS Statistics, Version 24.0; IBM Corp., Armonk, NY, USA); $p < 0.05$ was considered statistically significant.

RESULTS

In a five-year period, 22 SFT were done in MC pregnancies – 15 (68.18%) by BCC and seven (31.82%) by ILC.

Indications for BCC were sFGR in seven (46.67%), TTTS (stage III/IV) in four (26.67%) (Stage III in three and Stage IV in one), DFA in three (30%), and TRAP sequence in one case (4.56%). In the cases of DFA, the first anomalous fetus had multiple anomalies – agenesis of the distal part of the leg, polyhydramnios and bowel obstruction; the second had CNS anomaly (Dandy–Walker anomaly), while the third one had discordant chromosomal anomaly (45,X0) with cystic hygroma. Two cases were dichorionic triplets with sFGR and DFA. The average gestational age at intervention was 20.2 ± 1.8 weeks. In nine cases (60%) we performed an intervention that enables easier BCC performance (amniocentesis in five; amnioreduction in three, while one case had unsuccessful attempt of fetoscopic laser coagulation). Karyotype was done in eight cases (53.33%) – in three for maternal age, in three for DFA, in one for sFGR, and in one case of TRAP sequence. BCC was successful in all the cases. Trocar was directly introduced into the amniotic cavity of the “target” twin in 14 cases (93.3%). Accidental septostomy occurred in one case after introduction of a trocar through co-twin amniotic sac making monoamniotic (MA) pregnancy. There was no early fetal death, and there were two cases (13.33%) of late fetal death – one case of TTTS after 36 days as a consequence of cord entanglement due to iatrogenic MA pregnancy, and one case of DFA done at 16 + 4 weeks after 46 days for no obvious cause (Table 1.) Live birth after BCC was 86.7% (13/15). Preterm delivery occurred in 69.2%, and PPROM in 26.7%. The average gestational age at delivery was 33.8 ± 7 weeks. Cesarean section was performed in 84.6% (Table 2).

ILC was done for TRAP sequence in four (57.13%), and for DFA, sFGR, and TTTS in one case each (14.29%). The average gestational age at ILC was 16.5 ± 1.7 weeks. Karyotype was done in five cases (71.43%) – four CVS

Table 1. Bipolar cord coagulation – description of the cases related to the procedure

No.	Indications	GA at SFT (week)	Previous interventions	Duration (min.)	Early fetal death (< 24h)	Late fetal death
1	sFGR	21 + 5	AC – 17 + 1 gw	22	No	No
2	sFGR	23 + 5	AI	14	No	No
3	sFGR	21 + 6	/	16	No	No
4	sFGR	18 + 6	AI	23	No	No
5	sFGR	20 + 3	AC – 17 + 2 gw / AI	13	No	No
6	sFGR	19 + 5	AI	17	No	No
7	sFGR (DH triplets)	21 + 3	/	21	No	No
8	TTTS – R (St IV)	22 + 4	FLK – 19 + 5 / AD – 21 + 6 gw	19	No	No
9	TTTS – D (St III)	20 + 0	/	18	No	After 36 days – MA
10	TTTS – D (St III)	19 + 3	AC – 16 + 5 gw / AD – 18 + 3 gw / AI	15	No	No
11	TTTS – D (St III)	19 + 4	AC/AD – 18 + 5gw	16	No	No
12	TRAP	19 + 6	AC – 16gw	15	No	No
13	DFA	16 + 4	AC – 15 + 5gw	11	No	After 46 days
14	DFA	21 + 1	CC during BKP	19	No	No
15	DFA (DH triplets)	18 + 3	AC (in both MC)	15	No	No
		20.2 ± 1.8	AI-5, AD-3, FLC-1, AC/CC-8/1	16.9 ± 3.4		2/15 (13.3%)

sFGR – selective fetal growth restriction; TTTS – twin to twin transfusion syndrome; D – donor; R – recipient; TRAP – twin reversed arterial perfusion; DFA – discordant fetal anomaly; DH – dichorionic; GA – gestational age; gw – gestational week; SFT – selective fetal termination; AI – amnioinfusion; AD – amnio-derivation; FLC – fetoscopic laser coagulation; AC – amniocentesis; CC – cordocentesis

Table 2. Bipolar cord coagulation – description of the cases related to the pregnancy outcome

Indications	GA (week) Del/Ab	Beginning of delivery	Interval BCC – delivery (days)	Delivery mode	Body weight (g)	5' Apgar
1. sFGR	37 + 1	Spontaneous	108	Vaginal	3,200	10
2. sFGR	28 + 3	Spontaneous + breech	33	CS	1,200	4
3. sFGR	39 + 1	Spontaneous	121	CS	3,100	9
4. sFGR	32 + 5	PPROM	90	CS	1,650	7
5. sFGR	29 + 5	Spontaneous	74	CS	1,350	6
6. sFGR	33 + 2	Fetal distress	95	CS	2,350	8
7. sFGR (DH triplets)	29 + 3	PPROM	54	Vaginal	1,220 1,300	7 6
8. TTTS R	32 + 1	Spontaneous	68	CS	1,800	6
9. TTTS D	(25 + 1)	Co-twin death	36	Ab induction	(600)	/
10. TTTS D	36 + 1	Spontaneous – repeat CS	124	CS	2,400	9
11. TTTS D	32 + 2	PPROM – placental abruption	88	CS	2,200	8
12. TRAP	38 + 2	Repeat SC	129	CS	3,700	10
13. DFA	(23 + 1)	Co-twin death	46	Ab induction	(400)	/
14. DFA	38 + 5	St post IVF	133	CS	2,700	10
15. DFA (DH triplets)	31 + 6	Fetal distress (PPROM of SFT at 20 + 5)	101	CS	1,400 1,450	6 6
Total (n = 15)	32.5 ± 4.8	PPROM 26.7%	86.7 ± 33.7		1,951 ± 965	
Live births (n = 13)	33.8 ± 3.7	PPROM 30.8%	89.6 ± 33	SC – 11 (84.6%)	2,174 ± 824	7.7 ± 1.9

sFGR – selective fetal growth restriction; TTTS – twin to twin transfusion syndrome; D – donor; R – recipient; TRAP – twin reversed arterial perfusion; DFA – discordant fetal anomaly; DH – dichorionic; GA – gestational age; BCC – bipolar cord coagulation; Del – delivery; Ab – abortion; CS – cesarean section; PPROM – preterm pre-labor rupture of membranes

and one amniocentesis. ILC was successful in all cases. In one case uterine activity was registered. There were three early fetal deaths (42.86%) and no late fetal death (Table 3) Live birth after ILC was 57.1% (4/7). Preterm delivery occurred in 50%; PPROM in 14.3%. The average gestational age at delivery was 34.7 ± 4.5 weeks. Cesarean section was performed in 75% (Table 4).

Live birth was significantly higher after BCC than after ILC (86.7:57.1%). Gestational age at intervention was higher in BCC. Gestational age at delivery/abortion was lower for ILC; however, there were no differences when comparing live births only. There were no differences between procedure-to-delivery/abortion interval; however,

the interval was significantly higher after ILC when comparing live births only. There was no difference in PPROM, preterm delivery, Cesarean section rate, neonatal body weight, or Apgar score (Table 5).

DISCUSSION

SFT is a treatment option in well-selected cases of complicated MC twin pregnancy [1, 2]. Imperative in those cases is immediate, permanent, and complete obliteration of the umbilical cord. Different techniques are used, each of them with its own challenges, as well as operative

Table 3. Interstitial laser coagulation – description of the cases related to the procedure

No.	Indications	GA at SFT (week)	Previous intervention	Uterine activity	PPROM	Early co-twin death	Late co-twin death
1	TRAP	14 + 2	CVS	No	No	/	/
2	TRAP	15 + 3	CVS	No	No	/	/
3	TRAP	14 + 6	CVS	No	No	/	/
4	TRAP	16 + 4	CVS	Yes	No	Yes	/
5	DFA	17 + 5	AC	No	No	Yes	/
6	TTTS (Gr IV)	18 + 3	/	No	No	Yes	/
7	sFGR	18 + 1	/	No	No	/	/
Total	TRAP – 4 DFA – 1 sIUGR – 1 TTTS – 1	16.5 ± 1.7	CVS – 4 AC – 1				

TRAP – twin reversed arterial perfusion; DFA – discordant fetal anomaly; TTTS – twin to twin transfusion syndrome; sFGR – selective fetal growth restriction; GA – gestational age; PPROM – preterm pre-labor rupture of membranes

Table 4. Interstitial laser coagulation – description of the cases related to the pregnancy outcome

Indications	GA (week) Delivery/Ab	Beginning of delivery	Interval ILC-Delivery (days)	Delivery mode	Body Weight (g)	5' Apgar
1. TRAP	39+2	Spontaneous	175	Vaginal	3300	10
2. TRAP	32+1	Spontaneous	117	CS	2200	9
3. TRAP	29+5	PPROM	104	CS	1450	8
4. TRAP	(17+0)	Co-twin death	(3)	Ab induction	(180)	/
5. DFA	(18+1)	Co-twin death	(3)	Ab induction	(250)	/
6. TTTS	(18+5)	Co-twin death	(2)	Ab induction	(220)	/
7. sIUGR	37+4	Spontaneous	136	CS	2950	10
Total	27.5 ± 9.5	PPROM 14.3%	77.1 ± 73.0		1,507 ± 1,340	
Live births	34.7 ± 4.5	PPROM 25%	133.0 ± 30.9	CS – 75%	2475 ± 823	9.2 ± 1

TRAP – twin reversed arterial perfusion; DFA – discordant fetal anomaly; TTTS – twin to twin transfusion syndrome; sFGR – selective fetal growth restriction; GA – gestational age; ILC – interstitial laser coagulation; PPROM – preterm pre-labor rupture of membranes; CS – Cesarean section; Ab – abortion

Table 5. Pregnancy outcome after bipolar cord coagulation and interstitial laser coagulation

Outcome	BCC (n = 15)	ILC (n = 7)
Live birth n (%)	13/15 (86.7)	4/7 (57.1)*
GA at intervention (week)	20.2 ± 1.8	16.5 ± 1.7*
GA at delivery/abortion	32.5 ± 4.8	27.5 ± 9.5*
GA at delivery	(33.8 ± 3.7)	(34.7 ± 4.5)
Interval: intervention-delivery/ abortion (days)	86.7 ± 33.7(36–133)	77.1 ± 73.0 (2–175)
Intervention-delivery (days)	89.6 ± 33	133.0 ± 30.9*
PPROM / total n (%)	4/15 (26.7)	1/7 (14.3)
Delivery	4/13(30.8)	1/4 (25)
Preterm delivery n (%)	9/13 (69.2)	2/4 (50)
Cesarean section n (%)	11/13 (84.6)	3 /4 (75)
Body weight (g) – total	1,951 ± 965	1,507 ± 1,340
Live birth	2,174 ± 824	2,475 ± 823
5' Apgar score	7.7 ± 1.9	9.2 ± 1.0

*p < 0.05

BCC – bipolar cord coagulation; ILC – interstitial laser coagulation; GA – gestational age; PPROM – preterm pre-labor rupture of membranes

and preoperative risks [1, 5–9]. In selected cases we used equipment available at our institution – BCC in 68.18% and ILC in 31.82%.

The indications for SFT are well defined. In most studies, TTTS presents the major indication for the procedure (25–72%) and is performed in stages III–IV when previous therapeutic procedures were ineffective and/or if fetal demise is expected. It may be done either in the donor or

in the recipient twin. In severe cases of early presentation of sFGR, when fetal death of sFGR fetus is expected, SFT may be the only option for the survival of the eutrophic twin. sFGR is reported to be 2–56% of indications for SFT. TRAP sequence is reported to be done in 12–40% with cardiac overload of the pump twin. Discordant fetal anomaly is done in about 35% of all SFT [3, 6–9]. In our series, indications differ between different techniques. BCC is done mostly for sFGR and TTTS, while ILC is done predominantly in TRAP sequence.

Gestational age plays an important role in SFT survival rate. The general attitude is that optimal results in SFT after 18–20 weeks are done by umbilical occlusion, while intrafetal methods are the choice in earlier gestation [3, 6, 8]. BCC is the best option after 18 weeks, to avoid introduction of a relatively large instrument into still small uterus. Pregnancy loss is reported to be 41% if done at 16–17 weeks, and 3% if done after 18 weeks. After 24 gestational weeks, umbilical diameter may exceed the forceps diameter, making complete and immediate occlusion impossible by BCC [6, 8]. ILC is best done in earlier gestation, as it is a needle method with the 17-gauge diameter needle. Failure of ILC if done after 18 gestational weeks is a consequence of enlarged vessels' diameter [3]. In our series, gestational age at BCC was optimal, done after 18 gestational weeks and before 24 weeks in 14 cases. Gestational age at ILC was lower, and complications occurred at higher gestational age.

Previous studies report that desirable instrument approach in BCC is directly into the amniotic sac of the “target” twin, which can be achieved in about 63% of cases. In cases with oligohydramnios in severe forms of sFGR or TTTS, amnioinfusion may be done previously. Occasionally, the instrument may be introduced through the healthy twin amniotic sac in order to avoid transplacental approach or if twins are in an unfavorable position, sometimes causing septostomy and iatrogenic MA pregnancy [3, 12]. We performed amnioinfusion in five cases and amnio-derivation in three cases, while in one case the instrument was introduced through the co-twin amniotic sac with accidental septostomy and late death of the co-twin. Operating time was not influenced by placental position or accessibility of the target twin amniotic sac, as we had previously performed amnion fusion. No previous intervention was done before ILC as intrafetal methods do not require previous interventions. SFT was successful in all cases regardless of the technique.

Early fetal death was registered three times (42.86%) after ILC; while late fetal death twice (13.33%) after BCC [6, 8]. As different techniques carry different perioperative risks, previous studies concluded that late fetal death is more frequent after BCC, while early fetal loss is more frequent after ILC [6, 8, 10]. Early fetal death in ILC may be the consequence of difficult needle maintenance in the abdomen for repeat coagulation and divergent energy dissemination, and/or prolonged time for complete cessation of blood flow with the risk of co-twin damage, which may explain three early co-twin deaths in ILC [12, 13, 14]. The cause of late fetal death, that may not always be explained, may be cord entanglement, compression of the co-twin with fibrous occluded cord, or amniotic band syndrome [5, 6, 9]. In our small series, there were two deaths of the co-twin after BCC. In one case, late death of the co-twin occurred as a consequence of the cord entanglement in iatrogenic MA pregnancy, while the other, which occurred at 16 + 4 weeks, could not be explained.

PPROM is reported to happen in 10–30% and is responsible for most preterm births [5, 6, 7, 10]. In our series, PPRM was registered in 22.73% (26.7% in BCC and 14.3% in ILC), while preterm birth occurred in 64.7% (69.2% in BCC and 50% in ILC).

Overall survival rate in MC pregnancies was 77.27%, but the difference was found according to the applied technique – 86.67% in BCC and 57.14% in ILC. Previous studies report both smaller and larger series of cases of SFT, with the survival rate similar to our own [5–9, 12, 15, 16, 17]. Less survival after ILC may be the consequence

if recruitment – fetal loss occurred only if SFT had been done after 16 gestational weeks, while BCC was always done at optimal gestational age. Concerning the limitations of the gestational age and technique, as well as the survival rate, BCC is the method of choice for SFT, except in cases where urgent SFT is required before 16 gestational weeks. Results from other authors about survival according to different indications for SFT report best survival in TTTS after BCC and in TRAP sequence after intrafetal methods, due to difficult BCC in short edematous cord in TRAP sequence [3, 15, 16, 17]. In our study comparison by indication could not have been done due to a relatively small number of cases.

Few studies report neonatal morbidity and mortality after SFT, and even fewer evaluate neurological or psychomotor development, reporting normal development in the age of two years in 70–92%, explaining impaired development by prematurity [15–20]. In our series, no specific neonatal morbidity was reported after both BCC and ILC, except for those that are a consequence of prematurity.

CONCLUSION

We may conclude that there is no ideal method of SFT in MH twins. Risk of co-twin death is lower after BCC than after ILC. There is no difference in the frequency of PPRM and PTD between the two methods. Success of each SFT method in MH twins depends upon correctly set indication, gestational age at procedure, and SFT technique. BCC is a method of SFT optimally done between 18 and 22 weeks in the cases when normal amniotic fluid is present in the “targeted” fetus amniotic sac and there is enough space for instrument manipulation. If that is not the case, previous amnioinfusion may be done. Interstitial methods may be the choice in the cases of severe oligohydramnios or anhydramnios, early gestation with small fetal volume and/or short umbilical cord of the targeted twin. ILC represents ultrasound-guided SFT method optimally done in 16 weeks, without the need for previous interventions. Concerning the fact that ILC is followed by great risk of early co-twin death, this method should be applied in selective cases with low dynamic circulation, or a less risky method should be applied. As better results were achieved after BCC at the Narodni Front Clinic for Gynecology and Obstetrics, this method became a standard for SFT in MH twins, except in cases of TRAP sequence before 16 weeks.

Conflict of interest: None declared.

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Селективна фетална терминација код монохорионских близанаца – исход трудноће после биполарне коагулације пупчаника и интерстицијалне ласерске коагулације

Весна Мандић-Марковић^{1,2}, Жељко Миковић^{1,2}, Дејан Филимоновић^{1,2}

¹Универзитет у Београду, Медицински факултет, Београд, Србија;

²Гинеколошко-акушерска клиника „Народни фронт“, Београд, Србија

САЖЕТАК

Увод/Циљ Циљ рада је приказати перинатални исход после селективне феталне терминације (СФТ) код монохорионских (МХ) трудноћа урађених биполарном коагулацијом пупчаника (БКП) и интерстицијалном ласерском коагулацијом (ИЛК).

Метод Током петогодишњег периода СФТ је урађена код 22 МХ трудноће – БКП код 15, а ИЛК код седам случајева. Регистровани смо индикацију за СФТ, гестациску доб приликом СФТ, рану и касну смрт другог близанца, *PPROM* (пре-терминско прснуће плодних овојака), гестациску доб на порођају/побачају, период од интервенције до порођаја/побачаја, начин порођаја, телесну масу неонатуса и петоминутни индекс Апгар.

Резултати Живорођеност је била значајно виша после БКП него после ИЛК (86,7 : 57,1%). Гестациска доб приликом СФТ је била виша код БКП (20,2 ± 1,8 : 16,5 ± 1,7 недеља). Гестациска доб на порођају/побачају је била нижа код ИЛК (32,5 ± 4,8 : 27,5 ± 9,5 недеља), али разлика није била значајна кад су поређени само живорођени (33,8 ± 3,7 : 34,7 ± 4,5 не-

деља). Није постојала разлика у периоду између интервенције и порођаја/побачаја (86,7 ± 33,7 : 77,1 ± 73 дана), али је период био значајно већи после ИЛК кад су поређени само живорођени (93,3 ± 33 : 133 ± 30,9 дана). Није постојала разлика у учесталости *PPROM* (26,7 : 14,3%), претерминског порођаја (69,2 : 50%), царског реза (84,6 : 75%), телесне масе неонатуса (2174 ± 82,4 : 2475 ± 823 g), ни индекса Апгар (7,7 ± 1,9 : 9,2 ± 1).

Закључак Не постоји идеални метод СФТ код МХ трудноћа, а успех сваке методе зависи од правилно постављене индикације, гестациске доби приликом интервенције и технике СФТ. Степен живорођености је већи после БКП него после ИЛК. Пошто су у ГАК „Народни фронт“ бољи резултати постигнути после БКП, ова метода је постала стандард за СФТ код МХ трудноћа, осим у случајевима секвенце *TRAP* пре 16 гестациских недеља.

Кључне речи: селективна фетална терминација; монохорионске трудноће; биполарна коагулација пупчаника; интерстицијална ласерска коагулација



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Corneal collagen cross-linking in pediatric patients with keratoconus

Svetlana Stanojlović^{1,2}, Vedrana Pejcin¹, Tanja Kalezić^{1,2}, Jelica Pantelić^{1,2}, Borivoje Savić²

¹University of Belgrade, Faculty of Medicine, Belgrade, Serbia;

²Clinical Center of Serbia, Clinic for Eye Diseases, Belgrade, Serbia

SUMMARY

Introduction/Objective The aim of this study was to report visual, refractive, and tomographic outcomes of corneal collagen cross-linking (CXL) in pediatric keratoconus.

Methods This retrospective study included 17 eyes of 12 patients with progressive keratoconus who underwent epithelium-off CXL at the age ≤ 18 years. Following data were analyzed at baseline and postoperatively at one, three, six, nine, 12 months for all the patients, and annually where available: uncorrected distant visual acuity (UDVA) and best spectacle-corrected distant visual acuity (CDVA), refraction and corneal tomography.

Results Mean UDVA improved significantly from 0.52 ± 0.38 at baseline to 0.24 ± 0.29 logarithm of minimum angle resolution (log MAR) at one year ($p = 0.011$) and remained stable at two-year follow-up (0.21 ± 0.34 log MAR). Mean CDVA was 0.15 ± 0.21 at baseline and 0.06 ± 0.13 log MAR at one year ($p = 0.248$). Maximum keratometry showed a significant flattening of 1.30 ± 1.99 D ($p = 0.011$) after a year and remained stable two years after CXL. Minimum keratometry significantly decreased with a mean change of 1.34 ± 1.37 ($p = 0.001$). Mean reduction of corneal thickness after CXL was 55.35 ± 64.42 μm ($P = 0.003$). After a year, seven (42%) eyes showed Kmax regression, nine (53%) stabilization, and one (5%) progression.

Conclusion In our study CXL effectively prevented progression of keratoconus in 95% of pediatric patients after a year, while improving UDVA and keratometry values. One patient with eye rubbing behavior showed signs of keratoconus progression after CXL treatment.

Keywords: corneal collagen cross-linking; keratoconus; pediatric patients; CXL

INTRODUCTION

Keratoconus is a progressive, bilateral, and most commonly asymmetric ectatic disorder associated with localized corneal thinning and protrusion [1]. Keratoconus usually begins in puberty and progress during adolescence. Progression of keratoconus with subsequent corneal steepening induces irregular astigmatism and myopia leading to a decrease in visual acuity. Indeed, earlier age of onset is associated with faster progression. Keratoconus severity was also greater at the time of diagnosis in children and adolescents; almost 30% of pediatric keratoconus presented at stage four compared with 8% of their adult counterparts [2]. Therefore, it is critical to perform corneal collagen cross-linking (CXL) as early as possible to stop progression of pediatric keratoconus. The introduction of this procedure reduced the need for penetrating keratoplasty, which is usually required for advanced cases of keratoconus. This is particularly important for children since it was found that younger age is associated with a sevenfold increased risk of corneal transplantation [2].

The biomechanical resistance of the cornea in keratoconus is only 60% of the normal cornea [3]. Corneal CXL using ultraviolet light A and riboflavin as the photosensitizer was introduced by Wollensak et al. [4]. This treatment is aimed to increase the biomechanical stiffening

of the cornea and its biomechanical resistance to collagenase activity [5, 6]. The safety and efficacy of CXL for keratoconus has already been demonstrated in both adults and children [7, 8]. However, CXL in pediatric patients with keratoconus has been significantly less studied. It was also suggested that the effect of CXL in children may be temporary [7].

The aim of this study was to evaluate visual, refractive, and tomographic outcomes after standard corneal CXL for progressive keratoconus in patients younger than 19 years of age.

METHODS

Patients and methods

This retrospective study was conducted in compliance with the institutional review board regulations, informed consent regulation and adhered to the tenets of the Declaration of Helsinki. Our single-centered study comprised 17 eyes of 12 pediatric patients with progressive keratoconus who underwent an epithelium-off CXL at the age ≤ 18 between June 2015 and June 2017. These patients were followed up one, three, six, nine months, and one year postoperatively (all patients, and annually where available).

A diagnosis of keratoconus was based on clinical findings and/or corneal images obtained

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Correspondence to:

Svetlana STANOJLOVIĆ
Clinic for Eye Diseases
Clinical Center of Serbia
Pasterova 2
11000 Belgrade, Serbia
stanojlovic.svetlana@gmail.com

by the Orbscan IIz Corneal Tomographer (Orbtek; Baush and Lomb, Salt Lake City, UT, USA). All patients underwent a complete ophthalmic evaluation before CXL and at all follow-up visits after undergoing CXL. Data analysis included uncorrected distant visual acuity (UDVA), best spectacle-corrected distant visual acuity (CDVA), refraction (spherical equivalent, refractive astigmatism), corneal tomography, slit-lamp evaluation and particularly associated allergic conjunctivitis. All UDVA and CDVA were recorded using Snellen chart and then converted to log MAR for statistical analysis. The following tomographic parameters were analyzed: simulated keratometry (SimK), maximum keratometry (Kmax), minimum keratometry (Kmin), minimum corneal thickness (MCT), anterior and posterior best-fit-sphere (ABFS and PBFS respectively), radius of anterior and posterior BFS, highest posterior elevation (HPE). The magnitude of highest posterior elevation was noted using the cursor within the central 8 mm zone in the best-fit-sphere map. The preoperative cone location was determined by the location of the highest posterior elevation. If it was within central 3 mm zone, it was termed a central cone. If it was outside this zone, it was termed paracentral (within central 3–5 mm zone) and peripheral (outside central 5 mm zone). The Amsler-Krumeich classification based on average keratometry was used to classify keratoconus as mild (< 48 D), moderate (48–53 D) and severe (> 53 D).

Inclusion criteria were pediatric patients underwent CXL in one or both eyes at the Clinic for Eye Diseases affiliated to the University of Belgrade and being followed up for at least one year. Exclusion criteria was preoperative minimum corneal thickness less than 350 μm . Changes in Kmax were defined as Kmax regression (> 1 D decrease in Kmax), Kmax stabilization (< 1 D change in Kmax), and Kmax progression (> 1 D increase in Kmax), as described by Koller et al. [9].

Surgical procedure

CXL with riboflavin and ultraviolet A (UV-A) was performed according to the standard (Dresden) protocol [4]. Inclusion criteria was preoperative minimum corneal thickness $\geq 400 \mu\text{m}$ (16 eyes of 11 patients). Most children were able to successfully tolerate surgical procedure under topical anesthesia alone, while adjunctive sedation before the procedure was required in 4 eyes of 2 patients. After insertion of lid speculum, an 8-mm marker was used to mark the central corneal epithelium; then the epithelium was removed with a blunt metal spatula and isotonic 0.1% riboflavin-20% dextran solution (10 mg riboflavin-5-phosphate in 10 ml dextran solution) was applied for 30 minutes at two-minute intervals. Ultrasonic pachymetry was obtained immediately after central epithelial removal and 30 minutes after the start of riboflavin drops. If the thinnest corneal thickness was less than 400 μm , hypotonic riboflavin was applied until the thinnest corneal stroma had swollen to 400 μm . Central cornea was then exposed to UV-A irradiation using a UV light lamp (Intacs XL corneal crosslinking system, Addition Technology, Des Plaines, IL,

USA) at 3 mW/cm² for 30 minutes (5.4 J/cm² total energy dosage) with reapplication of isotonic riboflavin solution every three minutes to ensure saturation. At the end of surgery, a therapeutic soft contact lens was applied until reepithelization of the cornea was completed. The postoperative treatment included ofloxacin eye drops four times a day (qid) for a week; fluorometholone eye drops qid with taper a month and artificial tears qid for six months.

In one eye a technique of contact lens-assisted collagen cross-linking (CACXL) was applied due to the estimated preoperative corneal thickness < 400 μm (367 μm). Surgical procedure was performed as previously described by Jacob et al. [10]. Briefly, after epithelial removal, isotonic 0.1% riboflavin-20% dextran solution was applied every two minutes for 30 minutes. An ultraviolet barrier-free soft contact lens (0.09 mm thickness, 14 mm diameter) soaked in isotonic 0.1% riboflavin for 30 minutes was placed on the cornea. Once the minimum corneal thickness with the contact lens was confirmed to be greater than 400 μm , CXL was proceeded. The UVA irradiance was performed for the next 30 minutes with reapplication of isotonic 0.1% riboflavin over and underneath the contact lens every three minutes. Postoperative treatment included soft contact lens and antibiotic drops as previously described for children underwent standard Dresden protocol.

RESULTS

A total of 17 eyes of 12 patients with the average age at surgery of 15 ± 1.7 years (range: 13–18) were included in this study. There were one (8.3%) female and 11 (91.7%) male patients. Preoperative, and follow-up data at one, three, six, nine and 12 months was available for all patients; two-year follow-up was available for eight patients; three-year follow-up for four patients. Tomographic values from patients exceeding one year of follow up are presented but have not been subjected to statistical analysis, as the sample size was considered insufficient. The changes in visual acuity, refractive and tomographic variables at baseline and one year after CXL are demonstrated in Tables 1 and 2.

Table 1. Preoperative and postoperative one-year visual acuity and refractive values and their statistical significance

Parameter	Preoperative	Postoperative (1 year)	p
UDVA (logMAR)	0.52 ± 0.38	0.24 ± 0.29	0.011
CDVA (logMAR)	0.15 ± 0.21	0.06 ± 0.13	0.248
Spherical Eq., D	-2.83 ± 2.15	-2.42 ± 1.89	0.67
Refractive astig., D	-2.69 ± 3.6	-4.0 ± 1.64	0.61

UDVA – uncorrected distance visual acuity; CDVA – corrected distance visual acuity; Spherical Eq. – spherical equivalent; Refractive astig. – refractive astigmatism

Eight patients (11 eyes) had a history of asthma and hay fever, three patients had no history of allergic eye diseases (five eyes), whereas one patient (one eye) had a history of eye rubbing behavior without atopy.

Interestingly, 13 eyes of 10 patients (76.5%) presented at stage two at the time of diagnosis with average Kmax

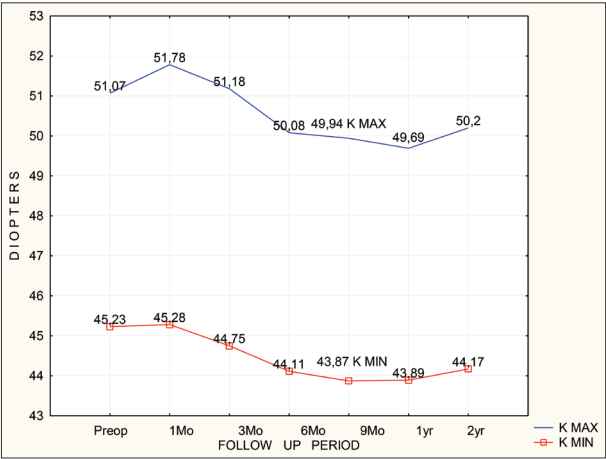


Figure 1. Changes in Kmax and Kmin over a two-year follow-up period; Kmax – maximum keratometry; Kmin – minimum keratometry

of 49.67 ± 1.48 D, whereas only four eyes of three patients (23.5%) presented at stage three, showing average Kmax of 55.62 ± 1.50 D. All patients had cone located inside the central 3 mm topographic zone.

Visual acuity and refraction

Mean UDVA improved significantly from 0.52 ± 0.38 at baseline to 0.24 ± 0.29 log MAR after a year ($p = 0.011$) (Table 1) and remained stable at the two-year follow-up (0.21 ± 0.34 log MAR). Mean spectacle CDVA was 0.15 ± 0.21 at baseline and 0.06 ± 0.13 log MAR after a year. However, this improvement was not significant ($p = 0.248$).

The mean preoperative and postoperative spherical equivalent and refractive astigmatism data are shown in Table 1. There was no significant difference between the preoperative and postoperative refractive values as well ($p > 0.05$). Mean spherical equivalent was 2.42 ± 1.89 D ($p = 0.67$); mean refractive cylinder was 4.0 ± 1.64 D ($p = 0.61$) after a year.

Tomography

Maximum keratometry value showed a significant flattening of 1.30 ± 1.99 D ($P = 0.011$) at one year and remained stable at two year follow-up (Figure 1). The baseline and follow-up measurements demonstrated that Kmax value decreased significantly six months after CXL and this improvement remained stable afterwards (Figure 1). Minimum keratometry value significantly decreased with a mean change of 1.34 ± 1.37 at one year compared with baseline ($p = 0.001$). A significant flattening of Kmin was observed at three month ($p = 0.039$) and remained statistically significant along the entire follow-up period (Figure 1). The SimK average values showed statistically significant worsening after three months, after CXL ($p = 0.036$), becoming statistically insignificant after the sixth month until the end of follow-up period (Table 2).

As presented in Table 2, compared with the baseline, the mean anterior elevation BFS decreased significantly one year after CXL ($p < 0.01$). In contrast, a significant

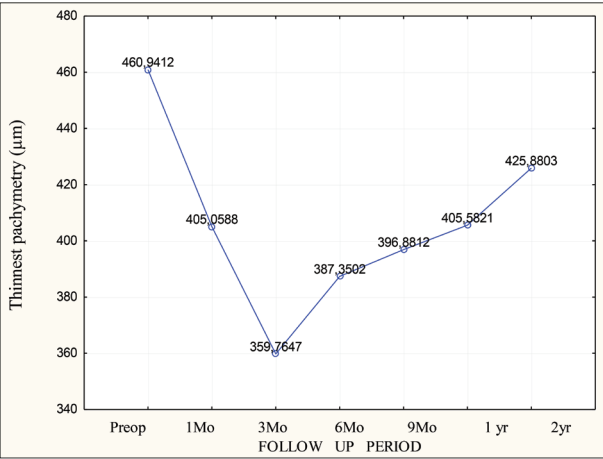


Figure 2. Changes in the thinnest corneal pachymetry over a two-year follow-up period

Table 2. Preoperative and postoperative one-year corneal tomography values and their statistical significance

Parameter	Preoperative	Postoperative (1 year)	p
SimK, D	5.52 ± 2.04	5.68 ± 1.89	0.702
Kmax, D	51.07 ± 2.97	49.69 ± 3.11	0.011
Kmin, D	45.23 ± 2.31	43.89 ± 2.57	0.011
MCT, μm	460.94 ± 44.94	405.58 ± 86.86	0.003
ABFS, D	42.79 ± 1.01	42.23 ± 1.33	0.003
ABFSr, mm	7.88 ± 0.2	7.95 ± 0.23	0.002
PBFS, D	53.7 ± 2.03	55.25 ± 1.95	0.008
PBFSr, mm	6.29 ± 0.23	6.11 ± 0.26	0.008
HPE, mm	0.2 ± 0.29	0.09 ± 0.04	0.658

SimK – simulated keratometry; Kmax – maximum keratometry; Kmin – minimum keratometry; MCT – minimal corneal thickness; ABFS – anterior best-fit-sphere; ABFSr – radius of the anterior best-fit-sphere; PBFS – posterior best-fit-sphere; PBFSr – radius of the posterior best-fit-sphere; HPE – highest posterior elevation

steepening of posterior elevation BFS was observed a year after CXL treatment ($p < 0.01$).

After a year, in comparison with baseline values, seven (42%) eyes showed Kmax regression; nine (53%), stabilization; and one (5%), progression. Keratoconus progressed in one eye with steepening of >1 D in both orthogonal meridians at one year. Interestingly, at one year majority of treated eyes (12/17) showed flattening of Kmin in combination with either stabilization (six eyes) or regression (six eyes) of the steeper orthogonal meridian. At two-year follow up, five out of eight eyes showed stabilization of both orthogonal meridians, whereas in three eyes regression ≥ 1 D of both, Kmax and Kmin meridian, was observed.

Pachymetry

Average preoperative pachymetry at the thinnest point as measured by Orbscan was 460.94 ± 44.95 μm. Only one patient had pachymetry value under 400 μm (368 μm). The changes of pachymetry over time are shown in Figure 2. There was a significant reduction of minimum corneal thickness after CXL in comparison with baseline values, with a mean reduction of 55.35 ± 64.42 μm after a year ($p = 0.003$) (Table 2).

Statistical analysis

Statistical analysis was performed using the SPSS software (IBM Corp. Armonk, NY, USA) version 23.0. The significance of the difference between the preoperative and postoperative variables was tested using a two-tailed paired samples Student's *t* test. The value of $p < 0.5$ was considered statistically significant. All values were expressed as mean \pm SD. Visual acuity was converted to logMAR for statistical analysis.

DISCUSSION

Different studies have confirmed that standard epithelium-off CXL protocol is safe and effective for the treatment of pediatric keratoconus [11]. Due to the rarer corneal stiffness in pediatric population, CXL is not as effective in children as it is in adults [12]. Recently, a 24% regression rate was contemplated in patients who were aged 15 years and younger at the time of inclusion in the treatment protocol [13].

In our study, we evaluated visual, refractive, and tomographic results in a group of pediatric patients with a mean age of 15 ± 1.7 years who had been treated with corneal CXL for progressive keratoconus. Majority of eyes (76.5%) presented at stage two at time of diagnosis with average Kmax of 49.67 ± 1.48 D. Both UDVA and CDVA improved at the one-year follow-up and remained stable two years after CXL procedure; however, the improvement in CDVA was not statistically significant. Similar to other studies [7, 8, 14], spherical equivalent and refractive astigmatism did not show any significant differences in comparison with preoperative values. Although the main objective of CXL treatment is to prevent keratoconus progression, flattening of the cornea is commonly reported [7, 15]. In ours, as well as in similar studies [8, 16], initial steepening of both keratometric indices, Kmax and Kmin was observed during the first three months. This has been suggested to be the result of early epithelial remodeling [17]. We also demonstrated continuous improvement in corneal topographic values with significant flattening of both Kmax and Kmin a year following CXL procedure; however, slight steepening was noticed after two years for available patients (eight eyes). This is in accordance with the results of previous studies with a follow-up duration ranging from one to three years [16]. Improvement in keratometric values was associated with significant decrease of ABFS suggesting global corneal flattening as well. Although PBFS increased at one-year follow up, no significant variation of highest posterior elevation has been observed indicating the effectiveness of the CXL treatment.

Interestingly, majority of eyes in our study (12/17) demonstrated flattening of Kmin in combination with either stabilization or regression of the Kmax. Corneal response to CXL treatment showed wide variability in reported studies and this was also observed in ours. Vinciguerra et al. [8] reported significant flattening of the flatter meridian but not of the steeper meridian at the two-year follow up. Some

other studies and ours also demonstrated no significant differences in simulated keratometry at one-year follow-up.

In pediatric patients, keratoconus is often more advanced in the worse-affected eye at diagnosis as compared with adult patients [2]. Chatzis and Hafezi [7] found a preoperative progression rate of 88% and recommended CXL treatment as soon as the diagnosis of keratoconus has been confirmed in children. In our study, all children subjected to CXL treatment had history of significant visual impairment accompanying keratoconus progression. We generally perform pediatric corneal CXL at presentation in the eye with more advanced stage of keratoconus, rather than to wait for documented progression. Until the age of 16, all patients were followed at three-month intervals. Serial tomographies were performed for both treated and untreated eyes to identify early keratoconus progression, which may occur after CXL as well. Chatzis and Hafezi [7] also observed that an initially significant improvement in Kmax in the first two years was lost by the third year in pediatric keratoconus.

In our case series, 42% of eyes showed keratoconus regression a year after the standard epi off CXL treatment, which was manifested as flattening of the steepest keratometry meridian more than 1D; whereas, 53% of treated eyes remained stable with average changes in Kmax less than 1D. One patient with compulsive eye rubbing behavior (5%), showed signs of keratoconus progression after CXL treatment with an increase of both orthogonal meridians. Allergy, atopy, and eye rubbing are identified as possible causes of keratoconus progression after CXL treatment [2, 18]. Therefore, patients should be counseled to avoid eye rubbing. The paracentral cone location and the thinnest corneal thickness below 450 μ m were also linked to possible keratoconus progression [19]. However, all patients in our case series exhibited central topographic pattern. The average minimum pachymetry corneal thickness was 460.94 ± 44.95 μ m. The CXL procedure was well tolerated by all patients with corneal re-epithelization completed three days postoperatively. We did not observe any side effects of the procedure. Mild temporarily corneal haze was noticed in all patients. This was also described in similar studies [13, 20].

For pediatric keratoconus, it is of vital importance to avoid more aggressive procedures, such as keratoplasty, even in patients with advanced form of the disease. Jacob et al. [10] have recently described CACXL technique for performing cross-linking in thin corneas with less than 400 microns after epithelial abrasion. Endothelial cell counts have been shown to remain unaffected after CACXL [10]. Here we also observed that CACXL was effective and safe in stabilization of keratoconus progression at one-year follow up in a patient with minimum corneal thickness of 367 microns. Alternative protocols, such as transepithelial CXL may also be effective in stabilizing corneal topography [21]. However, several studies showed inferior efficacy of the epithelium on CXL procedure in comparison with standard CXL treatment [22, 23]. Due to the reduced treatment time, accelerated CXL is also likely to be better tolerated in pediatric patients than standard CXL treatment.

The long-term efficacy of accelerated pediatric CXL is yet to be determined.

CONCLUSION

We confirmed efficacy and good safety profile of pediatric corneal CXL. In this age group, keratoconus remained stable without signs of progression in 95% of eyes following standard epithelium off CXL treatment at the two-year follow up. Keratoconus in younger patients is often more aggressive and the effect of CXL may be temporary. Progression of pediatric keratoconus after CXL may also

be related to the intense eye rubbing habit. Furthermore, special attention should be given to the pediatric population with more advanced stages of keratoconus. Alternative protocols, such as contact lens assisted CXL might be considered in eyes with thin cornea.

NOTE

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Conflict of interest: None declared.

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Корнеални колагени крос-линкинг код педијатријских болесника са кератоконусом

Светлана Станојловић^{1,2}, Ведрана Пејин¹, Тања Калезић^{1,2}, Јелица Пантелић^{1,2}, Боровоје Савић²

¹Универзитет у Београду, Медицински факултет, Београд, Србија;

²Клинички центар Србије, Клиника за очне болести, Београд, Србија

САЖЕТАК

Увод/Циљ Циљ овог рада био је да прикажемо видну оштрину, рефракционе и томографске резултате после корнеалног колагеног крос-линкинга (ККЛ) због прогресивног кератоконуса код деце.

Метод Ретроспективна студија обухватила је 17 очију код 12 болесника узраста до 18 година код којих је урађен ККЛ са уклањањем епитела. Анализирани су преоперативни и постоперативни подаци свих болесника који су добијени на прегледима један месец, три месеца, шест, девет и 12 месеци после урађеног ККЛ, као и једном годишње код болесника са дужим периодом праћења. Анализа је обухватила некориговану видну оштрину (НКВО), најбоље кориговану видну оштрину (КВО), рефракцију и корнеалну томографију.

Резултати Средња НКВО значајно се побољшала од $0,52 \pm 0,38$ до $0,24 \pm 0,29$ логаритама минималног угла резолуције (логМУР) после годину дана ($p = 0,011$). Ова вредност остала је стабилна до краја друге године праћења ($0,21 \pm 0,34$ логМУР).

Преоперативна средње КВО износила је $0,15 \pm 0,21$ логМУР, а годину дана после ККЛ $0,06 \pm 0,13$ логМУР ($p = 0,248$). Највећа средња кератометријска вредност смањила се за $1,30 \pm 1,99$ Д ($p = 0,011$). Најмања кератометријска вредност смањила се за $1,34 \pm 1,37$ Д ($p = 0,001$). Дебљина рожњаче смањила се за $55,35 \pm 64,42$ микрометра ($p = 0,003$). После годину дана седам (42%) очију показало је смањење максималне кератометријске вредности; девет (53%) стабилизацију максималне кератометријске вредности; једно (5%) око напредовање кератоконуса.

Закључак У нашој студији ККЛ је ефикасно спречио напредовање кератоконуса код 95% педијатријских болесника уз побољшање НКВО и кератометријских вредности. Код једног болесника, који има навику да трља очи, дошло је до напредовања кератоконуса после крос-линкинга рожњаче.

Кључне речи: корнеални колагени крос-линкинг; кератоконус; педијатријски болесници



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Smoking and inflammation in laryngeal squamous cell carcinoma

Jelena Sotirović¹, Aleksandar Perić¹, Danilo Vojvodić², Nenad Baletić¹, Milanko Milojević¹, Ljubomir Pavićević¹

¹Military Medical Academy, Department of Otorhinolaryngology, Belgrade, Serbia;

²Military Medical Academy, Institute for Medical Research, Belgrade, Serbia

SUMMARY

Introduction/Objective Epidemiological studies have established cigarette smoking as one of the most significant risk factors in pathogenesis of laryngeal squamous cell carcinoma (LSCC). One of the possible underlying mechanism is chronic inflammation, but published data regarding the effect of tobacco on systemic immune response is inconsistent.

The goal of this study was to evaluate concentrations of serum proinflammatory cytokines [interleukin (IL)-6, IL-1 β , and tumor necrosis factor (TNF)- α] in patients with LSCC and in healthy subjects according to cigarette smoking.

Methods Fifty-nine LSCC patients and 44 healthy controls were enrolled in the study. Samples of peripheral blood and details of tobacco use were gathered from the examinees. Flow cytometry was performed to analyze serum concentrations of IL-6, IL-1 β , and TNF- α . The results were compared according to active smoking status.

Results Statistical analysis revealed no significant difference between smoking LSCC patients and smoking healthy subjects. Additionally, investigated cytokines were not significantly different in healthy subjects according to smoking status. In non-smoking participants with LSCC, concentrations of serum IL-1 β and TNF- α were higher ($p < 0.05$) in comparison with smoking LSCC patients.

Conclusion Findings of our study may indicate that smoking leads to the suppression of proinflammatory response in LSCC patients, whilst proinflammatory response is unaffected by cigarettes in healthy subjects.

Keywords: smoking; IL-6; IL-1 β ; TNF- α ; laryngeal squamous cell carcinoma

INTRODUCTION

Carcinogenesis is a multifactorial and multistage process in which gene–environment interactions play crucial role. Smoking is well-established as a significant risk factor in laryngeal squamous cell carcinoma (LSCC). One of the most accepted hypotheses in carcinogenesis is chronic inflammation. Inflammation and immune modulation induced by tobacco and asbestos are broadly associated with lung cancer, alcohol consumption, and inflammation of the pancreas with pancreatic cancer, hepatitis B infection with liver cancer, inflammatory bowel disease (Crohn's disease and ulcerative colitis) with colorectal cancer. Despite the established evidence of the causal relationships between smoking and elevated cancer risk, the underlying mechanism has not been completely understood. The fact that not all smokers develop cancer suggests individual susceptibility for developing malignant disease. Recently published literature reports genetic and epigenetic changes induced by tobacco carcinogens in head and neck carcinoma [1]. Additionally, in previously published literature, nicotine was found to exert both pro-inflammatory and anti-inflammatory effects [2].

Virchow noticed over a 100 years ago that histologic appearance of tumor tissue resembles

the histologic change seen in unhealed wound [3]. Conversely, Coley [4] reported regression of the malignant tumor following bacterial infection. Today, inducing strong infection and inflammation by *Mycobacterium bovis*, bacillus Calmette–Guerin (BCG) in bladder carcinoma is standard antitumor therapy.

Association between cancer and inflammation is reflected by the presence of numerous proinflammatory cytokines in cancer. It is believed that mediators released by host inflammatory cells or cancer cells are involved in tumor initiation, promotion, and progression. Given that inflammation can have both protumorigenic and anti-tumorigenic effect, it seems that the role of inflammation in tumorigenesis depends on the interaction between tumor cells, immune cells, and inflammatory cells. Since deregulated inflammation is a significant factor in carcinogenesis of numerous malignant tumors, identifying the mechanisms by which inflammation is deregulated in cancer may improve antitumor therapeutic strategies.

The goal of this research was to reveal the relations between smoking and concentrations of serum proinflammatory cytokines TNF- α , IL-6, and IL-1 β in patients with LSCC and in healthy subjects.

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Correspondence to:

Jelena SOTIROVIĆ
Military Medical Academy
Crnotravska 17
11000 Belgrade
Serbia
j.sotirovic@gmail.com

METHODS

The research was performed as a cross-sectional study of 59 patients with LSCC (40 smokers, 19 non-smokers). All the patients were diagnosed at a tertiary referral center. The diagnosis of LSCC was confirmed clinically, histopathologically, and radiologically. The control group included 44 subjects (14 smokers, 30 non-smokers), healthy volunteers with normal fiberoptic laryngeal findings.

Informed consent was collected from both patients and controls following the hospital's ethics committee-approved protocol. Exclusion criteria were as follows: any other previous or present malignant or autoimmune disease, history of allergies, co-existing infectious disease, systemic corticosteroid or any immunomodulating therapy.

We defined active smoking as consuming more than 20 cigarettes per day during the period of the last five years.

Samples of peripheral venous blood (5 ml) were taken from all LSCC patients and healthy individuals included in the study, then allowed to clot for 30 minutes. Blood samples were centrifuged at 1,000 g for 15 minutes. Serum was separated, aliquoted and stored at -80°C until cytokine detection. Flow cytometric kit (FlowCytomix™ Multiple Analyte Detection System, Human FlowCytomix™ Inflammation Panel, eBioscience, Thermo Fisher Scientific Inc., Waltham, MA, USA) was used to measure the serum levels of TNF- α , IL-6, and IL-1 β on the flow cytometer (Beckman Coulter XL-MCL, USA), which was connected with BMS FlowCytomix Pro 2.2 Software in accordance with the manufacturer's instructions. By the manufacturer's instructions, the standard range was 27–20,000 for TNF- α , IL-6, and IL-1 β .

Statistical tests were performed using GraphPad Prism 5 (Graph Pad Software, San Diego, CA, USA). Mann-Whitney U (nonparametric) test was used for comparison between the groups. The results were rendered as mean \pm SD (standard deviation). If p was < 0.05 , we considered the difference statistically significant.

RESULTS

Cytokine levels in smoking LSCC patients and smoking control groups

Concentrations of serum cytokines in smoking LSCC patients and smoking control individuals are presented in Table 1. No statistically significant difference was observed between these two groups of patients.

Table 1. Distribution of cytokine levels in smokers

Cytokine	Cytokine level, mean \pm SD (pg/mL)		p
	LSCC smokers	Control smokers	
IL-6	39.40 \pm 69.54	53.93 \pm 91.18	0.7894
IL-1 β	191.3 \pm 351.9	239.3 \pm 408.4	0.6711
TNF- α	143.2 \pm 231.3	178.8 \pm 312.7	0.7002

LSCC – laryngeal squamous cell carcinoma; SD – standard deviation

Cytokine levels in LSCC patients according to smoking

Statistical analysis revealed significantly higher concentrations ($p < 0.05$) of IL-1 β and TNF- α in non-smoking LSCC patients compared to smoking patients. The results are shown in Table 2, Figure 1, and Figure 2.

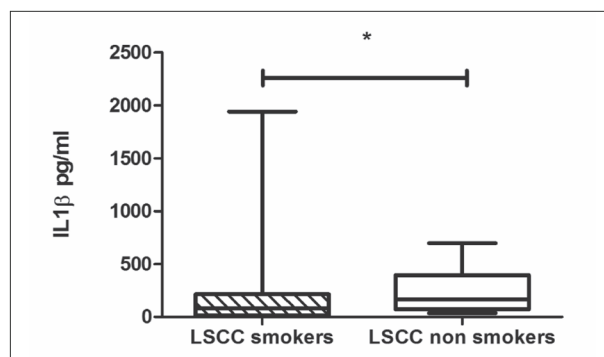


Figure 1. Comparison of interleukin (IL)-1 β serum levels in smoking and non-smoking laryngeal squamous cell carcinoma (LSCC) patients

* $p < 0.05$

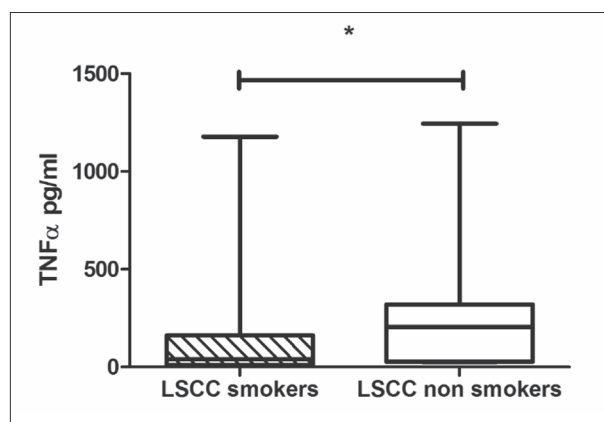


Figure 2. Comparison of interleukin TNF- α serum levels in smoking and non-smoking laryngeal squamous cell carcinoma (LSCC) patients

* $p < 0.05$

Cytokine levels in the Control Group according to smoking

Proinflammatory cytokines were not significantly different between controls who smoke and controls who do not smoke (Table 2).

DISCUSSION

As chronic infection and inflammation may lead to malignant cell transformation, a malignant tumor may also induce chronic inflammation. The intrinsic inflammatory pathway activated by genetic changes that cause neoplasia leads to an excessive production of inflammatory cytokines. This mechanism is observed in the activation of oncogenes such as MYC, RAS, RET, or inactivation of tumor suppressors. On the other hand, both extrinsic (alcohol)

Table 2. Distribution of cytokine levels in laryngeal squamous cell carcinoma patients and control subjects according to smoking

Cytokine	Cytokine level mean ± SD (pg/mL)		p	Cytokine level mean ± SD (pg/mL)		p
	LSCC patients			Controls		
	Smokers	Non-smokers		Smokers	Non-smokers	
IL-6	39.4 ± 69.54	45.56 ± 48.16	0.4336	53.93 ± 91.18	55.42 ± 67.81	0.1895
IL-1β	191.3 ± 351.9	247.7 ± 199.3	0.0450	239.3 ± 408.4	161.6 ± 158.4	0.5812
TNF-α	143.2 ± 231.3	282.2 ± 343.7	0.0304	178.8 ± 312.7	120 ± 142.1	0.7314

LSCC – laryngeal squamous cell carcinoma; SD – standard deviation

and intrinsic (K-RAS) pathways of inflammation play a role in pathogenesis of pancreatic cancer [5].

TNF- α is prototypical proinflammatory cytokine and has significant role in host defense to bacterial, viral, and parasitic infections [6]. Although originally found to be toxic for cancer cells in high doses, TNF- α increases the colonization of the peritoneum and neovascularization of developing tumor deposits in ovarian cancer [7]. *In vitro* studies revealed therapeutic effect of TNF- α antibodies in liver, colorectal, and pancreatic cancer, although the exact mechanism remains unclear [8]. Infliximab, a specific TNF- α inhibitor, displays potential as an antitumor drug [9].

IL-6 is regarded as a key growth factor for both malignant and inflammatory cells. It is associated with cell cycle progression and suppression of apoptosis. Previous studies demonstrated the role of IL-6 in pathogenesis of multiple myeloma [10]. It has been reported that elevated serum concentrations of IL-6 can be found in HNSCC; they can also represent an independent factor of long-term prognosis of LSCC patients [11, 12]. Several authors also showed elevated serum concentrations of IL-6 in LSCC compared to healthy subjects [13, 14].

IL-1 β is strongly connected to inflammatory diseases and cancer. This cytokine has a significant role in the host defense from bacteria, viruses, and fungi [15]. Some recent studies show that epigenetic changes of IL-1 β may represent an important factor in the carcinogenesis [16].

Inflammation due to smoking is one of the proposed mechanisms in cancer. It is interesting to note that the incidence of HNSCC in the Basque region is one of the highest in Europe, while tobacco and alcohol consumption is one of the lowest compared to other regions in Europe [17]. It is clear that carcinogenesis depends on the interaction between environmental factors, such as smoking, and genetic and immune host factors.

When we compared serum cytokine profile of LSCC patients who are active smokers and smoking healthy subjects, we did not observe any difference (Table 2). Surprisingly, according to our results, inflammation is not greater in cancer patients who smoke compared to inflammation in healthy smoking individuals.

Correspondingly, after comparing serum proinflammatory cytokines in control subjects, statistical analysis showed no difference between smokers and non-smokers (Table 2). In contrast to our results, Zeidel et al. [18] found increased production of the pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α in asymptomatic smokers.

More than 60 carcinogens are identified in the cigarette smoke, although the underlying mechanism of smoking

in carcinogenesis is still unclear. [19]. Chronic exposure to tobacco carcinogens leads to mutations of the K-RAS oncogene and the p53 tumor suppressor gene, oxidative damage, deregulated apoptosis, and cell cycle [19]. Epigenetic changes are also considered vital in the metabolism of tobacco carcinogens, thus enlarging the effect of smoking in carcinogenesis.

Statistical analysis on subgroups of LSCC patients who actively smoke and of those who do not, revealed that non-smokers had statistically significant ($p < 0.05$) elevated serum concentrations of TNF- α and IL-1 β compared to smokers (Table 2, Figures 1 and 2). According to our results, cigarette smoking leads to a reduced proinflammatory response in LSCC patients. These observations may suggest that patients with LSCC are more susceptible to bacterial, viral, parasitic, and fungal infections, considering the role of IL-1 β and TNF- α in host defensive mechanisms [6, 18].

Data regarding the effect of tobacco on systemic immune response is inconsistent. Suppression of inflammatory response is in accordance with Shiels et al. [20], who concluded that smoking leads to the suppression of systemic immune marker levels. *In vitro* studies also showed decreased production of IL-1 β , IL-2, IFN- γ , and TNF- α by nicotine [21, 22]. Conversely, other authors showed increment of serum proinflammatory cytokine due to smoking [23, 24].

It is questionable whether inflammation is a sufficient factor to promote carcinogenesis. Chronic inflammation is observed in many other diseases apart from cancer. Chronic inflammation is present in Chronic obstructive pulmonary disease (COPD), while macrophage innate response, pro Th-1 and Th-17 response to bacteria is suppressed [25, 26]. Although the most prevalent, tobacco and inflammation, cannot be considered the only etiological factors in laryngeal carcinogenesis. Several studies have suggested an association between laryngeal cancer and heavy metal exposure, industrial heat, mustard gas, hair dye, nickel, wood dust, rubber, diesel and gasoline fumes, formaldehyde, asbestos, organic solvents, mineral oil, coal dust.

Studies which include subjects' self-reported data on tobacco and alcohol consumption have certain limitations. This is primarily related to the fact that the measures of smoking exposure rely on self-reported data. Khariwala et al. [27] revealed that the carcinogen exposure in HNSCC patients does not correlate with self-reported tobacco use. The possible explanations for such inaccuracies could be that the patient is facing physicians' expectations, fear, or guilt as he is treated for malignancy. Likewise, in healthy subjects, potential shame or embarrassment because of unhealthy habit can occur. The need for a more objective analysis of

tobacco exposure and carcinogen dose is also reflected in the fact that the number of cigarettes per day may not be the accurate measure of exposure. Variability in puffs per cigarette, depth of inhalation, type of cigarette or cigar can significantly influence the actual carcinogen exposure.

Like in our study, most of the published data refer to the serum cytokine levels. It is possible that cytokines serum levels may not represent the adequate tumor-host interaction since it may differ from the concentrations of immune mediators in tumor microcirculation.

CONCLUSION

The results of our study demonstrate the complex relationship between carcinogenesis, inflammation, environmental factors, and host factors. Our results show that smoking leads to significantly decreased ($p < 0.05$) serum levels of TNF- α and IL-1 β in smoking LSCC patients compared to non-smoking patients. This data may suggest that these patients are more susceptible to bacterial, viral, parasitic, and

fungal infections, reflecting an immunosuppressive effect of cigarette smoking in LSCC patients, while we did not perceive this effect of smoking in healthy subjects. Further investigations are needed to elucidate perplexed network of smoking, carcinogenesis, and host immunity.

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All authors conceived and planned the work that led to the paper and interpreted the evidence it presents. All authors participated in data collection and analysis, in writing of the paper, and they all approved the final version.

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Пушење и инфламација код планоцелуларног карцинома ларинкса

Јелена Сотировић¹, Александар Перић¹, Данило Војводић², Ненад Балетић¹, Миланко Милојевић¹, Љубомир Павићевић¹

¹Војномедицинска академија, Клиника за оториноларингологију, Београд, Србија;

²Војномедицинска академија, Институт за медицинска истраживања, Београд, Србија

САЖЕТАК

Увод/Циљ Епидемиолошке студије јасно показују да је пушење цигарета један од најзначајнијих етиолошких фактора у патогенези ларингеалног планоцелуларног карцинома (LSCC). Једно од могућих објашњења дејства дувана на карциногенезу је хронична инфламација. Међутим, подаци из литературе су често опречни у погледу утицаја пушења на системски имунски одговор.

Ова студија је имала за циљ одређивање концентрација проинфламаторних цитокина у серуму [фактор некрозе тумора (TNF)- α , интерлеукин (IL)-6, IL-1 β] код болесника са LSCC и здравих испитаника у односу на пушење цигарета.

Метод У испитивању је учествовало 59 болесника са LSCC и 44 здрава испитаника. Од свих учесника у студији узети су подаци о пушењу цигарета, као и 5 ml периферне венске крви. Проточном цитометријом урађено је израчунавање концентрација цитокина у крви. Статистичком анализом

поређене су концентрације цитокина испитаника у односу на пушење.

Резултати У групи испитаника са LSCC, серумске концентрације цитокина IL-1 β и TNF- α биле су статистички значајно веће ($p < 0,05$) у групи непушача поредећи их са пушачима. Примењени статистички тестови нису показали постојање значајне разлике концентрација испитиваних цитокина у контролној групи у односу на то да ли испитаници пуше. Такође, концентрације испитиваних проинфламаторних цитокина у групи пушача са LSCC нису се разликовале у односу на здраве пушаче.

Закључак Пушење има имunosупресивни ефекат на проинфламаторни одговор код болесника са LSCC. Код здравих пушача нема имunosупресивни ефекат. Такође, нема разлике у системском проинфламаторном одговору између пушача са LSCC и здравих пушача.

Кључне речи: пушење; IL-6; IL-1 β ; TNF- α ; планоцелуларни карцином ларинкса

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effects of early rehabilitation treatment on the functional recovery and quality of life in patients three months after breast cancer surgery

Sanja Tomić¹, Goran Malenković^{1,2}, Nensi Lalić^{1,3}, Marko Bojović³, Slobodan Tomić⁴¹University of Novi Sad, Faculty of Medicine, Department of Nursing, Novi Sad, Serbia;²Oncology Institute of Vojvodina, Sremska Kamenica, Serbia;³Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia;⁴University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia**SUMMARY****Introduction/Objective** Breast cancer surgery is associated with the risk of developing functional constraints that may negatively affect the quality of patients' lives.

The objective of the study was to determine the impact of early postoperative exercises three months after surgery on functional recovery and the quality of life of patients who were operated on.

Methods A group of 149 patients was tested, divided by the type of surgery into two groups. The assessment of the quality of life by the SF-36 questionnaire and functional testing were done three months after surgery; the extent of movement in the shoulder joint and of the limbs was measured as well.**Results** On basic measurements of the quality of life, the average results of SF-36 showed the highest values in the domain of physical functioning, while the lowest value was in the vitality and energy domain. After the realized rehabilitation activities, the results of the SF-36 questionnaire indicated the increase in all domains and components at the significance level of $p = 0.001$, except for the general health domain ($p = 0.04$). Preoperatively, a moderate negative association of mobility and the SF-36 questionnaire component with the overall health parameter was determined, whereby the lower value of the SF-36 questionnaire was followed by a larger deviation in the flexion movements and abduction of the shoulder joint.**Conclusion** The results of our study support the concept of early-initiated rehabilitation interventions and confirm the positive impact on the quality of life of patients operated on for breast cancer in the three-month follow-up period.**Keywords:** breast cancer, surgery; quality of life; SF-36 questionnaire; early rehabilitation**INTRODUCTION**

Breast cancer is one of the most common malignancies that affects both women in the world and in the territory of the Republic of Serbia and of the Autonomous Province of Vojvodina [1].

Despite its great prevalence and the increase in new cases, advances in early detection, therapy and follow-up modalities have made this group of patients one of the largest within the oncological population with a five-year survival period [2, 3].

Breast cancer is classified by the tumor, node, and metastasis (TNM) classification and the medical treatment requires a multidisciplinary approach – surgery, chemotherapy, hormonal, biological (immunotherapy), and most commonly combined treatment. Within medical modalities of breast cancer treatment there is a wide variety of treatments with similar and positive effects, but with differences in regards to their effects on the patient's quality of life (QoL) [4–7]. One of the most important aspects of breast cancer treatment is surgery. Its extent depends on the size and spread of the tumor, its mobility with regards to the underlying chest muscles, skin infiltration and the tumor

breast size ratio. Although all surgical methods are invasive and can lead to soft tissue injury leading to scarring and contributing to the development of contractures of breast muscles and those located around the shoulder joint [4].

Dysfunction of the shoulder joint manifests itself as a decreased/limited movement range of the shoulder joint with decreased muscle strength often followed by pain and fatigue [4–8]. Facts of the available literature show that in most of the patients that underwent surgery there are one or two functional disorders. The limitation of the shoulder joint movement is one of the most common complications [9, 10, 11].

The early rehabilitation program after breast cancer surgery at the Institute for Oncology of Vojvodina in Sremska Kamenica promotes a multidisciplinary approach and all the interventions that we apply to the in- or outpatients are individualized in order to accommodate a new, changed need of our patients who had been operated on. The importance of range of motion exercises (ROM) in the prevention and preservation of shoulder function, including the improvement of synovial drainage and lymph flow by activating physiological

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University of Novi Sad
Faculty of Medicine
Department of Nursing
Hajduk Veljkova 3
21000 Novi Sad, Serbia
sanja.tomic@mf.uns.ac.rs

mechanisms (trans-synovial pump), prompted early rehabilitation to start two days after surgery [12].

Personalized approach to patients is based on the evidence of previous research, whose results prove that individually adjusted exercise programs in patients recovering from breast cancer surgery increase movement range and muscle strength and can significantly improve the function of the shoulder joint without risk of lymphedema [12, 13].

The objective of this study is to estimate the effect of early rehabilitation on the QoL of patients that have undergone breast cancer surgery.

METHODS

Breast cancer patients who started oncology treatment with a surgical procedure at the Clinic in the March–November period of 2015 participated in this prospective, repeated trans-sectional, descriptive study. Participation in this research was on the voluntary basis. The patients were given and have signed an informed consent form. The exclusion criteria were the return of tumor, repeated surgery, use of chemotherapy before surgery, existence of contractures and/or lymphedema on the affected arm.

An early postoperative rehabilitation treatment consisted of active and/or assisted ROM exercises (five to six exercises) with repetition twice a day for 30 minutes under the supervision of a physiotherapist. The average number of days of hospitalization was six. Education on the early signs of secondary lymphoma (self-monitoring), introduction to preventable risk factors for the emergence of functional complications, and recommendations for the hygienic and dietary regime were carried out during the hospitalization.

The evaluation of the functional status included the measurement of both upper extremity movements and lymphedema screening. Lymphedema was determined by measuring the circumference of the affected arm in seven points and also measuring the contra-lateral side. The size of the lymphedema expressed as the ratio between the circumference of the healthy and the affected arm is calculated by the following formula: $[(\text{total diameter of the affected arm} - \text{total diameter of the affected arm}) / \text{total circumference of the healthy arm}] \times 100$.

The evaluation of the ROM of an upper extremity was performed by using a goniometer, and the mobility of the shoulder joint in terms of flexion, extension, abduction; internal and external rotation were also measured.

The measurements were repeated on the last day of hospitalization (basal measurement), and again three months after patient discharge (follow-up). The validity of the functional estimation test was verified by five specialist clinical nurses and physiotherapists.

In order to determine the QoL, we used the Medical Outcomes Study Short Form Health Survey SF-36. It is a theoretically grounded and empirically tested operationalization of two health concepts – physical and mental health and their two manifestations: functioning and wellbeing [14].

The score registered in each domain of the questionnaire is transformed into standard values on a unified scale

that has a theoretical minimum of 0, and a maximum of 100 points. Higher scores pointed to a better QoL.

This way of scoring enabled quantitative comparison of different manifestations of health within the domains that were measured by the questionnaire, and the interpretation of the total value expressed through the total health (TH) parameter and the differentiation of eight domains and two components. Domains of the SF-36 test are as follows: PF – physical functioning; RP – limitations according to physical difficulties; RE – limitations because of emotional difficulties; VT – vitality and energy; MH – emotional well-being; SF – social functioning; BP – pain; GH – general health perception; components of the SF-36 are the following: PCS – physical health; MCS – mental health.

The reliability of the short form of the SF-36 scale was analyzed by determining the Cronbach's alpha coefficient ($\alpha = 0.71\text{--}0.92$).

For statistical analysis, the sample was stratified with regards to the type of the surgical intervention (group 1 – mastectomy; group 2 – breast-conserving surgery). Data analysis estimated the effectiveness of the intervention after three months by using the Student's t-test and Leven test, while the correlation between the functional status, socio-demographic variables and the QoL was presented by using the Spearman's coefficient.

For analyzing the differences in frequency distribution, for attributive variables we used the nonparametric χ^2 test, Cronbach's alpha coefficient – to determine the reliability of the questionnaire in its entirety and its various subscales and components. All statistical data were entered into StatSoft software (Statistica 10.0, StatSoft Inc., Dell, Round Rock, TX, USA); for all inferential statistical analyses, significance was defined as $p \leq 0.05$.

The study protocol was approved by the Ethics Council of the Institute for Oncology of Vojvodina in Sremska Kamenica and by the Ethics Committee of the Faculty of Medicine, University of Novi Sad.

RESULTS

A total of 187 participants were enrolled into the research, and a certain number of patients did not come to the follow-up examination three months after surgery; some of the patients incorrectly filled out the questionnaires and were excluded from the study.

The final sample consisted out of 149 appropriately filled out questionnaires (response of 79.67%). The average age of the surveyed participants was 58 ± 13 years (min = 20; max = 80; median = 60). Mastectomy was performed in 67 patients, who were assigned to group 1, while patients in group 2, totaling 82, had breast-conserving surgery.

The patients were divided into two groups according to the type of surgery and did not show differences with regards to demographic variables (Table 1).

At the base QoL measurement, the average SF-36 scores showed that both groups of patients scored highest in the domain of physical functioning (group 1: 57.46 ± 30.88 vs. group 2: 66.28 ± 25.88).

Table 1. Demographic and clinical characteristics of breast cancer patients

Variables	Total (n = 149) Mean ± SD	Group 1 (n = 67) Mean ± SD	Group 2 (n = 82) Mean ± SD	t/χ ²	p
Age		57.13 ± 13.720	58.34 ± 11.590	0.584*	0.56
Education levels				2.644**	0.61
Grade school	31 (20.3%)	15 (22.4%)	16 (18.5%)		
High school	82 (55.4%)	33 (49.3%)	49 (65%)		
Undergraduate	17 (11.5%)	10 (14.9%)	7 (8.6%)		
Graduate	19 (12.8%)	9 (13.4%)	10 (12.3%)		
Vocation				9.510**	0.14
Manual labourer	46 (16.9%)	23 (36%)	23 (28.4%)		
Office worker	41 (27.7%)	22 (32.8%)	19 (23.5%)		
Housewife	16 (10.8%)	7 (10.4%)	9 (11.1%)		
Retiree	45 (30.4%)	15 (22.4%)	30 (37%)		
Marital status				4.12**	0.39
Married	95 (63.8%)	39 (58.2%)	56 (68.3%)		
Divorced	31 (20.8%)	16 (23.9%)	15 (18.3%)		
Not married	9 (6%)	5 (7.5%)	4 (4.9%)		
Widow	14 (9.4%)	7 (0.4%)	7 (8.5%)		
Hobby				0.001**	0.93
No	105 (70.5%)	47 (70.1%)	58 (70.7%)		
Yes	44 (29.5%)	20 (29.9%)	24 (29.3%)		

*t-test;

χ² testTable 2.** Baseline scores of the SF-36 questionnaire items among study groups

SF-36 domains	Baseline			t-test	
	Total (n = 149) Mean ± SD	Group 1 (n = 67) Mean ± SD	Group 2 (n = 82) Mean ± SD	t	p
PF	62.19 ± 28.54	57.46 ± 30.88	66.28 ± 25.88	-1.86	0.05
RP	46.19 ± 27.72	43.47 ± 28.02	48.39 ± 27.28	-1.08	0.28
RE	56.19 ± 27.39	51.24 ± 26.48	60.16 ± 27.46	-2.0	0.04
VT	39.52 ± 22.82	37.31 ± 21.89	41.23 ± 23.42	-1.04	0.29
MH	60.13 ± 21.62	57.53 ± 22.7	62.37 ± 20.47	-1.36	0.17
SF	52.95 ± 22.93	49.62 ± 23.53	55.64 ± 22.06	-1.6	0.11
BP	55.23 ± 27.58	50.37 ± 26.46	59.35 ± 27.83	-2	0.07
GH	50.23 ± 16.66	49.55 ± 17.6	50.97 ± 16.3	-0.51	0.60
TH	51.62 ± 17.51	48.6 ± 18.41	54.08 ± 16.44	-1.91	0.05
PCS	53.54 ± 18.68	50.21 ± 19.32	56.25 ± 17.79	-1.98	0.04
MCS	49.70 ± 18.16	46.98 ± 19.15	51.59 ± 17.1	-1.65	0.10

Group 1 – mastectomy; Group 2 – breast-conserving surgery; PF – physical functioning; RP – limitations due to physical difficulties; RE – limitations due to emotional difficulties; VT – vitality and energy; MH – emotional well-being; SF – social functioning; BP – pain; GH – general health perception; TH – total health; PCS – physical health; MCS – mental health

The most common drop in scores was in the domains of vitality and energy (group 1: 37.31 ± 21.89 vs. group 2: 41.23 ± 23.42). Significant differences among the groups have been shown in physical functioning, limitation due to emotional difficulties, components of physical abnormalities, and overall health ($p \leq 0.05$) (Table 2).

Postoperative evaluation of the QoL three months after discharge and after performing rehabilitation activities at home pointed to an increased average scores of all components and domains of the SF-36 questionnaire for both groups (Table 3).

Significant differences were expressed in the limitation of emotional difficulties, emotional well-being, social functioning, and mental health components ($p \leq 0.05$).

Table 3. Postoperative scores of the SF-36 questionnaire items among study groups

SF-36 domains	Follow-up			t-test	
	Total (n = 149)	Group 1 (n = 67)	Group 2 (n = 82)	t	p
PF	75.67 ± 21.45	73.25 ± 23.91	77.62 ± 19.16	-1.63	0.06
RP	64.27 ± 21.1	62.59 ± 21.44	65.62 ± 20.72	-1.08	0.28
RE	68.18 ± 22.16	64.80 ± 21.16	70.83 ± 22.61	-2	0.04
VT	57.81 ± 19.16	56.25 ± 18.59	59.22 ± 19.54	-0.94	0.06
MH	62.63 ± 20.18	58.80 ± 20.43	65.48 ± 19.62	-2.03	0.04
SF	70.27 ± 18.35	67.16 ± 18.82	72.71 ± 17.58	-1.85	0.05
BP	76.23 ± 20.46	73.28 ± 20.82	78.68 ± 19.84	-2	0.06
GH	51.79 ± 15.29	51.79 ± 15.06	51.58 ± 15.59	0.08	0.90
TH	65.37 ± 13.64	63.25 ± 14.33	67.07 ± 12.89	-1.7	0.09
PCS	66.99 ± 14.23	65.26 ± 15.1	68.38 ± 13.41	-1.32	0.18
MCS	63.71 ± 14.53	61.20 ± 14.75	65.76 ± 14.11	-1.92	0.05

Group 1 – mastectomy; Group 2 – breast-conserving surgery; PF – physical functioning; RP – limitations due to physical difficulties; RE – limitations due to emotional difficulties; VT – vitality and energy; MH – emotional well-being; SF – social functioning; BP – pain; GH – general health perception; TH – total health; PCS – physical health; MCS – mental health

The evaluation of SF-36 questionnaires using the Student's t-test for repeated measurements examined the differences in domains, the total parameter, and the components for the whole sample. A statistically significant difference existed in all the domains and questionnaire components ($p \leq 0.05$) (Table 4).

The results of functional testing by measuring the circumference of the movement indicated the greatest deviation for the abduction and flexion movements of the shoulder joint in both measurement periods without statistically significant differences among the groups (Table 5). The measurement of the extremities in both groups of patients did not show any deviation either before or after surgery, and the results are not shown.

By calculating correlations, we determined a mild negative connection between the lower score of mental health on the base measurement and the higher deviation in abduction and flexion of the shoulder joint in patients after mastectomy ($\rho = -0.353$, $p = 0.01$ vs. $\rho = -0.368$, $p = 0.02$), as well as in the group of patients with breast-conserving surgery ($\rho = -0.338$, $p = 0.04$ vs. $\rho = -0.409$, $p = 0.02$).

After three months, we did not detect a connection between the QoL and the functional status in group 1, while there was a mild negative connection in group 2, namely the greater the deviation in shoulder joint flexion – the lower the scores in the physical and mental health components

Table 4. Differences in mean values of SF-36 scores between the baseline and follow-up measurements for the complete sample

SF-36 domains	Scoring Mean \pm SD; n = 149			t	p
	Baseline	Follow-up	Difference		
PF	62.19 \pm 28.54	75.67 \pm 21.45	-13.47 \pm 1.11	-12.11	0.001
RP	46.19 \pm 27.72	64.27 \pm 21.1	-18.07 \pm 1.67	-10.78	0.001
RE	56.19 \pm 27.39	68.18 \pm 22.16	-11.96 \pm 1.17	-10.16	0.001
VT	39.52 \pm 22.82	57.81 \pm 19.16	-18.41 \pm 1.22	-15.08	0.001
MH	60.13 \pm 21.62	62.63 \pm 20.18	-2.28 \pm 0.84	-2.68	0.001
SF	52.95 \pm 22.93	70.27 \pm 18.35	-17.28 \pm 1.22	-14.12	0.001
BP	55.23 \pm 27.58	76.23 \pm 20.46	-20.93 \pm 1.2	-17.36	0.001
GH	50.23 \pm 16.66	51.79 \pm 15.29	-1.34 \pm 0.66	-2.02	0.04
TH	51.58 \pm 17.56	65.37 \pm 14.34	-13.78 \pm 0.69	-19.77	0.001
PCS	53.46 \pm 18.72	66.99 \pm 14.22	-13.52 \pm 0.75	-17.82	0.001
MCS	49.7 \pm 18.21	63.74 \pm 14.57	-14.01 \pm 0.74	-18.82	0.001

Group 1 – mastectomy; Group 2 – breast-conserving surgery; PF – physical functioning; RP – limitations due to physical difficulties; RE – limitations due to emotional difficulties; VT – vitality and energy; MH – emotional well-being; SF – social functioning; BP – pain; GH – general health perception; TH – total health; PCS – physical health; MCS – mental health

Table 5. Descriptive indicators of average movement range grouped by the type of surgery

Type of movement	Baseline		Follow-up	
	Group 1 (n = 67) Mean \pm SD	Group 2 (n = 82) Mean \pm SD	Group 1 (n = 67) Mean \pm SD	Group 2 (n = 82) Mean \pm SD
Abduction	118.28 \pm 8.41	119.45 \pm 8.18	158.28 \pm 8.46	159.45 \pm 6.18
Flexion	118.43 \pm 8.78	119.51 \pm 8.26	158.43 \pm 8.88	159.51 \pm 6.26
Extension	25.4 \pm 2.45	25.7 \pm 1.91	39.4 \pm 2.54	39.7 \pm 1.81
Internal rotation	49.25 \pm 3.16	49.63 \pm 1.88	69.25 \pm 3.04	69.63 \pm 1.88
External rotation	69.18 \pm 3.76	69.33 \pm 2.85	79.18 \pm 3.67	79.33 \pm 2.65

Group 1 – mastectomy; Group 2 – breast-conserving surgery

Table 6. Correlation of the quality of life (total score of SF-36 components) and movement range in the shoulder joint

Type of surgery	Type of movement		Components of SF-36					
			Baseline			Follow-up		
			PCS	MCS	TH	PCS	MCS	TH
Mastectomy	Abduction	ρ	-0.17	-0.35	-0.26	-0.22	-0.26	-0.25
		p	0.30	0.03	0.12	0.18	0.12	0.14
	Flexion	ρ	-0.22	-0.36	-0.30	-0.27	-0.26	-0.28
		p	0.18	0.02	0.07	0.10	0.11	0.10
Breast-conserving surgery	Abduction	ρ	-0.25	-0.33	-0.27	-0.28	-0.26	-0.26
		p	0.12	0.04	0.10	0.09	0.10	0.12
	Flexion	ρ	-0.26	-0.40	-0.30	-0.33	-0.32	-0.33
		p	0.10	0.01	0.06	0.04	0.05	0.04

ρ – Spearman coefficient; PCS – physical health; MCS – mental health; TH – total health; $p \leq 0.05$

and the TH of the SF-36 questionnaire ($\rho = -0.333$, $p = 0.04$; $\rho = -0.324$, $p = 0.05$; $\rho = -0.323$, $p = 0.04$) (Table 6).

DISCUSSION

A heterogeneous rehabilitation approach with specific rehabilitation interventions and different methodological approaches are described in numerous studies [5–10, 12, 13]. Most authors reported their positive influence on the QoL of those suffering from and being treated for breast cancer [15–24].

The advantages and disadvantages of rehabilitation in different times from the moment of diagnosing the disease, applying medical treatment, and during recovery period still cause confusion. Most authors have determined that active and/or assisted ROM started from one to three days after surgery compared to ROM started four days after surgery have more positive effects on shoulder flexion and abduction. The benefits of early-started exercises (24–72 hours after surgery) without increased risk from seroma and difficulties in treatment complications like postoperative pain and lymphedema are well documented [3, 6, 8, 10, 12]. The reason why we chose the early-start intervention program was the fact that ROM is a safe, efficient, and feasible intervention for breast cancer surgery patients which includes a reduction of pain, fatigue, and depression [3, 12, 15–18, 21, 22].

In our study by assessing the QoL at base point we detected distinctly low levels of vitality and energy. A total of 105 (70.5%) patients reported that they were unsettled throughout the last four weeks and more than 50% of them were discouraged and depressed. Such data did not differ significantly depending on the type of planned surgical intervention. Strong emotional reactions such as fear, uneasiness, sadness, and uncertainty with regards to possible outcomes have been described in other studies [5–8].

By analyzing the responses within the limitation domain according to physical difficulties, we noticed that more than 50% of the patients had avoided or had not realized their usual activities mostly related to housework (ironing, vacuuming, meal preparation, etc.) out of fear of potential postoperative complications. Consequently, patients who displayed such behavior reported more limitations regarding the type of job and activity and spent less time working.

In our study, effects of the early rehabilitation program three months after surgery point to an increase in average summation scores in all domains and components in both patient groups. These results are also supported by studies done in Denmark, Poland, and Spain [2, 17, 19, 20, 25].

The greatest difference (-20.93 ± 1.2) in favor of the repeated measurement was

detected in the domain of pain, without any difference according to the type of surgical procedure. In comparison with the results of our study, many other papers point out that after fatigue, pain is the most commonly reported symptom, presented in about 27–79% of women in the first months after surgery [3–11]. It would be expected that prevalence rate has to decrease with the process of healing, but a systemic review of about 30 studies undertaken by Wang et al. [26] shows that 12–82% of women report pain even one year after surgery.

High scores in the BP domain three months after surgery in our study pointed to the fact that both patient groups three months after surgery have had fewer limitations induced by body pain. Such results of our research can be explained by regular post-surgical recovery and the effects of rehabilitation. Among the patients from our study there were no early or late post-operative complications. Standard personalized physiotherapeutic approach in guiding and controlling pain after a surgical intervention of breast cancer encompasses a spectrum of exercises, myofascial stretching, non-pharmacological methods and educating patients so that they can identify positions and activities that could relieve pain. The personalized approach makes sure that planned therapeutic exercises are carried out up to the individually determined pain and discomfort limits. On the repeated measurement, the patients reported that daily exercises supervised by physiotherapists and nurses helped them eliminate fear and increase knowledge regarding the healing process and allow them the use of the affected arm at home. Such accounts of our patients support the findings of other authors who claim that appropriate pain guidance in the early stages of breast cancer treatment is necessary in the prevention of the long-term-related pain invalidity [3, 4, 17, 21, 22].

After surgery, a significant increase has been reported in the domains of emotional difficulties, emotional well-being, social functioning, and mental health components in both groups.

Significant differences regarding the type of surgery indicate that the patients from group 1 were less depressed and/or discouraged than those in group 2 ($\chi^2 = 10.56$; $df = 2$; $p = 0.03$). They indicated that due to the physical or mental problems they neglected their usual social activities with family and friends ($\chi^2 = 8.50$; $df = 2$; $p = 0.03$).

Unlike ours, the results of the study by M. Kamińska et al. [27] indicate that the level of depression and anxiety is more pronounced in the patient group after mastectomy.

Before the admission, all the patients from our study received recommendations for continuing the exercise

program in home conditions, with education aimed at preventing possible complications. We cannot say with certainty that all the patients adhered to the given recommendations when exercising at home, but the results of the functional assessment of the mobility of the shoulder joint indicated that they did. However, shoulder joint flexion and abduction of the affected arm showed the greatest deviation from the normal motion range during the first three months, which matches the results of other researches [4, 6, 8, 13, 22, 25]. Additionally, the patients achieved high scores in the domain of physical functioning. Reported discrepancies in the motility of the shoulder joint of the affected arm, compared to the other one, do not have a negative effect on physical functioning and independence in daily life activities.

Furthermore, our research shows that there is a mild negative connection between the MCS component and shoulder motility in the affected arm in both groups of patients during base measurement. We did not find any connection between the QoL and functional status in group 1 after three months. In group 2 there was a moderate negative connection. As the patients had higher deviations in the flexion movement of the shoulder joint, lower scores on PCS and MCS components and TH ensued ($\rho = -0.333$, $p = 0.04$; $\rho = -0.324$, $p = 0.05$; $\rho = -0.323$, $p = 0.04$, respectively).

The influence of social and demographic variables of the respondents on the QoL in our study manifested only in the case of age and existence of a hobby. Namely, as the age of the patients increases and if they had a hobby, the limitations caused by emotional difficulties decreased ($\rho = -0.311$, $p = 0.001$; $t = 4.47$; $p = 0.001$) regardless to the type of surgery.

Regarding TH and physical functioning, the QoL was similar between the women in the early post-operative period after mastectomy and those who underwent breast-conserving surgery.

CONCLUSION

Early rehabilitation contributes to the functional recovery of the affected arm while promoting independence in daily life activities and increases the QoL. The findings of our study have shown that the early rehabilitation program did not influence the risk and incidence of early and/or late complications caused by breast cancer surgery.

Conflict of interest: None declared.

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Ефекти раног рехабилитационог третмана на функционални опоравак и квалитет живота болесника три месеца после операције карцинома дојке

Сања Томић¹, Горан Маленковић^{1,2}, Ненси Лалић^{1,3}, Марко Бојовић³, Слободан Томић⁴

¹Универзитет у Новом Саду, Медицински факултет, Катедра за здравствену негу, Нови Сад, Србија;

²Институт за онкологију Војводине, Сремска Каменица, Србија;

³Институт за плућне болести Војводине, Сремска Каменица, Србија;

⁴Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Хируршке интервенције карцинома дојке повезане су са ризиком развоја функционалних ограничења која могу негативно утицати на квалитет живота оперисаних. Циљ студије био је да се утврди утицај раног рехабилитационог третмана на функционални опоравак и квалитет живота оперисаних болесника три месеца после операције карцинома дојке.

Метод Испитивану групу чинило је 149 болесника, подељених према врсти хируршке интервенције у две групе. Процена квалитета живота извршена је упитником SF-36, а функционалним тестирањем мерен је обим покрета у раменом зглобу и обим екстремитета пре и три месеца после операције.

Резултати На базном мерењу квалитета живота, просечни резултати упитника SF-36 показали су највеће вредности

у домену физичког функционисања, а најнижу вредност имао је домен виталности и енергије. После реализованих рехабилитационих активности резултати упитника SF-36 указују на пораст свих домена и компонената на нивоу значајности од $p = 0,001$, осим домена општег здравља ($p = 0,04$). Преоперативно је утврђена умерена негативна повезаност покретљивости и компонената упитника SF-36 са параметром укупног здравља, при чему ниже вредности упитника SF-36 прати веће одступање у покретима флексије и абдукције раменог зглоба.

Закључак Резултати наше студије подржавају концепт рано започетих рехабилитационих интервенција и потврђују њихов позитиван утицај на квалитет живота оперисаних због карцинома дојке у тромесечном периоду праћења.

Кључне речи: карцином дојке, хирургија; квалитет живота; упитник SF-36; рана рехабилитација

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Profile of motor abilities of children with cerebral palsy as a predictor of their functional independence in self-care and mobility

Milena Milićević

Institute of Criminological and Sociological Research, Belgrade, Serbia

**SUMMARY**

Introduction/Objective Limitations of mobility and motor deficits are identified as predominant in the clinical picture of cerebral palsy.

This research aimed to describe the profile of motor abilities of children with cerebral palsy, which included gross motor, manual, and bimanual fine motor functions, and to determine the extent to which their functional independence in self-care and mobility was influenced by the profile of their motor abilities.

Methods A convenience sample of 117 participants with cerebral palsy (56.4% males), aged 7–18 years ($M = 13.2$, $SD = 3.4$), was included. The Gross Motor Function Classification System – Expanded and Revised, Manual Ability Classification System, Bimanual Fine Motor Function and the Functional Independence Measure – Version for Children, were used. Data was analyzed by descriptive statistics and hierarchical multiple regression.

Results More than a half of sample exhibited different levels of gross motor, manual, and bimanual function. Lower functional independence in self-care and mobility was associated with higher functional limitations. Manual abilities were the strongest predictor of functional independence in self-care ($\beta = -0.63$, $p < 0.001$), while gross motor functions were the strongest predictor in the mobility domain ($\beta = -0.65$, $p < 0.001$).

Conclusion Improvement of gross motor and manual abilities of children with cerebral palsy is confirmed as one of the basic preconditions for achieving a greater independence and for minimizing or eliminating a need for assistance in mobility and in everyday self-care activities.

Keywords: cerebral palsy; functional performance; mobility; self-care; motor functions

INTRODUCTION

Motor impairments of varying severity caused by a brain lesion in the early development are dominant in the clinical picture of cerebral palsy (CP) [1]. It is the most common cause of severe physical childhood disability, considered as a physical impairment that affects motor development. The basis of this heterogeneous state is chronic, non-progressive motor disorder, visible through muscular weakness, limited range of motion, spasticity, pathological reflexes, and contractures. Associated and accompanying disorders are frequent, including visual and/or hearing impairment, intellectual disability, epilepsy, speech and behavioral disorders, and secondary musculoskeletal problems [2, 3].

In the daily activities of persons with CP, a number of functional limitations of different severity restrict or even unable their active participation, and participation in society [4]. Depending on the severity of limitations, among other things, children experience difficulties in performing daily and self-care activities [5]. The aforementioned associated and accompanying disorders in the clinical picture of CP have an additional or aggravating effect on the developmental capacity of the child to learn

and perform everyday tasks. Consequently, the improvement of functional abilities and the gradual increase of independence in activities of everyday life is undoubtedly one of the key goals of their rehabilitation [6, 7].

The diversity of clinical characteristics makes each case of CP a unique one, constantly posing new challenges in everyday clinical work. An adequate assessment of functional abilities, with an understanding of the importance and impact that these abilities, taken together or individually, have on the everyday life of children from this population, represents the first step in planning the provision of appropriate service support during childhood and in the period of transition from adolescence to adulthood.

One of the frequently asked research questions is related to the relationship between motor abilities and functional status of children with CP. The characteristics of mobility and self-care, including the independence level, are usually examined only in relation to gross motor abilities or in relation to gross motor and fine manual abilities [5, 8–12]. Besides, the effects of different types of treatment were examined and the factors influencing the development of functional independence in children with CP identified [6, 7, 13, 14]. In other words,

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Correspondence to:

Milena MILIĆEVIĆ
Institute of Criminological and
Sociological Research
Gračanička 18
11000 Belgrade, Serbia
mileninaadresa@gmail.com

previous empirical research did not take into account the overall profile of motor abilities of children with CP that, in addition to both gross motor function and manual abilities, includes bimanual fine motor function. Therefore, this research was conducted with the twofold aim: firstly, to describe the profile of motor abilities of children with CP aged 7–18 years and, secondly, to examine its impact on the level of their functional independence in self-care and mobility. Broadly speaking, the results could be useful in counseling work with families in a clinical context, in giving a prognosis, as well as for appropriate planning and evaluation of interventions.

METHODS

A convenience sample of 117 participants with CP, 66 (56.4%) boys and 51 (43.6%) girls, was included. The average age of participants was 13 years and three months (SD = 3 years 4 months). The dominant clinical form of CP was spastic, diagnosed in almost two-thirds of the sample, specifically in 77 (65.8%) participants. The most frequent spastic CP was quadriplegia, found in 33 (28.2%) participants. Spastic diplegia was diagnosed in 27 (23.1%), hemiplegia in 17 (14.5%), while the mixed form was noted in 20 (17.1%) participants. Other clinical forms were approximately the same in percentage; ataxic CP was found in eight (6.8%), and dyskinetic/athetoid CP in 12 (10.3%) participants.

The research was conducted in cooperation with health, educational and social welfare institutions, and associations or societies of persons with CP from June 2014 to April 2015 on the territory of 32 municipalities of the Republic of Serbia. The general inclusion criteria were as follows: children of both sexes, aged 7–18 years, with CP diagnosed according to the tenth revision of the International Statistical Classification of Diseases and Related Health Problems – ICD-10 [15]. After the informed signed consent was obtained, the data were collected from the available personal medical, educational, or psychological records. The study was approved by the Professional Ethics Boards of The University of Belgrade (No. 61206-2385/2-14).

The profile of motor abilities of each participant contained the data on gross motor, manual, and bimanual fine motor functions, with added information about the type of CP. The functional independence level is described as a consistent and usual performance of an activity, while the level of independence is defined according to the level of assistance that children need in order to perform the tasks of everyday life [16].

The Gross Motor Function Classification System (GMFCS) and The Gross Motor Function Classification System – Expanded and Revised (GMFCS-E&R) determine the level that best represents the child's current gross motor abilities and limitations, based on the assessment of self-initiated movements, meaningful in everyday life, with a special emphasis on sitting, transfer, and mobility [17]. We followed the child's usual performance, and not what is known that it can do best (capability), as well as the impact

of environmental (physical, social, attitudes) and personal factors (motivation, interests, preferences).

The Manual Ability Classification System (MACS) describes how the child uses its hands to handle objects in the activities of daily life [18]. MACS is designed to evaluate the child's self-initiated ability to handle age-appropriate objects, and the need for assistance or adaptation to accomplish everyday life tasks. The assessment is based on a typical performance, without considering the functional differences between the hands, the functioning of each hand separately or explaining the causes of impairment of manual abilities.

The Bimanual Fine Motor Function (BFMF) classifies bimanual fine motor functions based on the child's ability to catch, hold, and handle objects in each hand separately [4]. The possible asymmetry of the upper extremity functions is considered, but the dominant lateralization is not taken into account.

In contemporary disability studies, GMFCS, MACS, and BFMF are considered the leading classifications of mobility, fine motor abilities, and the level of actual use of the upper extremities. Numerous studies have confirmed the reliability and the overall stability of these instruments, as well as their discriminatory, constructive, and predictive validity [4, 18–23]. They are five-level ordinal scales with a higher level indicating a greater functional limitation. MACS and BFMF levels are designed to match GMFCS levels. Taken together, they provide useful information that completes the CP clinical picture [19].

The level of functional independence is assessed by the Functional Independence Measure (FIM), version for children (WeeFIM) [16, 24]. This standardized pediatric instrument for children with acquired or congenital impairments or developmental delays is designed to measure the influence of development strengths and difficulties on the independence at home, school, and in the community, with the aim of identifying priorities in the improvement of functional results and providing support to the family. Three main domains (self-care, mobility, and cognition) are covered with 18 items. The scores are given on a seven-point ordinal scale ranging from 1 – Total Assistance to 7 – Complete Independence. The total maximum score is 126 (subtotals for self-care: 8–56, mobility and cognition: 5–35). Each score is obtained by summing points of each task, with a higher score indicating a higher independence level of participants. Psychometric characteristics are reported earlier [16, 24, 25].

Descriptive statistics and χ^2 test were used to characterize the sample and the outcomes. In order to examine whether the profile of motor abilities, as a set of variables, can predict a significant percentage of variance in self-care and mobility domains, after statistically removing the possible influence of control variables, hierarchical multiple regressions were applied. Taking into account the higher percentage of male participants (56%) and a wide age range (7–18 years), sex and age in months were selected as the control variables. All analyses were performed in SPSS, Version 23.0. (IBM Corp., Armonk, NY, USA) with the significance level set at $p = 0.05$.

RESULTS

Mild gross motor limitations (GMFCS I–II) are predominant in participants with spastic hemiplegia (70.6%) and ataxia (50%). Severe gross motor limitations (GMFCS IV–V) are more frequent in participants with spastic quadriplegia (84.9%) and dyskinetic/athetoid CP (66.6%) than in other clinical forms (Figure 1). These frequencies were significantly different, $\chi^2(20) = 68.15$, $p < 0.001$.

More than a half of our sample exhibited different levels of function measured by GMFCS, MACS and BFMF (Figure 2). For example, the group classified in BFMF level

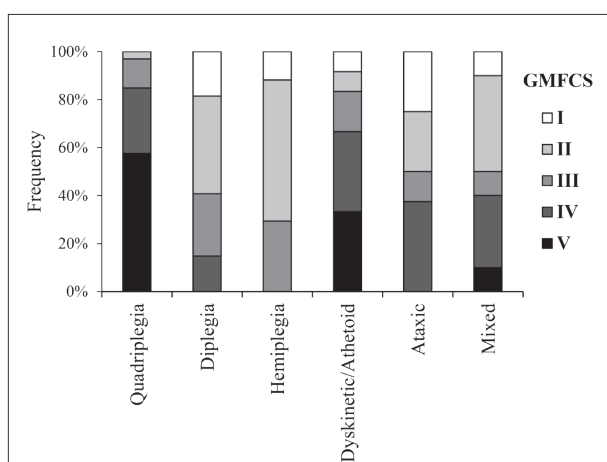


Figure 1. Distribution of gross motor function (GMFCS) in relation to cerebral palsy type

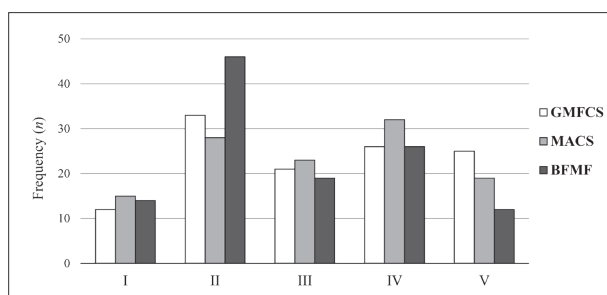


Figure 2. Profile of motor abilities of participants with cerebral palsy; GMFCS – gross motor functions; MACS – manual motor functions; BFMF – bimanual fine motor functions

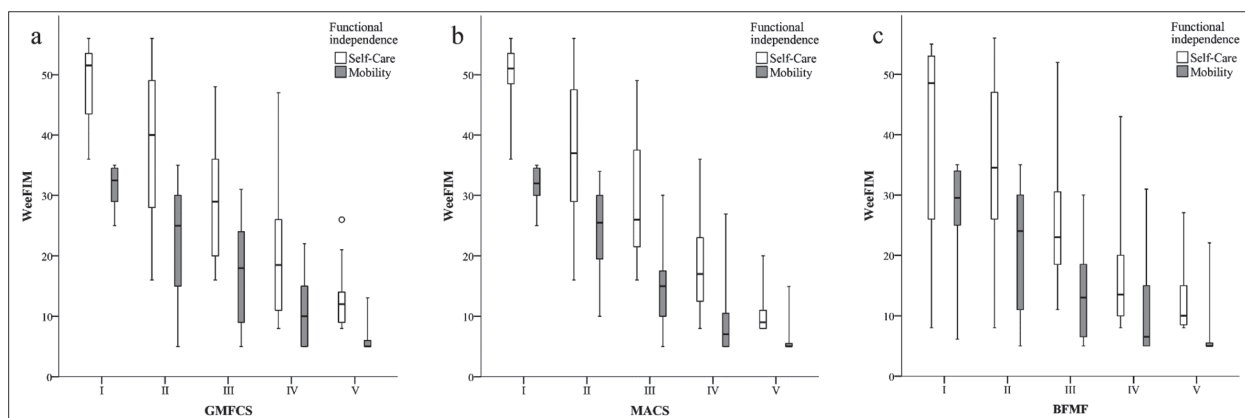


Figure 3. The level of functional independence of participants with cerebral palsy in self-care and mobility domains in relation to the level of: a) gross motor functions, b) manual motor functions and c) bimanual fine motor functions; GMFCS – gross motor functions; MACS – manual motor functions; BFMF – bimanual fine motor functions

II included participants at all five different GMFCS levels, while the group classified in MACS level V included only participants who performed at the GMFCS levels IV–V. Overlapping of GMFCS and MACS levels are found in 54 (46.2%) participants, and in 61 (52.1%) when considering GMFCS and BFMF levels.

Lower levels of functional independence in both self-care and mobility domains are noted in participants with higher functional limitations measured by GMFCS, MACS, and BFMF (Figure 3).

As a control strategy, sex and age were entered in the first block (Step 1) of hierarchical multiple regression (Table 1). The overall model explained only 1% of the total variance in the self-care domain, without reaching the statistical significance. After the variables of the profile of motor abilities were entered (Step 2), the overall model explained 76% of the total variance. The profile of motor abilities, as a whole, explained additional 75% of variance, after controlling sex and age parameters. However, only two variables made a unique contribution, with the MACS level having a higher standardized coefficient ($\beta = -0.63$, $p < 0.001$) than the GMFCS level ($\beta = -0.30$, $p < 0.01$). With each increasing of limitations in manual abilities (MACS), there is a decrease in the level of functional independence in self-care by 7.41 points, or by 3.46 points when it comes to limitations in gross motor function (GMFCS). Neither sex, age, nor BFMF level made a unique contribution as predictors.

Only partially comparable results were obtained when predicting of functional independence in the mobility domain was examined (Table 1). Sex and age together explained only 4% of the total variance of mobility, without statistical significance (Step 1). When the profile of motor abilities was entered (Step 2), the overall model explained 77% of the total variance. Accordingly, the profile of motor abilities, as a whole, explained an additional 73%, after controlling for sex and age. Similar to the previous analysis, only two motor abilities made a unique contribution, with the GMFCS level having a higher standardized coefficient ($\beta = -0.65$, $p < 0.001$) than the MACS level ($\beta = -0.35$,

Table 1. Prediction of the functional independence of participants with cerebral palsy in self-care and mobility based on the profile of motor abilities – results of hierarchical multiple regression

Predictor/Model		Step 1				Step 2			
		B	SE (B)	β	t	B	SE (B)	β	t
Self-care	Sex ^a	2.84	2.92	0.09	0.97	1.55	1.46	0.05	1.07
	Age ^a	0.01	0.04	0.02	0.20	0.03	0.02	0.08	1.58
	GMFCS					-3.46	1.04	-0.30	-3.34*
	MACS					-7.41	0.83	-0.63	-8.94**
	BFMF					0.25	0.97	0.02	0.26
	R ²	0.01				0.76			
	Adj.R ²	0.00				0.75			
	ΔR^2	0.01				0.75**			
	F (df1, df2)	0.47 (2, 114)				70.19 (5, 111)**			
Mobility	Sex ^a	2.86	2.01	0.13	1.42	2	1.00	0.09	2
	Age ^a	-0.03	0.02	-0.11	-1.13	-0.01	0.01	-0.05	-1.11
	GMFCS					-5.28	0.57	-0.65	-9.28**
	MACS					-2.75	0.71	-0.35	-3.86**
	BFMF					0.91	0.66	0.10	1.37
	R ²	0.04				0.77			
	Adj.R ²	0.02				0.76			
	ΔR^2	0.04				0.73**			
	F (df1, df2)	2.15 (2, 114)				73.86 (5, 111)**			

B – unstandardized beta coefficient; β – standardized coefficient; R² – coefficient of determination; Adj.R² – adjusted coefficient of determination;

ΔR^2 – multiple correlation coefficient change;

^acontrol variables;

*p < 0.01;

**p < 0.001

p < 0.001). Therefore, increasing of the gross motor limitations (GMFCS) causes a decline of the functional independence in mobility by 5.28 points. When considering the unique influence of manual abilities (MACS), in this model, with their reducing, there is a decline of the functional independence in mobility by 2.75 points.

DISCUSSION

The research results confirmed a strong association between the functional independence in self-care and mobility and the motor abilities of participants with CP. As functional limitations in the domains of gross motor, manual and bimanual fine functions increase, the functional independence in self-care and mobility decrease, and *vice versa*. In the case of self-care, hierarchical multiple regression showed that manual abilities of participants with CP, measured by the MACS, explained the most of its variance. Contrarily, most of the mobility variance of was explained by the gross motor function, measured by the GMFCS.

The variations in the dimension of mobility largely explained the relationship between GMFCS and level of disability [26]. Specifically, the severity of present gross motor disability was singled out as a strong indicator of the level of disability in the domains of physical independence, mobility, occupation, and social integration [26]. Later, the secondary analysis confirmed that GMFCS level was the most significant predictor of restriction in mobility, with BFMF and IQ as significantly contributing variables [4]. Intellectual level often referred to as the educational level or cognitive functional level is one of the personal features listed as possible factors determining the func-

tional independence of persons with CP [14]. This may be caused by the association between the number of additional neuroimpairments in the individual child, including the cognitive impairments, and CP type and GMFCS level, because of major brain malformations and/or severe compromise at birth [4, 27]. Moreover, a decrease in the need for assistance in everyday activities is associated with the improvement of gross motor functions after a five-month functional goal-directed therapy (physical therapy with the emphasis on exercising of functional activities) [7]. After all, the need for caregiver assistance was strongly related to GMFCS level and accomplishment of activities [10].

Next, functional difficulties in different domains of everyday functioning are more common in children with CP who are classified in GMFC IV–V. In one study, it was shown that daily living skills were statistically significantly different among school-aged children with CP compared to their gross motor functions [11]. Functional limitations in daily living skills were more likely for children in GMFCS IV–V (wheelchair needs) in comparison to children in GMFCS I (walking) and GMFCS II–III (restricted ambulation).

Comparable results were obtained on a sample of younger children with CP aged between two years and seven and a half years [10]. As the strongest overall predictor, gross motor limitations, classified according to the GMFCS, explained 84% of the variance in mobility, or 82% and 63% of the variance in caregiver assistance, and modification needed. Mobility was also a significant contributory factor in self-care and some aspects of social functioning [10]. Furthermore, our findings are close to those reported in other studies when analyzing the relationship between GMFCS and MACS levels and mobility

and self-care activities of children with CP [5, 9]. Generally, limitations in self-care increased progressively with MACS level [5].

After considering confirmed overlapping of GMFCS and MACS levels in almost half of our sample, it can be concluded that GMFCS and MACS classifications are mutually complementary to each other in determining of the functional limitations. In particular, data on the overlapping of GMFCS and MACS levels in 46% of our sample is in accordance with the previous empirical findings according to which the complete agreement is seen in 49% of participants [18]. An absolute agreement of 39.2% was found on a sample of 222 participants aged 2–17 years [28]. Next, an agreement of 77% was calculated between MACS and BFMF levels [23].

In other words, when considering functional and motor profile of a person with CP, the data on GMFCS and MACS levels are mutually complementary, and are not to be used as an equivalent in the clinical practice. This outcome of the analysis is consistent with previous theoretical and empirical findings; GMFCS and MACS are two distinct classification systems that are constructed on different conceptual bases. Therefore, the influence that the gross motor functioning has on manual function and their interrelation are possible explanations of our findings [29]. Namely, while GMFCS is simpler and more focused on basic motor patterns (head control, sitting, ambulation, transfers), MACS includes a complex motor-cognitive dimension of manual abilities because the functions of upper extremities are closely related to cognitive abilities and voluntary motor control [17, 18, 19]. Specifically, one of the key components of performing self-care activities is manual skills [10]. Additionally, the relationship between the MACS scale and the BFMF scale can be described similarly, bearing in mind that these two systems describe close, but different aspects of the function of the upper extremities. More precisely, the MACS is more focused on the evaluation of activity, while the BFMF is based on the assessment of the level of impairment and the level of capacity [4].

It is necessary to have a closer look at the finding that there was no statistical significance for BFMF as a predictor. Individually, changes in BFMF levels are at least reflecting on the level of functional independence in both mobility and self-care domain, as well. This can be explained by the findings of a study conducted on a sample of 185 children with spastic CP in which the association of GMFCS and MACS was confirmed, with the highest correlation coefficient in the subgroup of children with quadriplegia and the lowest in the subgroup of children with hemiplegia [12]. Moreover, this finding is a reflection of the consequences that impairment of the muscles of trunk, upper and lower extremities, as well as the greater presence of cognitive problems have on the clinical picture of quadriplegia. As a result, there is an association of gross motor abilities of the child and his ability to handle objects in daily life. Contrarily, the assumed asymmetry in the clinical picture of hemiplegia leaves the possibility that the child can handle objects by using unaffected or less affected hand [12]. The need to make a clearer differentiation between the capacity

of fine motor abilities and normal manual performance in children with unilateral spastic CP and the clinical significance for treatment planning and evaluation of outcomes can be read in previous reports [23].

Besides, when compared to the terminology and definitions given in the International Classification of Functioning, Disability and Health, it can be seen that the BFMF classification relies more on the determination of capability as “executing tasks in a standard environment” (what a child can do in a controlled environment) [30]. However, the MACS classification is based on the assessment of performance as “executing tasks in the current environment (what a child really does in everyday settings)” [8]. Further, since the BFMF is more based on the assessment of the symmetry of the upper extremities function, from the aspect of the present impairment, it can be concluded that its predictive power is limited when determining functional independence in self-care and movement. Applied together, these classifications can provide complementary information on the difference between the fine motor capacities (measured by the BFMF) and the actual use of the upper extremities in daily life (measured by the MACS). By assessing those motor functions that are meaningful in everyday life based on the usual achievements in the home, school and community, the functional independence of a child with CP in the activities of daily life can be determined to a considerable extent, regardless of the lateralization of motor impairment.

CONCLUSION

Based on the presented results, gross motor abilities of children with CP determine largely the level of their functional independence in mobility. At the same time, the level of functional independence in self-care is largely determined by manual abilities. Therefore, it can be concluded that the improvement of gross motor and manual abilities is one of the basic preconditions for achieving greater independence for children from this population, that is, for minimizing or eliminating the need for assistance in mobility and in everyday self-care activities. Developing the independence of children with CP largely relies on increasing or improving the level of development of gross motor and manual abilities. Finally, although the symmetry of the function of upper extremities does not determine statistically the level of functional independence in the examined domains, the data on developmental level of fine bimanual functions complement the data that make the profile of motor abilities of children with CP.

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Профил моторичких способности деце са церебралном парализом као предиктор њихове функционалне независности у самозбрињавању и мобилности

Милена Милићевић

Институт за криминолошка и социолошка истраживања, Београд, Србија

САЖЕТАК

Увод/Циљ Ограничења мобилности и моторички недостаци су идентификовани као преовлађујући у клиничкој слици церебралне парализе.

Циљ истраживања је да се опише профил моторичких способности деце са церебралном парализом, који укључује грубе моторичке, мануелне и бимануелне fine моторичке функције, и да се утврди у којој мери је њихова функционална независност у самозбрињавању и мобилности под утицајем профила моторичких способности.

Метод Пригодан узорак се састојао од 117 испитаника са церебралном парализом (56,4% мушког пола), узраста 7–18 година ($M = 13,23$, $SD = 3,36$). Примењени су Систем класификације грубих моторичких функција – проширена и измењена верзија, Систем класификације мануелних способности, Бимануелне fine моторичке функције и Тест функционалне независности за децу. Подаци су анализирани дескриптивном статистиком и хијерархијском вишеструком регресијом.

Резултати Код више од половине узорка утврђени су различити нивои грубих моторичких, мануелних и бимануелних функција. Нижа функционална независност у самозбрињавању и мобилности је повезана са већим функционалним ограничењима. Мануелне способности су најјачи предиктори функционалне независности у самозбрињавању ($\beta = -0,63$, $p < 0,001$), а грубе моторичке функције најјачи предиктори у домену мобилности ($\beta = -0,65$, $p < 0,001$).

Закључак Побољшање грубих моторичких и мануелних способности деце са церебралном парализом је потврђено као један од основних предуслова за постизање веће независности и за минимизирање или елиминисање потребе за асистенцијом у мобилности и свакодневним активностима самозбрињавања.

Кључне речи: церебрална парализа; функционално извршавање; мобилност; самозбрињавање; моторичке функције



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Knowledge of and attitudes to major depressive disorder and its treatment in a sample of the general population in Serbia

Ivona Milačić-Vidojević¹, Marija Čolić¹, Branka Drašković²

¹University of Belgrade, Faculty for Special Education and Rehabilitation, Belgrade, Serbia;

²Metropolitan University, FEFA, Belgrade, Serbia

SUMMARY

Introduction/Objective The objective of this paper was to examine the mental health literacy of the general population in Serbia and their attitudes towards persons with a mental illness.

Methods This was a cross-sectional study with structured interview using the vignette of a person with major depressive disorder (MDD). The attitudes towards people with mental illness were assessed by the Department of Health Attitudes to Mental Illness Questionnaire. A convenient sample consisted of 504 participants.

Results A total of 72% of the sample recognized the presence of some sort of mental health problem, of which 40.9% correctly labeled the symptoms as MDD. The majority of participants believed that MDD was caused more by stress than by biological factors. A psychologist, a close friend, and a psychiatrist were often rated as helpful for the person described by the vignette. Vitamins and healing herbs were rated as the most helpful remedy. Antidepressants were considered both helpful and harmful. The attitudes towards people with mental illness were moderately positive.

Conclusion Mental health literacy in Serbia is moderate. Risk factors for negative attitudes included older age and lower education.

Keywords: mental health literacy; major depressive disorder; attitudes towards people with mental illness

INTRODUCTION

According to the World Health Organization, major depressive disorder (MDD) will become the second largest cause of disability in the world and the leading cause in the developed countries by 2020 [1]. Based on research conducted in Serbia in 2000, MDD was ranked as the fourth most prevalent disorder among 18 health disorders [2]. Despite the relatively high prevalence of mental disorders, many affected people do not receive any sort of professional help [3]. One of the reasons for the lack of appropriate treatments is the absence of help-seeking behavior. One study suggested that early help-seeking for mental health problems promotes early intervention and positive long-term outcomes [4]. There are multiple factors related to the poor help-seeking behavior and one is low mental health literacy [5].

Mental health literacy is a construct arising from the domain of health literacy that focuses on the ability of people to better understand and adhere to medication treatments. It has been demonstrated that health literacy is closely related to significant health outcomes [6]. The concept of mental health literacy, introduced by Jorm et al. [7] in 1997, includes the ability to recognize specific disorders, knowledge about causes and risk factors, and available medical help, self-help knowledge, and attitudes that could lead to a better recognition of disorders and search for adequate treatment.

Mental health literacy is important so that not only the person affected can recognize a mental disorder and seek appropriate help, but also family members and close friends, who can spot early signs and direct the person towards appropriate professionals. Although numerous studies have explored mental health literacy in different countries [5, 6, 7], to the best of our knowledge, this construct has not been examined in Serbia. Determination of the current level of mental health literacy in Serbia could help in the identification of specific areas for improvement and could aid the tailoring of education programs concerning mental health. Similar actions were realized in Australia through a National Survey of Mental Health Literacy in 1995, in which specific areas for improvement were pinpointed and then a campaign for increasing mental health literacy was implemented. The results of the most recent study indicated that there has been a significant progress in recognizing different kinds of mental illnesses over the years, an increase in beliefs about the effectiveness of specific treatments prescribed by mental health specialist, and beliefs about the efficiency of medications, especially antidepressants [8].

The present cross-sectional survey was designed to provide an initial overview of the current mental health literacy and attitudes in a sample of the general population in the Republic of Serbia towards persons who experienced

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Correspondence to:

Marija ČOLIĆ
Faculty of Special Education and
Rehabilitation
University of Belgrade
Visokog Stevana 2
11000 Belgrade, Serbia
colicmarija@outlook.com

symptoms of MDD. The objectives of the present study were to examine (1) the public's recognition of the symptoms of MDD and their beliefs about the causes of depression and the effectiveness of various treatments, (2) attitudes towards people with mental illness, and (3) to explore the correlation among socio-demographic factors and the attitudes towards people with mental illness in the sample of the general population in Serbia.

METHODS

Sample

The convenient sample consisted of 504 participants from different cities in the Republic of Serbia. The majority of the sample (60.1%) had a high school diploma, followed by a bachelor's degree (32.5%), middle school diploma (4.2%), and a master's or a doctoral degree (3.2%). Table 1 presents more information on the demographic characteristics of the sample.

Table 1. Distribution of the participants based on their age and sex

Parameter			Age range (years)				Total
			17–19	20–39	40–59	60–80	
Sex	Male	Count	23	161	45	3	232
		Within sex	9.9	69.4	19.4	1.3	100%
		Within Age range	50	46.9	42.9	30	46.0%
	Female	Count	23	182	60	7	272
		Within sex	8.5	66.9	22.1	2.6	100%
		within age range	50	53.1	57.1	70	54%
Total	Count	46	343	105	10	504	
	Within sex	9.1	68.1	20.8	2	100	
	Within age range	100	100	100	100	100	
Median						25	
Mean						30.59	
SD						12.23	

The instruments were administrated by fourth-semester students at the Faculty of Special Education and Rehabilitation of the University of Belgrade, trained in conducting the interview and administering the questionnaires. Each student was asked to apply the questionnaires to six respondents of different sex, age, and level of education during 2016. The students recruited the participants via personal contacts or by word of mouth and conducted an individual interview with each participant. All the participants were informed that their responses would stay anonymous and they provided verbal consent. The participants were interviewed in person and none of the questionnaires were self-administrated. The study was done in accord with standards of the institutional committee on ethics.

Instruments and procedure

After the participants provided their consent for participation, they completed several demographic questions (sex, age, and level of education), followed by a series of

questions related to the variety of their contacts with persons with a mental illness. The participants were asked close-ended questions, such as, "Have you ever lived, or do you live now with a person with a mental illness?"

To assess the components of mental health literacy, a vignette of a person suffering from a mental disorder, without disclosing the diagnosis, was presented. The vignette was developed by Jorm et al. [7] and described a person who met ICD-10 criteria for MDD.

After being shown the vignette, an interview with closed-ended questions was conducted. In the first part of the interview, the participants were asked four yes/no questions related to their experience with symptoms similar to those depicted in the vignette.

In the second part of the interview, the questions used in the study by Jorm et al. [7] were applied. The respondents were asked two open-ended questions: "What, if anything, is wrong with Maria?" and "What kind of help does Maria need?" The rest of the interview consisted of questions aimed at determining the respondents' rating on the three-point Likert scale about different sources of help and about the effectiveness of possible treatments. Finally, the respondents were asked about the likely result for the individual in the vignette if she did or did not receive professional help that the respondent rated as the most appropriate.

Attitudes towards mentally ill persons were assessed by the Attitudes to Mental Illness Questionnaire (AMI) of the UK Department of Health. The AMI was originally developed in 1993 but the questions used in this study were from 2011 and 2014 [9]. The AMI includes 26 items from the 40-item Community Attitudes toward the Mentally Ill scale (CAMI) and an added item on employment-related attitudes [10]. The items explore attitudes related to fear and exclusion of people with mental disorder, understanding and tolerance of mental disorder, and integration of people into the community. The participants rated the 27 statements on a five-point Likert scale ranging from "1 = strongly disagree" to "5 = strongly agree" [9, 11]. The AMI is validated in various languages and has been used in studies conducted in Sweden, China, and Spain [12, 13, 14].

RESULTS

Previous contact with a person with mental illness

To understand the previous experience and relationships participants have had with a person with a mental illness, a descriptive statistic was performed. The results indicated that 6.7% of the participants are living or have lived with a person with mental illness, 34.9% have or had a neighbor, 12.7% have or had a coworker, and 12.1% reported having a close friend with mental illness.

Furthermore, the results showed that 34.3% of the participants had a family member or a close friend with problems similar to those described in the vignette. The responses showed that 13.9% of the respondents had personally experienced some of the problems described in

the vignette and 5.8% received treatments for these symptoms. A total of 0.8% of the participants self-reported that they have a mental illness diagnosis, while 3.2% reported that they were taking antidepressants at the time of the interview. Further analysis revealed that two out of 16 participants who self-reported antidepressant consumption disclosed a diagnosis of depression, while 14 participants did not report a mental illness diagnosis. A total of 56% of the participants who self-reported consumption of antidepressants were less than 40 years old.

Recognition of disorder, beliefs about causes, first aid, treatment, and outcomes

The responses to the question, “What, if anything, is wrong with Maria?” are summarized in Table 2, which shows that 72.8% of the sample identified a mental health issue, while 41% of the sample correctly recognized MDD.

As shown in Table 3, most of the participants (82%) believed that stressful life events caused the person's problems, while 6.9% of the sample thought it is due to biological factors.

For the question, “How could Maria best be helped?”, 42.5% of the participants rated professional help as the most important support, and 12% of the participants rated conversation with family or friends as important (Table 4).

Table 2. Assessment of the problems described in the vignette

Problem	%
MDD	40.9
Psychological problems	21.8
Psychological problems / MDD	10.1
I do not know	7.7
Problems related to work	6.0
Something else (including health problems, e.g. cancer)	3.6
Multiple causes	10.1

MDD – major depressive disorder

Table 3. Percentage of the participants' rating of the causes of the person's behavior

Perceived cause	%
Stressful life events	81.7
Stressful life events and biological factors	10.3
Biological factors	6.9
Magic, evil spirits	4
Missing data	6

Table 4. Participants' ratings of the help which the person in the vignette needs

Type of help	%
Counseling or psychotherapy	23.8
Help from a psychologist	18.7
Conversation with family or friends about current problems	12.3
Engagement in some other activity (e.g. taking a summer vacation or some other pleasant activity)	6
Taking a medication	2.2
Help from a primary physician	1.6
Multiple sources of help	35.4

The respondents were asked to rate whether different types of help would be helpful or harmful. (Table 5). Most of the respondents regarded support from a psychologist as helpful, followed by help from a friend or a family member and a psychiatrist.

The respondents were given a list of various treatments to rate as helpful or harmful. Table 6 shows that the consumption of vitamins or/and minerals was rated the most helpful, followed by antidepressants, and healing herbs and tea.

The results of the participants' opinion on the person's prognosis with and without the help they thought was the most appropriate are presented in Table 7. Most of the participants believed that the person in the vignette could completely recover with adequate help, and 55.6% of the sample responded that the condition would deteriorate without adequate help and treatment.

Attitudes to mental illness

Following Rüscher et al. [11] study results of the explanatory analysis of AMI, two mean composite scores were calculated. In their study, two factors were extracted – “prejudice and exclusion” and “tolerance and support for community care.” The average factor score for prejudice and exclusion subscale in the present study was 2.4 (SD = 0.58), while the score for tolerance and support for community care subscale was 3.72 (SD = 0.52). In addition, the mean composite score for AMI was computed as in other studies and the result was 3.54 (SD = 0.47) [15, 16]. The Cronbach α for the prejudice and exclusion subscale was 0.77 (a total of 14 items), while the Cronbach α for the tolerance and support for community care subscale was 0.72 (a total of 13 items). Both subscales were negatively correlated ($r = -0.51$). For the AMI composite score, the Cronbach α was 0.82.

To provide an easier interpretation, the reverse items within the prejudice and exclusion subscale and the tolerance and support for community care subscale were re-coded in the direction so that higher scores indicated more prejudice and exclusion, or tolerance and support. In addition, in the second step, all negative items were re-coded so that a higher composite score of the AMI scale presented more positive attitudes.

In addition, 2 (sex) \times 4 (level of education) univariate analysis of variance (ANOVA) on the AMI scores revealed the main effect of education ($F(1,496) = 4.085$, $p < 0.01$, partial eta-squared (η_p^2) = 0.024). The post hoc Scheffé's test showed that the participants who had finished middle school (eight years of education) held the most negative attitudes ($M = 3.23$, $SD = 0.63$) among all four groups; $p = 0.044$, $M = 3.52$, $SD = 0.47$ were the results for the participants with a high school diploma; $p = 0.011$, $M = 3.58$, $SD = 0.42$ were the results for the participants with a bachelor's degree, and $p = 0.019$, $M = 3.68$, $SD = 0.47$ for the participants with a master's or doctoral degree. No main effect of sex or an interaction was found.

Furthermore, 2 (sex) \times 4 (level of education) ANOVA on tolerance and support for community care subscale showed a main effect of education ($F(1,496) = 3.914$,

Table 5. The participants' evaluation of the effect of potential help (%)

Type of help	Total sample			Participants who identified MDD		
	Helpful	Neither helpful nor harmful	Harmful	Helpful	Neither helpful nor harmful	Harmful
Help from a psychologist	81.3	16.5	2.2	81.1	14.6	4.4
Help from a close friend or a family member	76.4	19.6	4	78.2	17	4.9
Help from a psychiatrist	69	23	7.9	71	21.4	7.8
Help from a social worker or a counselor	52.2	40.7	7.1	49	44.7	6.3
Help from a primary physician	37.1	56.5	6.3	30.6	62.1	7.3
Help from a priest	28.8	50.8	20.4	26.7	50	23.3
Help from an alternative medicine specialist	25.6	48.6	25.8	27.2	49.0	23.8

MDD – major depressive disorder

Table 6. The participants' evaluation of the effect of different remedies (%)

Remedies	Total sample			Participant who identified MDD		
	Helpful	Neither helpful nor harmful	Harmful	Helpful	Neither helpful nor harmful	Harmful
Vitamins and minerals	45.6	47.8	6.5	45.1	48.1	6.8
Antidepressants	41.7	23.2	35.1	40.8	21.4	37.9
Tea and healing herbs	40.5	50.6	8.9	39.3	52.4	8.3
Tranquilizers	34.1	29.4	36.5	28.2	30.6	41.3
Sleeping pills	30.8	27.6	41.7	25.2	28.6	46.1
Pain medicine (e.g. aspirin)	20	43.8	36.1	16	43.7	40.3

MDD – major depressive disorder

Table 7. Assessment of the outcome in relation to the provided help (%)

Outcome assessment	Complete recovery	Condition will worsen	Neither
What do you think will be the outcome for Maria with the help which you think is the best?	78	1.6	20.4
What do you think will be the outcome for Maria without the help which you think is the best?	13.3	55.6	31.2

$p < 0.01$, $\eta_p^2 = 0.023$). Post hoc Scheffé's test showed that participants who finished middle school (eight years of education) held the most negative attitudes ($M = 3.37$, $SD = 0.78$) compared to participants with high school diploma ($p = 0.040$, $M = 3.71$, $SD = 0.52$) and with a bachelor's degree ($p = 0.009$, $M = 3.78$, $SD = 0.48$). No main effect of the sex or effect of interaction was established. Furthermore, no main effect of sex, age, or their interaction on the prejudice and exclusion scale was found.

Pearson's correlation between age and prejudice and the exclusion scale was significant ($r = 0.124$, $p < 0.01$). The results indicated that with increasing age, the participants held more negative attitudes on the prejudice and exclusion subscale. No correlations between age and the AMI composite score or the tolerance and support for community care scale were found.

DISCUSSION

The present study examined the mental health literacy and attitudes in relation to MDD among a sample of the general population in Serbia. The results showed that 34.3% of

the respondents reported that someone in their family or a close friend had problems similar to the one presented in the vignette and 13.9% of the respondents had personally experienced them. In the research by Reavley and Jorm [8], almost two-thirds of respondents revealed that a family member or a close friend had experienced similar problems, and 33% stated they had a personal experience similar to those presented in the vignette. The difference between the study by Reavley and Jorm [8] and the present study could be contributed to campaigns about mental health that had been active in Australia for over 15 years. Research indicated that in areas where there had been active campaigns to improve mental health literacy, a greater number of people identified themselves or family members to have MDD [8].

Although 13.9% of the respondents in the current study self-reported experience with problems similar to the ones presented in the vignette, only 3.2% reported taking antidepressants. This result is in accordance with an analysis in Serbia which showed that the use of antidepressants is low compared to the number of people with MDD [17]. Interestingly, only two out of 16 respondents who reported taking antidepressants disclosed the diagnosis of depression. Evidence suggests that people with mental health problems often fear stigma and this may influence help-seeking behavior or adherence to treatment [18]. In the present study, a definition of antidepressants was not provided, which could have left space for its different interpretation by the respondents (such as using over-the-counter medication). Further research is warranted to examine whether this discrepancy is evident among a larger sample of people who consume antidepressants and what factors could contribute to it.

Knowing that early recognition and early treatment are positively related to the long-term outcome of a disorder,

the importance of recognizing mental health disorders at an early stage is a clear indication for seeking professional help [19]. Although recognition of a mental health problem was high in the present sample, only 40% of the participants correctly recognized MDD, which is considerably lower compared with the 86% recognition in a study conducted in Australia [20]. Recognition of the disorder in the present sample was at the same level as that in Australia 21 years ago [21]. That an active campaign is effective is evident in the study in which Jorm and associates showed improvement in depression recognition from 39% to 67% in the span of 8 years (1995 to 2003) [21].

The respondents in the present study believed that stress contributed more to the development of MDD than biological factors. This is in agreement with the findings that the general public favors psychosocial explanations over biological explanations for different mental health disorders, including depression [22].

When respondents were asked about the helpfulness of various people, psychologists were highly rated, followed by friends and psychiatrists. The slightly lower rating of help from a psychiatrist could be due to the less severe symptoms presented by the person in the vignette. On the other hand, studies in Australia showed that a general practitioner (GP) would be recommended first, followed by a counselor and a family member [7, 8]. The difference among these results could be explained by the different organization of the health system in Serbia and Australia. In Serbia, people who experience symptoms of mental illness are under the primary care of a psychiatrist, bypassing services provided by a GP. It is notably that in Serbia, only 39% of the patients who are treated by a psychiatrist initially visited a general practitioner [23]. Directing patients towards a GP could lead to early recognition of mental disorder and adequate treatment. The importance of social support to persons with mental disorders was shown in an earlier study in the USA [24], and the present sample confirmed that help from friends was also highly rated in Serbia.

Ratings given for the helpfulness of various treatments are not consistent with the evidence of controlled trials, which have indicated that both antidepressants and psychotherapy are effective treatments for depression [25]. Respondents rated vitamins and healing herbs as the most helpful kind of the treatment. It seems that the general public prefer non-standard treatments over conventional medicine [26], suggesting that public do not share professionals' opinions about the efficacy of psychiatric treatment. Antidepressants were rated by 41% as helpful and by one-third as harmful treatment. This ambivalence indicates that the general population has different opinions on their effects. Jorm and associates showed that the belief in the effectiveness of antidepressants increased between 1997 [7] to 2011 [8] attributing the change to public education programs. Negative beliefs towards medications were present

in the Serbian sample, which is consistent with results from Australia [8].

The findings of the present study show that the public clearly sees the condition described in the vignette as treatable. The predominant belief that mental disorders are treatable has also been found in different studies [27, 28]. Research in Australia also showed optimism about the prospect for recovery with adequate help [7, 8].

Using AMI, it was noted that the public held moderately positive attitudes towards people with mental health disorders. However, it was indicated that with increasing age, the participants had more negative attitudes on the prejudice and exclusion subscale, which is in line with other research [29, 30]. One explanation could be that older people lived in the era of institutionalization of people with mental disorders in Serbia and hence, they had less contact with them, which might have contributed to their belief that people with mental disorders should be placed in an institution. Participants who had lower level of education held the most negative attitudes on the tolerance and support for community care subscale and the overall AMI score. Different studies suggest that individuals with higher level of education had more access to health information, better understanding of such information and greater knowledge of mental disorders [30].

Limitations of the study is that it included a convenient sample consisting mostly of young adults and the diagnostic vignette approach was used, which does not allow the entire domain of that which constitutes mental health literacy to be evaluated.

CONCLUSION

Although recognition of mental health problems in the sample was high, 41% of the participants recognized MDD based on the symptoms in the vignette. Moreover, the effectiveness of antidepressants was recognized by less than half of the sample. Furthermore, most of the participants thought that the only cause of the problems presented in the vignette was due to stressful life events. Strength in mental health literacy was seen in the rating of professional help as the most helpful, as well as the belief that the actor in the vignette could improve with adequate help. This was a pilot study on mental health literacy in Serbia that could help in the design of new research studies with focus on different variables that could contribute to mental health knowledge. In addition, the findings could help in the design of education programs to enhance knowledge about the common mental disorders, teach help-seeking skills, and mental health literacy. In the longer term, enhanced mental health literacy may be expected to result in early recognition of mental disorders and higher rates of help-seeking behavior.

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Знање и ставови према особама са депресивним поремећајем и начини третмана у узорку особа опште популације у Србији

Ивона Милачић-Видојевић¹, Марија Чолић¹, Бранка Драшковић²

¹Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија;

²Универзитет „Метрополитан“, ФЕФА, Београд, Србија

САЖЕТАК

Увод/Циљ Циљ студије је испитати писменост у области менталног здравља код узорка особа опште популације у Србији, као и ставове према особама са менталним болестима.

Метод Примењена је студија попречног пресека, са структурисаним интервјуом и вињетом која приказује особу са симптомима депресије. Ставови су процењени Упитником о ставовима према особама са менталним болестима британског сектора здравља. Пригодан узорак особа опште популације се састојао од 504 учесника.

Резултати Резултати су указали да је 72% испитаника препознало да је у питању неки проблем менталног здравља, док је 40,9% тачно идентификовало особу са депресивним

поремећајем. Више испитаника је веровало да је депресија узрокована стресом него биолошким факторима. Као најкориснија помоћ за особу приказану у вињети изабрана је помоћ психолога, блиског пријатеља и психијатра. Употреба витамина и лековитих биљака је процењена као најкориснији вид лечења. Антидепресиви се сматрају и корисним и штетним. Ставови према особама са менталним болестима су умерено позитивни.

Закључак Писменост у области менталног здравља у Србији је умерена. Фактори ризика за негативне ставове укључују старији узраст и нижи степен образовања.

Кључне речи: писменост у области менталног здравља; депресија; ставови према особама са менталним болестима



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Evaluation of the diagnostic utility of case definitions to detect influenza virus infection in Vojvodina, Serbia

Mioljub Ristić^{1,2}, Vladimir Petrović^{1,2}

¹University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;

²Institute of Public Health of Vojvodina, Novi Sad, Serbia

SUMMARY

Introduction/Objective A case definition recommended by the World Health Organization is commonly used for influenza surveillance worldwide.

The aim of this study was to evaluate prognostic values of proposed case definitions of Influenza Like Illness (ILI), Severe Acute Respiratory Illness (SARI) and Acute Respiratory Distress Syndrome (ARDS) for laboratory confirmed-influenza and to compare the age distribution of influenza patients across virus types and subtypes in Vojvodina.

Methods We conducted a descriptive epidemiological study using surveillance reports and laboratory data from October 1, 2010 to May 20, 2017 (seven surveillance seasons).

Results We included 2,937 participants, 48.6% of whom were laboratory-confirmed influenza cases, and most of the confirmed cases (30.1%) were detected in February. In the 15–29 years age group, the type A influenza (H3N2) was more frequent among patients with ILI (54.9% vs. 34.2%, $p = 0.040$), and less frequent in patients with SARI (39.4% vs. 65.8%, $p = 0.009$) compared with influenza type B. In patients aged 30–64 years with ARDS, influenza type B was more common than influenza type A (H3N2) (13.4% vs. 6.2%, $p = 0.032$), but less common in compared to influenza type A (H1N1) pdm09 (13.4% vs. 25.7%, $p = 0.017$). The SARI case definition of influenza was associated with an increased likelihood of laboratory-confirmed influenza for all age groups ($p < 0.05$). During the epidemic period, it was observed that the ILI case definition had the highest diagnostic value for influenza in the age group 5–14 (AUC = 0.733; 95% CI: 0.704–0.764), while the SARI and ARDS case definitions were the best predictors of influenza for patients 15–29 years of age (AUC = 0.565; 95% CI: 0.504–0.615 and AUC = 0.708; 95% CI: 0.489–0.708, respectively). The case definition of ARDS had the maximum sensitivity (100%) among patients 15–29 years of age.

Conclusion The proposed case definitions of influenza appeared to be good predictors of influenza and therefore can be useful for influenza surveillance, especially in the countries with limited laboratory capacities.

Keywords: influenza virus; epidemiology; virology; case definition; surveillance

INTRODUCTION

The aims of existing case definitions of influenza, proposed by the Centres for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC), and the World Health Organization (WHO) are for timely detection of the start and duration of the influenza season in order to monitor changes in the antigenicity of influenza viruses and provide guidelines for influenza vaccine policies. Early detection of circulating influenza strains in terms of clinical signs and symptoms is useful for clinicians in order to support the clinical decision and improve patients' management. Due to the lack of specificity of influenza symptoms, co-infection and co-circulation of other respiratory viruses, improving the current case definitions of influenza remains a significant public health challenge [1]. The optimal case definition should be applicable every year, despite seasonal variations, in all medical settings (outpatient and inpatient medical facilities) [2].

Influenza is usually a self-limiting infection, but it can exacerbate underlying medical conditions (chronic diseases, weakened immune

system), and present with primary influenza viral pneumonia or lead to secondary bacterial pneumonia, or can occur as part of a co-infection with other pathogens [3, 4, 5]. Although all humans can be affected by an influenza virus, clinical presentation of illness differs depending on the virus type-, subtype- and strain-specific properties as well as on the immunological and physiological characteristics of patient influenced by several factors such as age, chronic medical conditions, and pregnancy [6].

The main goal of this study was to analyze the utility of clinical case definition of Influenza Like Illness (ILI), Severe Acute Respiratory Illness (SARI) and Acute Respiratory Distress Syndrome (ARDS) to predict laboratory-confirmed influenza in outpatient and inpatient medical settings. Also, the comparison of the age distribution of virus types and subtypes for the seven influenza seasons was made.

METHODS

In Vojvodina – the northern region of Serbia with 1,931,809 inhabitants (26.9% of the total

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Correspondence to:

Mioljub RISTIĆ
Institute of Public Health
of Vojvodina
Futoška 121
21000 Novi Sad, Serbia
mioljub.ristic@mf.uns.ac.rs

Serbian population according to the 2011 Census) the surveillance of influenza is coordinated by the Institute of Public Health (IPH) of Vojvodina. As described in detail previously, data for this observational surveillance study were obtained from the sentinel (outpatients) and hospital (patients hospitalized at secondary or tertiary health care level) surveillance of influenza in Vojvodina [7, 8]. Data have been collected from October 1, 2010 to May 20, 2017 (seven influenza seasons) and entered into the database maintained by the Centre for Disease Control and Prevention, IPH of Vojvodina. We included participants who fulfilled the criteria for clinical case definitions of ILI and SARI, and those who met the American European Consensus Conference criteria for ARDS [9, 10]. The study was done in accordance with standards of the institutional committee on ethics.

Depending on the health care levels (outpatient or inpatient settings) across Vojvodina where the patients comprised, general practitioners and pediatricians, as well as the specialists in internal medicine, infectious disease and respiratory disease interviewed the patients. Demographic, clinical, and physical examination data were obtained from patients suspected of having acute influenza through face-to-face structured interviews, using a structured questionnaire.

Virological surveillance of influenza was conducted during the whole study period, from calendar week 40 of each year to calendar week 20 of the next year. Nasal and throat swabs samples were tested in the WHO National Influenza Centre, at the Centre of Virology of the IPH of Vojvodina in Novi Sad [11]. A real-time reverse transcription polymerase chain reaction (real-time RT PCR) assays were used for the detection of influenza virus types A and B and influenza A virus subtypes A(H1N1)pdm09 and A(H3N2) [12].

Statistical analysis

For categorical data, Fisher's exact test or χ^2 test were used where appropriate. Both univariate and multivariate analyses were stratified according to three case definitions of influenza. Differences in age, between the participants with laboratory-confirmed influenza and those without laboratory confirmation, for the three clinical case definitions, were compared by odds ratio (OR) with 95% confidence intervals (95% CI). To control for possible confounding variables, the adjusted OR was calculated using logistic regression, including sex and calendar month of symptom onset. A surveillance period was divided into an epidemic period with high influenza activity (December, January, February, and March) and a period of low influenza activity (October, November, April, and May).

The diagnostic value of the case definitions (ILI, SARI, ARDS) during the epidemic period was measured using sensitivity, specificity, and area under curve (AUC) with 95% confidence intervals. The sensitivity was defined as the probability of having the case definition in a case of laboratory-confirmed influenza, while the specificity was defined as the probability of not having the case definition when the patient did not have laboratory-confirmed influenza infection. The AUC, as a global measure of algorithm

performance for the identification of laboratory-confirmed influenza patients, takes both sensitivity and specificity into account.

Validation of proposed case definitions during the epidemic period was stratified by age group (0–4, 5–14, 15–29, 30–64, ≥ 65 years).

A p value below 0.05 was considered significant. Statistical analysis was done using the SPSS Statistics software Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, 2,937 specimens from patients with ILI, SARI, or ARDS, were tested for influenza, and 1,427 samples were identified as influenza type A or B positive (48.6%). Among study participants, 53.7% (1,576/2,937) were males. The median age of all cases was 43 years (IQR: 15–62 years), and decreasing to 37 years (IQR: 10–60 years) among laboratory-confirmed influenza.

Observed by clinical diagnosis, the majority of participants had the SARI clinical diagnosis (56.7%; 1,665/2,937). Out of total number of participants, 2,477 (84.3%) cases were registered in the four-month period (from December to March), with the highest detection rate in February (30.1%; 429/1,427) (Table 1).

Table 1. Influenza-positive and negative participants included in the study by sex, age distribution, case definitions, and months in Vojvodina, from 2010/2011 to 2016/2017 influenza seasons

Variable	All participants (n = 2,937) n (%)	Influenza-positive (n = 1,427) n (%)	Influenza-negative (n = 1,510) n (%)
Sex			
Male	1,576 (53.7)	764 (53.5)	812 (53.8)
Age group (years)			
0–4	347 (11.8)	173 (12.1)	174 (11.5)
5–14	370 (12.6)	262 (18.4)	108 (7.2)
15–29	384 (13.1)	176 (12.3)	208 (13.8)
30–64	1,236 (42.1)	529 (37.1)	707 (46.8)
≥ 65	600 (20.4)	287 (20.1)	313 (20.7)
Mean age (\pm standard deviation)	39.7 (\pm 25.5)	37.4 (\pm 26.3)	41.9 (\pm 24.6)
Median age (Q1–Q3 interquartile range)	43 (15–62)	37 (10–60)	46 (20–62)
Case definition			
ILI	956 (32.5)	595 (41.7)	361 (23.9)
SARI	1,665 (56.7)	719 (50.4)	946 (62.6)
ARDS	316 (10.8)	113 (7.9)	203 (13.5)
Months of symptom onset			
October	73 (2.5)	1 (0.1)	72 (4.8)
November	84 (2.9)	1 (0.1)	83 (5.5)
December	415 (14.1)	245 (17.1)	170 (11.3)
January	557 (19)	243 (17)	314 (20.8)
February	787 (26.8)	429 (30.1)	358 (23.7)
March	718 (24.4)	379 (26.6)	339 (22.4)
April	276 (9.4)	129 (9)	147 (9.7)
May	27 (0.9)	0 (-)	27 (1.8)

ILI – influenza-like illness; SARI – severe acute respiratory illness; ARDS – acute respiratory distress syndrome

Comparing different influenza virus types and subtypes, there were few significant differences among groups of patients with distinct clinical case definitions of influenza stratified by age. In patients aged 15–29, influenza type A (H3N2) virus was more frequently registered among patients with ILI (54.9% vs. 34.2%, $p = 0.040$), and less frequently in patients with SARI (39.4% vs. 65.8%, $p = 0.009$) compared with influenza type B virus. Among patients aged 30–64 years with ARDS, an influenza B was more common than influenza A (H3N2) (13.4% vs. 6.2%, $p = 0.032$), but less common in comparison with an influenza A (H1N1) pdm09 (13.4% vs. 25.7%, $p = 0.017$). No significant differences were detected among patients with different clinical case definitions of influenza regarding the frequency of influenza virus types and subtypes in the remaining age groups (Table 2).

Univariate and multivariate logistic regression analyses were performed in order to identify predictor values of proposed clinical case definitions for the entire study period. When three clinical case definitions of influenza were classified and compared with the youngest age group (0–4 years), the SARI case definition of influenza was associated with the increasing probability of having influenza for all age group, while the ILI case definition was a useful diagnostic predictor of laboratory-confirmed influenza in patients aged 5–14 ($p < 0.05$). The influenza positive cases with ARDS were registered only among participants aged 15 and older, but the ARDS case definition had a poor diagnostic value for detecting influenza virus infection ($p > 0.05$) (Table 3).

When the performance of case definitions was tested only in the epidemic period, the ILI case definition had the highest accuracy in those aged 5–14 years (AUC = 0.733; 95% CI: 0.704–0.764); the SARI and ARDS case definitions had the highest AUC values among the 15–29-year-olds (AUC = 0.565; 95% CI: 0.504–0.615 and AUC = 0.708; 95% CI: 0.489–0.708, respectively). The ILI case definition showed a high sensitivity value (above 90%) for all age groups, with the highest sensitivity among the youngest age group (95.4%). The sensitivity values of SARI case definition ranged 81.3–95.2% between different age groups, with a total sensitivity value of 89.3%. During the epidemic period, the ARDS case definition had the maximum sensitivity value (100%) in patients aged 15–29 years. Total specificity values of ILI and SARI case definitions were 15% and 19.8%, while the ARDS had a specificity value of 43.4% (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study on the evaluation of influenza case definitions (ILI, SARI, and ARDS) conducted through the sentinel and hospital-based surveillance systems in our country. As the main advantage of our study, we conducted the most comprehensive effort to determine the accuracy of three clinical case definitions of influenza for the detection of laboratory-confirmed influenza virus infection during the seven post-pandemic seasons.

Table 2. Case definitions of influenza patients according to age group and influenza virus type and subtype by age groups in Vojvodina, from 2010/2011 to 2016/2017 influenza seasons

Age group (years)	Influenza type/subtype	ILI	SARI	ARDS
0–4 ($n^a = 173$)	B ^b $n = 33$; n (%)	27 (81.8)	6 (18.2)	0 (-)
	A ^c $n = 140$; n (%)	125 (89.3)	15 (10.7)	0 (-)
	A(H1N1) pdm09 $n = 54$; n (%)	48 (88.9)	6 (11.1)	0 (-)
	A(H3N2) $n = 80$; n (%)	73 (91.3)	7 (8.7)	0 (-)
5–14 ($n^a = 262$)	B ^b $n = 95$; n (%)	82 (86.3)	13 (13.7)	0 (-)
	A ^c $n = 167$; n (%)	148 (88.6)	19 (11.4)	0 (-)
	A(H1N1) pdm09 $n = 57$; n (%)	52 (91.2)	5 (8.8)	0 (-)
	A(H3N2) $n = 108$; n (%)	94 (87)	14 (13)	0 (-)
15–29 ($n^a = 176$)	B ^b $n = 38$; n (%)	13 (34.2)	25 (65.8)	0 (-)
	A ^c $n = 138$; n (%)	57 (41.3)	74 (53.6)	7 (5.1)
	A(H1N1) pdm09 $n = 65$; n (%)	18 (27.7)	45 (69.2)	2 (3.1)
	A(H3N2) $n = 71$; n (%)	39 (54.9)*	28 (39.4)*	4 (5.7)
30–64 ($n^a = 529$)	B ^b $n = 97$; n (%)	21 (21.7)	63 (64.9)	13 (13.4)
	A ^c $n = 432$; n (%)	101 (23.4)	269 (62.3)	62 (14.3)
	A(H1N1) pdm09 $n = 183$; n (%)	25 (13.7)	111 (60.6)	47 (25.7)*
	A(H3N2) $n = 228$; n (%)	71 (31.1)	143 (62.7)	14 (6.2)*
≥ 65 ($n^a = 287$)	B ^b $n = 40$; n (%)	2 (5)	33 (82.5)	5 (12.5)
	A ^c $n = 247$; n (%)	19 (7.7)	202 (81.8)	26 (10.5)
	A(H1N1) pdm09 $n = 56$; n (%)	5 (8.9)	43 (76.8)	8 (14.3)
	A(H3N2) $n = 176$; n (%)	13 (7.4)	148 (84.1)	15 (8.5)

ILI – influenza-like illness; SARI – severe acute respiratory illness;

ARDS – acute respiratory distress syndrome;

^aincluded all influenza (A and B type) cases;

^breference group;

^call influenza A type cases (A(H1N1)pdm09 and A(H3N2), and those that were not subtyped/characterized)

* p -value for the comparison with influenza type B patients of the same age group less than 0.05

Several studies reported no difference in clinical symptoms between patients with influenza type A compared with influenza type B viruses [1, 6]. However, different age groups may be preferentially affected by influenza during any given season depending on the pool of viruses that are circulating, which may result in a different disease burden [6].

By comparing the frequencies of influenza types A and B virus infections, we found that influenza type B was more commonly detected than influenza type A (H3N2) in patients with SARI aged 15–29 years, and among those with ARDS aged 30–64 years. Further, we found that influenza type A (H3N2) was more frequently registered than

Table 3. Case definitions of influenza associated with laboratory-confirmed influenza, stratified by age group in Vojvodina, from 2010/2011 to 2016/2017 influenza seasons

Age group (years)	ILI				SARI				ARDS			
	Positive n = 595 n (%)	Negative n = 361 n (%)	OR (95% CI)	adj. OR ^a (95%CI)	Positive n = 719 n (%)	Negative n = 946 n (%)	OR (95% CI)	adj. OR ^a (95%CI)	Positive n = 113 n (%)	Negative n = 203 n (%)	OR (95% CI)	adj. OR ^a (95%CI)
0–4	152 (25.5)	79 (21.9)	Reference		21 (2.9)	91 (9.6)	Reference		0 (-)	4 (1.9)	NA	
5–14	230 (38.7)	81 (22.4)	1.5 ^b (1–2.1)	1.5 ^b (1–2.2)	32 (4.4)	26 (2.8)	5.3 ^b (2.6–10.8)	5.8 ^b (2.8–12)	0 (-)	1 (0.5)	NA	
15–29	70 (11.8)	81 (22.4)	0.5 ^b (0.3–0.7)	0.5 ^b (0.3–0.7)	99 (13.8)	110 (11.6)	3.9 ^b (2.3–6.7)	4.5 ^b (2.6–7.8)	7 (6.2)	17 (8.4)	Reference	
30–64	122 (20.5)	104 (28.8)	0.6 ^b (0.4–0.9)	0.7 (0.5–1)	332 (46.2)	478 (50.5)	3 ^b (1.8–4.9)	3.3 ^b (2–5.4)	75 (66.4)	125 (61.6)	1.5 (0.6–3.7)	1.3 (0.5–3.6)
≥65	21 (3.5)	16 (4.5)	0.7 (0.3–1.4)	0.7 (0.3–1.4)	235 (32.7)	241 (25.5)	4.2 ^b (2.5–7)	4.3 ^b (2.6–7.1)	31 (27.4)	56 (27.6)	1.3 (0.5–3.6)	1.2 (0.4–3.5)

OR – odds ratio; CI – confidence interval; ILI – influenza-like illness; SARI – severe acute respiratory illness; ARDS – acute respiratory distress syndrome; NA – not applicable;

^aadjusted for the following variables: sex and months of symptom onset (influenza epidemic period and low influenza activity);

^bstatistically significant differences;
($p < 0.05$)

Table 4. Sensitivity, specificity, and area under curve value of the case definitions tested for influenza confirmation during epidemic period, stratified by age group in Vojvodina, from 2010/2011 to 2016/2017 influenza seasons

Age group (years)	Case definition	Se % (95 % CI)	Sp % (95 % CI)	AUC % (95% CI)
0–4	ILI	95.4 (90.7–98.1)	16.5 (9.1–26.5)	0.684 (0.644–0.716)
	SARI	95.2 (76.2–99.9)	9.9 (4.6–18)	0.259 (0.199–0.276)
	ARDS	NA	NA	NA
5–14	ILI	94.4 (90.5–97)	13.6 (7–23)	0.733 (0.704–0.764)
	SARI	81.3 (63.6–92.8)	15.4 (4.4–34.9)	0.517 (0.429–0.624)
	ARDS	NA	NA	NA
15–29	ILI	92.9 (84.1–97.6)	12.4 (6.1–21.5)	0.497 (0.443–0.537)
	SARI	85.9 (77.4–92.1)	30 (21.6–39.5)	0.565 (0.504–0.615)
	ARDS	100 (59–100)	58.8 (32.9–81.6)	0.708 (0.489–0.708)
30–64	ILI	91 (84.4–95.4)	18.3 (11.4–27.1)	0.575 (0.527–0.617)
	SARI	90.4 (86.7–93.3)	22 (18.3–26)	0.500 (0.475–0.521)
	ARDS	85.3 (75.3–92.4)	43.2 (34.4–52.4)	0.590 (0.526–0.638)
≥65	ILI	90.5 (69.6–98.8)	6.3 (0.2–30.2)	0.541 (0.489–0.628)
	SARI	89.8 (85.2–93.4)	14.9 (10.7–20.1)	0.519 (0.487–0.548)
	ARDS	83.9 (66.3–94.6)	41.1 (28.1–55)	0.563 (0.458–0.632)
All age groups	ILI	93.6 (91.3–95.4)	15 (11.4–19.1)	0.639 (0.619–0.658)
	SARI	89.3 (86.8–91.5)	19.8 (17.3–22.5)	0.498 (0.480–0.514)
	ARDS	85.8 (78–91.7)	43.4 (36.4–50.5)	0.585 (0.537–0.623)

ILI – influenza-like illness; SARI – severe acute respiratory illness; ARDS – acute respiratory distress syndrome; Se – sensitivity; Sp – specificity; AUC – area under curve; CI – confidence interval; NA – not applicable

influenza B in patients with ILI aged 15–29 years, and influenza type A (H1N1) pdm09 was more often detected than influenza type B virus in those with ARDS aged 30–64 years. Although the reasons for the mentioned differences are not completely clear, this result supports the results of previously reported findings, and it should be taken into consideration in future investigation [1, 4, 6]. Our results are in a good agreement with the fact that the interpretation of syndromic surveillance data without information on age may be misleading [13].

Aiming to detect the maximum number of influenza cases across the three case definitions, SARI was associated with the increasing risk of laboratory-confirmed influenza in all age groups, while the case definition of ILI was positively associated with influenza in patients under 15. Further, the case definition of ARDS had no diagnostic value for the detection of influenza infection. However, when the peak of influenza activity was distinguished by months (December, January, February and March), we found that the case definition of ILI among patients aged 15–14, and case definition of ARDS in patients aged 15–29, provided the most useful diagnostic value of laboratory-confirmed influenza. Although the majority of the confirmed influenza cases with ARDS belonged to patients aged 60 and older (66.4%; 75/113), the proposed case definition of ARDS is most useful for detecting of influenza among younger patients (aged 15–29) suspected of having influenza.

After examining the performance of the international case definitions of ILI commonly used for influenza surveillance among outpatients in France, Casalegno et al. [1] reported that the WHO ILI case definition (fever $\geq 38^{\circ}\text{C}$ with onset within the last seven days and cough) had the highest positive AUC values in comparison with the CDC ILI (sudden onset of fever $\geq 38^{\circ}\text{C}$, with absence of a known cause other than influenza, and at least one of the following symptoms: cough, and sore throat) and the ECDC ILI (sudden onset of at least one among following general symptoms: fever, feverishness, headache, malaise, myalgia, and at least one among respiratory symptoms: cough, sore throat,

shortness of breath). Our results showed higher AUC value of the WHO ILI case definition than those obtained by Casalegno et al. [1] (AUC = 0.639; 95% CI: 0.619–0.658 vs. AUC = 0.556; 95% CI: 0.547–0.566, respectively). The reason for that may be that Casalegno et al. [1] referred to the overall period, while we estimated the AUC value only for the epidemic period. However, after comparing the results only during influenza seasonal, i.e., epidemic period, higher sensitivity values were observed (93.6% vs. 88.9%), but still lower specificity values (15% vs. 21.3%) than in the cited study [1]. We believe that observed differences could be explained by the fact that the median age of all participants included in the French study was nine years, while the median age of our respondents was 43 years [1].

As it is known, the variety of other potential co-infecting pathogens among patients aged 0–4 years could be the reason for the lower performance of all case definitions in this age group [14, 15]. We found that the sensitivity value of ILI case definition for patients aged 0–4 months was above 95%, similar to the values of CDC ILI or ECDC ILI case definitions (93%) [1]. However, in line with previously published reports, we found a very low specificity of the proposed case definitions of ILI, which indicates that individuals without influenza infection are likely to be misclassified as false positive patients [1, 16].

Further, it was observed that the SARI case definition in patients from the youngest age group had the sensitivity above 95%, and specificity about 10%. Results of the study done by Peng et al. [17], who analyzed data from SARI cases in China (from 2011 to 2013), suggested the association of laboratory-confirmed influenza with increasing age of patients. Interestingly, the prevalence of laboratory-confirmed influenza among patients with SARI aged 0–4 years was only 5.2% (101/1,944), whereas the prevalence of influenza cases with SARI in the same age group in our research was 18.8% (21/112). Because two different case definitions were tested, those findings were not surprising. A similar study among hospitalized patients in India showed that sensitivity and specificity in patients with SARI were 28% and 84%, respectively [18]. Our results show that the sensitivity and specificity for all patients with SARI were 89.3% and 19.8%. Observed differences can

only be interpreted as a result of the implementation of different case definitions used in two studies. For improving the specificity of SARI case definition among our patients younger than five years, it can be useful to implement a more specific case definition, similar to the research cited above [17].

The importance of the sensitivity and specificity of case definitions varies according to which of the goals have the highest priorities [1, 16, 18].

Our results show that the applied case definitions of influenza provide a high sensitivity, which supports the goal of early diagnosis and treatment and timely identification of influenza outbreaks. However, if the goal is to increase efficiency in obtaining influenza virus-positive specimens and identify circulating influenza strains while minimizing unnecessary testing, then it is needed to improve the specificity of the proposed case definitions [19, 20, 21].

CONCLUSION

The proposed case definitions of influenza appeared to be good predictors for laboratory-confirmed influenza, and therefore can be useful for continuous surveillance in order to predict seasonal trends and prepare for a timely response to the influenza outbreak, particularly for the purpose of surveillance in resource-poor laboratory settings.

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Процена дијагностичке вредности дефиниција случаја у откривању инфекција изазваних вирусом грипа у Војводини, Србија

Миољуб Ристић^{1,2}, Владимир Петровић^{1,2}

¹Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија

²Институт за јавно здравље Војводине, Нови Сад, Србија

САЖЕТАК

Увод/Циљ У надзору над gripом, у свету се обично користи дефиниција случаја препоручена од стране Светске здравствене организације.

Циљ рада био је да се процени прогностички значај предложених дефиниција случаја обољења сличних gripу (ОСГ), тешке акутне респираторне болести (ТАРБ) и акутног респираторног дистресног синдрома (АРДС) за откривање лабораторијски потврђених случајева вируса инфлуенце и упоређи узрасна дистрибуција типова/подтипова вируса gripа у Војводини.

Метод Сprovedена је дескриптивна епидемиолошка студија употребом података из извештаја у надзору и лабораторијских података у периоду од октобра 2010. године до маја 2017. године (седам сезона надзора).

Резултати Од укупно 2937 укључених испитаника, лабораторијска потврда вируса инфлуенце добијена је код 48,6% тестираних, а већина оболелих (30,1%) регистрована је у фебруару.

У узрасту оболелих од 15 до 29 година, инфлуенца типа А (H3N2) чешће је регистрована код болесника са дијагнозом ОСГ (54,9% наспрам 34,2%, $p = 0,040$), али је ређе регистрована код оболелих са дијагнозом ТАРБ (39,4% наспрам 65,8%, $p = 0,009$) у поређењу са инфекцијом инфлуенце типа

Б. Међу болесницима узраста од 30 до 64 године са дијагнозом АРДС, вирус инфлуенце типа Б је био чешће регистрован него инфлуенца типа А (H3N2), (13,4% наспрам 6,2%, $p = 0,032$), али је био ређи у поређењу са вирусом инфлуенце типа А (H1N1) *pdm09* (13,4% наспрам 25,7%, $p = 0,017$).

Дефиниција случаја ТАРБ је позитивно корелирала са добијањем лабораторијски потврђених случајева инфлуенце у свим добним групама ($p < 0,05$).

Посматрано током епидемијског периода, дефиниција ОСГ је имала највишу дијагностичку вредност у узрасту од пет до 14 година ($AUC = 0,733$; 95% CI: 0,704–0,764), док су дефиниције случаја ТАРБ ($AUC = 0,565$; 95% CI: 0,504–0,615) и АРДС ($AUC = 0,708$; 95% CI: 0,489–0,708) биле најкориснији претсказатељи инфлуенце у узрасту од 15 до 29 година. У истом узрасту болесника са дијагнозом АРДС добијена је највиша сензитивност (100%).

Закључак Предложене дефиниције случаја gripа су се показале као добри претсказатељи за откривање вируса инфлуенце, тако да могу бити корисне у надзору над gripом, посебно у земљама са ограниченим лабораторијским капацитетима.

Кључне речи: вирус инфлуенце; епидемиологија; вирусологија; дефиниција случаја; надзор



CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Intrapulmonary solitary fibrous tumor

Aleksandra Lovrenski, Aleksandra Ilić, Ivan Kuhajda, Dragana Tegeltija, Jovan Lovrenski

University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

SUMMARY

Introduction Solitary fibrous tumor is a neoplasm that arises most commonly from the pleura, but can occur at other sites. Intrapulmonary solitary fibrous tumor has been rarely reported and therefore is not well recognized.

Case outline We report a case of an asymptomatic 63-year-old woman in whom a large, well-circumscribed mass was incidentally revealed on chest X-ray during preparation for ergometric cardiac testing. Chest computed tomography revealed an abnormal nodule in the lower right lung lobe. Mediastinal and hilar lymphadenopathy was not detected. After transthoracic fine needle aspiration, cytology showed a finding suspicious for spindle cell tumor. Consequently, right anterolateral thoracotomy with right lower lobectomy was performed. On gross examination, the lower right lobe was almost completely replaced with abnormal, white-yellow, well-demarcated solid nodule measuring 13.5 cm in its largest diameter surrounded by a pseudocapsule. After histological examination and applied immunohistochemical analysis, a diagnosis of intrapulmonary solitary fibrous tumor of low malignant potential was set. Due to the presence of unfavorable prognostic parameters (tumor size, as well as the presence of hypercellularity), more frequent follow-up check-ups were recommended. Eighteen months after surgery, the patient remained uneventful, with no evidence of tumor recurrence.

Conclusion Intrapulmonary solitary fibrous tumor is a rare entity challenging for diagnosis, because variegated histology and variability of its growth patterns can resemble other soft tissue tumors. The treatment of choice is complete excision with clear surgical margins, but since morphology cannot be a reliable predictor of clinical behavior, the patients need a long-term follow-up.

Keywords: solitary fibrous tumor; intrapulmonary; diagnosis; cytology; immunohistochemistry

INTRODUCTION

Soft tissue tumors represent a diverse group of neoplasms that are of mesenchymal origin, and are classified according to the tissue of origin and histological differentiation. These tumors rarely occur within lung parenchyma, and one of the rarest primary soft tissue tumors in the lung described is intrapulmonary solitary fibrous tumor.

Solitary fibrous tumors (SFTs) are rare, slow-growing spindle cell mesenchymal tumors whose behavior cannot be accurately predicted by histological findings. These neoplasms are ubiquitous, can arise in many different organs, but most often they arise from visceral pleura, leading the origin of the mesenchymal tissue cells that are found in the submesothelial layer of pleura [1]. Intrapulmonary SFT has been rarely reported and is therefore not well recognized.

We report a case of a 63-year-old woman with an abnormal nodule in the lower right lung detected on chest X-ray during preparation for ergometric cardiac testing. Histological examination revealed an intrapulmonary solitary fibrous tumor.

revealed on chest X-ray during preparation for ergometric cardiac testing. On chest computed tomography, an abnormal nodule about 13 cm in the largest diameter in the lower right lung lobe was detected. There was no mediastinal and hilar lymphadenopathy. The patient did not have a history of cough, shortness of breath, chest pain, fever, loss of weight and appetite, smoking, drinking alcohol, nor prior malignancy. Her past medical history revealed hypertension and hypertensive cardiomyopathy. Clinical and imaging studies did not reveal evidence of tumor elsewhere.

A diagnostic transthoracic fine needle aspiration cytology was performed, and cytological analysis showed a moderately cellular smear with the presence of small, oval-to-polygonal cells with uniform bland nuclei and scant cytoplasm, as well as rare spindle cells with moderately abundant pale cytoplasm and fusiform nuclei suspicious for spindle cell tumor (Figure 1). The patient was referred to the Department for Thoracic Surgery, where right anterolateral thoracotomy with right lower lobectomy was performed.

On gross examination, lower right lobe was almost completely replaced with abnormal, white-yellow, well-demarcated solid nodule measuring 13.5 cm in its largest diameter, surrounded with a pseudocapsule (Figure 2). The nodule was not attached to the overlying slightly thickened and whitish visceral pleura.

CASE REPORT

A 63-year-old woman was admitted to hospital after a large, well-circumscribed mass was

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Correspondence to:

Aleksandra LOVRENSKI
Doža Đerđa 17
21000 Novi Sad
Serbia
aleksandra.lovrenski@mf.uns.ac.rs

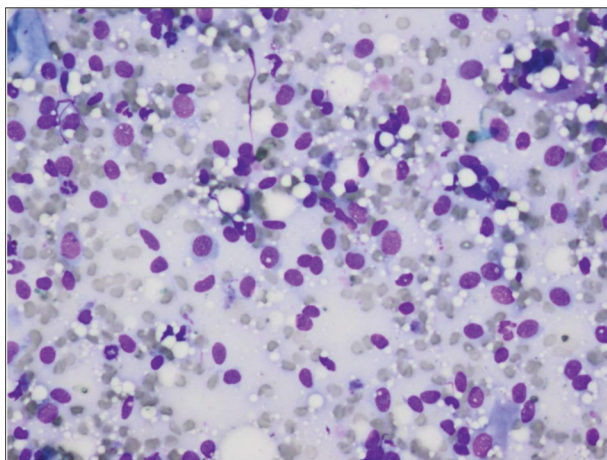


Figure 1. Fine needle aspiration cytology – moderately cellular smear composed of small, oval-to-polygonal cells with uniform bland nuclei and scant cytoplasm, as well as sparse spindle cell population with fusiform basophilic nuclei with no nucleoli

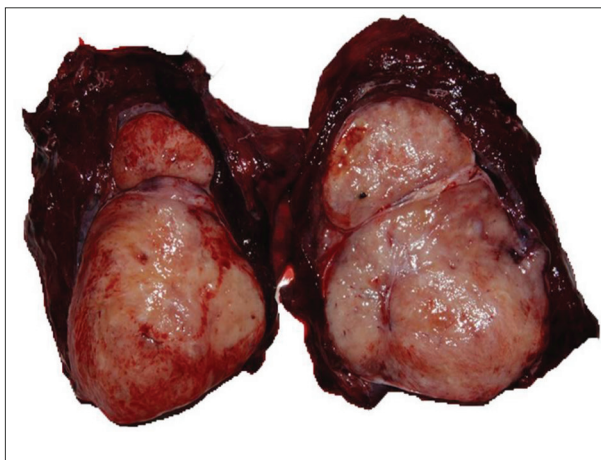


Figure 2. Right lower lobectomy – a white-yellow, well-demarcated solid nodule surrounded with pseudocapsule and without abutting visceral pleura

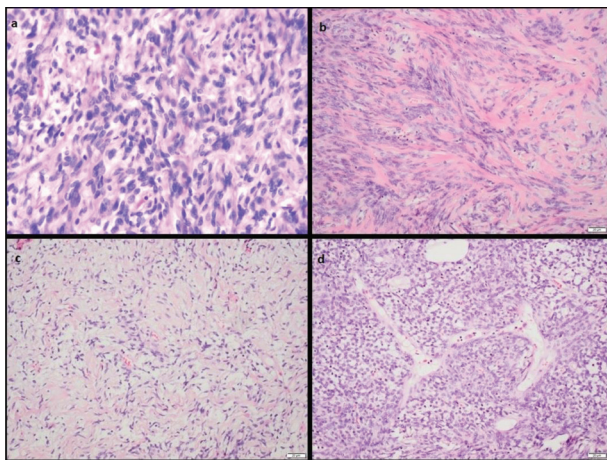


Figure 3. a) Hypercellular tumor tissue composed of spindle-to-oval-shaped cells arranged in a "patternless pattern" with elongated, somewhat overlapping nuclei; b) focal areas with dense hyalinized "ropy" stromal collagen; c) myxoid changes within the stroma, and d) branched, "staghorn-like" blood vessels

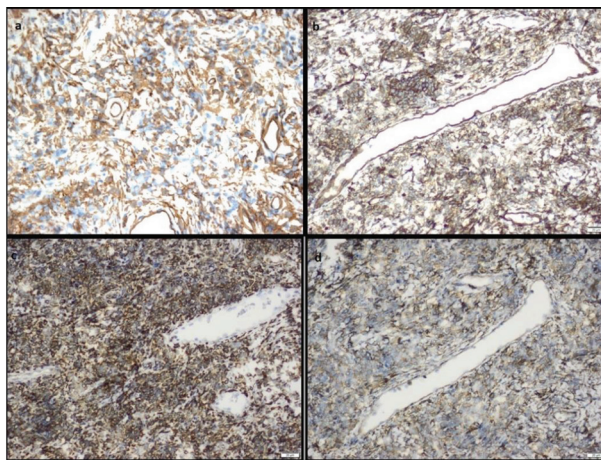


Figure 4. Positivity of tumor cells for a) vimentin; b) CD34; c) bcl-2, and d) CD99

Histological examination revealed a hypercellular tumor tissue, composed of spindle-to-oval-shaped cells with elongated nuclei with tapered ends and without prominent nucleoli. The tumor cells showed overlapping with a fascicular and "patternless pattern" appearance. Focal areas displayed dense hyalinized "ropy" stromal collagen, while others showed myxoid changes in the stroma. Blood vessels were branched, "staghorn-like," focally with thickened and hyalinized walls. Some of the tumor cells showed mild atypia. No mitotic figures or necrosis were seen (Figure 3).

Immunohistochemically, the tumor cells showed diffuse positivity for vimentin, CD34, bcl-2 and CD99 (Figure 4), and negative reaction for EMA, SMA, desmin, and S-100.

The final diagnosis was an intrapulmonary solitary fibrous tumor of low malignant potential. Due to the presence of unfavorable prognostic parameters (tumor size as well as the presence of hypercellularity), more frequent follow-up was recommended. Eighteen months after surgery, the patient has been feeling well with no evidence of tumor recurrence.

DISCUSSION

Solitary fibrous tumors are uncommon soft tissue tumors that mostly arise within the thorax, where more than 80% all of cases originate from the visceral pleura. For many years, SFTs were believed to be restricted to the pleura, but after implementation of immunohistochemistry in everyday work and demonstration of CD34 immunoreactivity in these tumors (tumor cells in these tumors correspond to a distinctive subset of fibroblasts characterized by CD34-positivity and the presence of elongated, dendritic cytoplasmic processes), extrapleural SFTs started to become recognized [2, 3]. These tumors may occur in various anatomical sites, including the head, neck, breast, abdomen, pelvis, extremities, as well as within the lung parenchyma, when it is termed an intrapulmonary SFT. This tumor may derive from the invagination of the visceral pleura, from interlobar septal connective tissue, or from pulmonary parenchymal fibroblasts [4].

Most of these tumors behave as slow-growing neoplasms. More than 50% of the patients with an intrapulmonary SFT are asymptomatic, but organ compression by the tumor sometimes result in chest pain, cough, fever, and dyspnea. One of the most prominent clinical features is hyperinsulinism. Patients usually present with severe hypoglycemia caused by production of insulin-like growth factor released by large tumors, as a part of paraneoplastic syndrome [4, 5]. Our patient was completely asymptomatic, without any clinical signs present at the time of diagnosis.

The detection of these tumors is often incidental and the definitive diagnosis requires an integrated approach including clinical, histological, immunohistochemical, and molecular findings [4, 6].

The use of fine needle aspiration cytology highly improves the management of soft tissue tumors. Microscopic examination usually shows moderately cellular smears composed of small, oval-to-polygonal-shaped elements with uniform bland nuclei, evenly distributed and finely granular chromatin, and scant cytoplasm. When a spindle cell population is present in the sample, the spindle cells have pale and relatively well-defined cytoplasm and fusiform or ovoid and basophilic nuclei with finely dispersed chromatin and without nucleoli. The cells are widely dispersed separately, but smears usually contain some irregular, loose aggregates of cells enmeshed in a collagenous matrix. The background contains irregular ropy fragments of collagen and a few inflammatory elements [7].

Histologically, they typically display zones of both hypercellular and hypocellular collagenized stroma in a so-called "patternless" architecture, focal zones of myxoid changes within tumor stroma and branched hemangiopericytoma-like blood vessels, which are all in accordance with our case [8]. However, these tumors can show tremendous degree of variability in histologic growth patterns, including fascicular, storiform, herringbone, neural-like, angiofibromatous, etc. [1, 2].

Immunohistochemistry is the most important method used to differentiate SFTs from spindle cell carcinoma, melanoma, sarcomatoid mesothelioma, peripheral nerve sheath tumors, sclerotic and cellular variant of sclerosing pneumocytoma, and a wide variety of primary and metastatic soft-tissue neoplasms, including thymic neoplasms and lymphomas [1, 3, 9]. Specifically, CD34 is positive in most SFTs, although CD34 positivity can be seen in a variety of other spindle cell neoplasms as well as in non-spindle cell lesions. On the other hand, recent studies have demonstrated that this marker may not be expressed in SFTs in up to 40% of cases. One should always keep in mind that in the appropriate context, positive staining for CD34 support a diagnosis of SFT, while negative staining does not rule it out [4, 5, 10]. Other markers which exhibit positivity in these SFTs are bcl-2 and CD99; however, these markers are also not specific and can be positive with many other tumors. These neoplasms are generally vimentin-positive and negative for epithelial markers (epithelial membrane antigen, cytokeratins), smooth muscle markers (actin, desmin), neural markers (S-100, neuron-specific enolase) and other specific markers of differentiation [1, 10]. Recent

molecular studies showed intrachromosomal rearrangement on chromosome 12q13 due to paracentric inversion of two overlapping genes, *NAB2* and *STAT6*, producing a *NAB2/STAT6* fusion gene. This fusion can be demonstrated using commercially available STAT6 monoclonal antibody, which is, at the moment, the most specific and highly sensitive marker for diagnosing this tumor [11, 12].

Although SFTs are tumors with a benign course, about 10–20% of them are locally aggressive or malignant. There are no unanimous criteria of malignancy for these tumors. Therefore, it is not always easy to make differential diagnosis between benign and malignant SFTs. A malignant SFT is usually characterized by the presence of infiltrative margins, large size (usually over 10 cm), pleomorphism, hypercellularity, mitotic index $> 4/10$ high-power field (HPF), necrosis, hemorrhage and stromal or vascular invasion [7, 10]. According to England et al. [13], the criteria for malignancy are hypercellularity, pleomorphism and overlapping of nuclei, the presence of necrosis or hemorrhage, and more than four mitoses per 10 HPF. However, only 55% of SFTs with these characteristics showed aggressiveness in the form of infiltration, recurrence, and metastasis [13]. Vallat-Decouvelaere et al. [14] found that the histological characteristics of SFTs were not always consistent with their behavior, showing that there are SFTs that have exhibited invasion of bone and chest soft tissue structures and recurrence, without fulfilling any of the abovementioned criteria for malignancy. On the other hand, Fletcher [15], one of the greatest names in modern pathology, believes that only the presence of more than four mitoses per 10 HPF can be considered a valid criterion for malignancy.

The clinical, histological, and immunohistochemical features do not appear to differ between pleural SFTs and intrapulmonary SFTs. The malignancy rate of an intrapulmonary SFT is reportedly 12.5%, although the precise rate is difficult to determine because of the small number of patients diagnosed with an intrapulmonary SFT [7].

Since primary intrapulmonary SFT is a relatively rare condition, a small number of case reports and case series has been reported in the literature [16–19]. The largest series ever reported were published by Rao et al [19]. In their study of 24 cases of intrapulmonary SFTs, the patients' ages ranged 44–83 years (mean being 58 years), and none of the patients had a history or evidence of a similar tumor in another location. The tumors ranged in size 2.3–22 cm in the greatest diameter (mean being 8.5 cm). They were histologically classified as low, intermediate, and high-grade lesions based on the degree of cytologic atypia, nuclear pleomorphism, necrosis, and mitotic activity [19]. As in our case, 21 cases showed features of a solitary fibrous tumor of low malignant potential with low mitotic activity (< 5 mitoses per 10 HPF), the absence of cytological atypia, nuclear pleomorphism, and necrosis. One case showed intermediate malignant potential (increased cellularity with plump, pleomorphic nuclei, and 5–10 mitoses per 10 HPF), while two cases showed high grade malignant potential (presence of areas resembling a pleomorphic high-grade sarcoma admixed with foci of conventional, low-grade SFT). Clinical follow-up in

18 patients showed that 14 were alive and well without evidence of disease from one month to 14 years after the initial diagnosis. Three patients died within seven years after surgery; one patient had a tumor with high-grade malignant potential, and in the other two, the initial tumor had been of low-grade malignant potential, but the recurrences and/or metastases showed a transformation to a high-grade tumor. This study indicated that beside tumors with obviously malignant features, tumors with low-grade malignant potential can behave in an aggressive manner, and that in many cases morphology cannot be a reliable predictor of tumor behavior [19].

In conclusion, intrapulmonary SFTs can present a challenge for diagnosis, because of their variegated histology

and variability of growth patterns due to which these tumors can resemble other soft tissue tumors. A helpful feature of intrapulmonary SFTs, which distinguishes these tumors from other soft tissue tumors, is the fact that an admixture of different growth patterns is usually present. Therefore, in samples taken from different areas of the lesion, the tumor may show variable histologic appearance. The treatment of choice is complete excision with clear margins and with additional chemotherapy and radiotherapy for metastatic or locally recurrent tumors. These tumors have unpredictable clinical behavior, so the patients need a long-term follow-up.

Conflict of Interest: None declared.

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Интрапулмонални солитарни фиброзни тумор

Александра Ловренски, Александра Илић, Иван Кухајда, Драгана Тегелтија, Јован Ловренски
Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија

САЖЕТАК

Увод Солитарни фиброзни тумор је неоплазма која најчешће води порекло из плеуре, али се може јавити и у другим органима. Интрапулмонални солитарни фиброзни тумор је редак ентитет, недовољно описан у медицинској литератури.

Приказ болесника Приказујемо случај болеснице старе 63 године код које је случајно током припреме за ергометријско испитивање на рендгену плућа откривена велика, добро ограничена туморска формација. Компјутеризованом томографијом грудног коша описана је туморска промена доњег десног режња, без присутне медијастиналне или хиларне лимфаденомегије. Цитолошком анализом материјала добијеног трансторакалном пункцијом постављена је сумња на вретенастоћелијски тумор, после чега је изведена десна антеролатерална торакотомија са десном доњом лобектомијом. Макроскопски, десни доњи режањ је скоро потпуно био замењен беложутим, солидним туморским тки-

вом окруженим псеудокапсулом, највећег промера 13,5 *cm*. Хистолошким прегледом и имунохистохемијском анализом постављена је дијагноза интрапулмоналног солитарног фиброзног тумора са малом могућношћу малигнитета. Због присуства неповољних прогностичких параметара (величине тумора и хиперцелуларности), препоручене су чешће контроле. Годину и по дана после операције болесница се добро осећа и нема знакове рецидива болести.

Закључак Интрапулмонални солитарни фиброзни тумор је ретка неоплазма која због шаролике хистолошке слике може да имитира друге мекоткивне туморе, те представља значајан дијагностички изазов. Императив у лечењу је комплетна ексцизија тумора, али с обзиром на то да морфолошка слика није поуздан претсказатељ понашања тумора, неопходне су редовне и доживотне контроле.

Кључне речи: солитарни фиброзни тумор; интрапулмонални; дијагноза; цитологија; имунохистохемија

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Spermatic cord angiomyolipoma misdiagnosed as inguinoscrotal hernia

Goran Aleksandrić¹, Vuk Aleksić², Perica Jockić³, Zorana Bokun⁴¹Zemun Clinical Hospital Center, Surgery Department, Belgrade, Serbia;²Zemun Clinical Hospital Center, Neurosurgery Department, Belgrade, Serbia;³Zemun Clinical Hospital Center, Urology Department, Belgrade, Serbia;⁴Zemun Clinical Hospital Center, Pathology Department, Belgrade, Serbia**SUMMARY**

Introduction Angiomyolipomas represent neoplasms of mesenchymal origin, made up of abnormal thick-walled blood vessels, smooth spindle muscle cells, and mature adipose cells. The most common site of origin are kidneys, and other localizations are extremely rare. We represent a case of a spermatic cord angiomyolipoma misdiagnosed as incarcerated inguinoscrotal hernia, and to our prudence this is second described case of an angiomyolipoma localized in the spermatic cord.

Case outline We present a case of a 63-year-old man presented with high fever and difficulty in walking due to pain and swelling in the right groin. According to the clinical examination and laboratory tests, presumptive diagnosis was incarcerated inguinoscrotal hernia, so the patient was immediately operated on. The exploration of the inguinal canal showed a tumorous mass, 9 × 9 cm in size, with the origin from the spermatic cord, so radical inguinal orchiectomy was performed with the removal of the tumor mass. Histopathological and immunohistochemistry examination suggested angiomyolipoma of the spermatic cord. The postoperative course was uneventful.

Conclusion Although rare, an angiomyolipoma of the spermatic cord must be included in the differential diagnosis of scrotal masses. Also, we advocate additional diagnostic procedures (ultrasound or computed tomography) for every inguinoscrotal mass before undertaking surgery, since a variety of different causes can be found. After definitive angiomyolipoma diagnosis is obtained, further investigation is needed, especially brain computed tomography due to possible tuberous sclerosis coexistence.

Keywords: angiomyolipoma; extrarenal neoplasm; spermatic cord tumor

INTRODUCTION

Angiomyolipomas (AML) are neoplasms of mesenchymal origin, made up of abnormal thick-walled blood vessels, smooth spindle muscle cells, and mature adipose cells, probably derived from perivascular epithelioid cells [1]. The kidneys are the most common site of origin, and AML represent the most usual benign resectable kidney tumors [2]. Other localizations are exceedingly uncommon [3].

We present a rare case of a spermatic cord AML misdiagnosed as incarcerated inguinoscrotal hernia.

CASE REPORT

We present a case of a 63-year-old man presented to our general surgery emergency department with high fever and difficulty in walking due to pain in the right groin for a few days. The clinical examination revealed irreducible inguinoscrotal swelling on the right side and tenderness to touch, measuring about 6 × 4 cm with overlying erythematous skin changes. The patient noticed an inguinal mass about one year ago, but without any other symptoms. Laboratory tests

showed leukocytosis (14,200 leukocytes/ μ L). Presumptive diagnosis was of an incarcerated inguinoscrotal hernia. The patient's medical history was significant for type 2 diabetes mellitus and arterial hypertension. The patient was immediately taken to the operating room. Surgery started with a right inguinal approach. The exploration of the inguinal canal was performed. The spermatic cord was dissected and showed a tumorous mass that was 9 × 9 cm in size. The urologist was immediately called to the operating room, and radical inguinal orchiectomy was performed, with high ligation of the right cord and removal of the entire tumor mass. Posterior inguinal wall weakness was observed and the defect was repaired using the Bassini technique. Postoperative histopathological examination (Figure 1) and immunohistochemistry (Figure 2) suggested an angiomyolipoma of the spermatic cord. After surgery, whole-body computed tomography (CT) was performed in order to exclude other tumors, and all findings were normal. Also, serum tumor markers (lactate dehydrogenase, alpha-fetoprotein, and beta human chorionic gonadotropin) were within normal limits. The postoperative course was uneventful and the patient was discharged on the fifth postoperative day.

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Vuk ALEKSIĆ
Department of Neurosurgery
Zemun Clinical Hospital Center
Vukova 9
11080 Belgrade
Serbia
aleksicvuk@hotmail.com

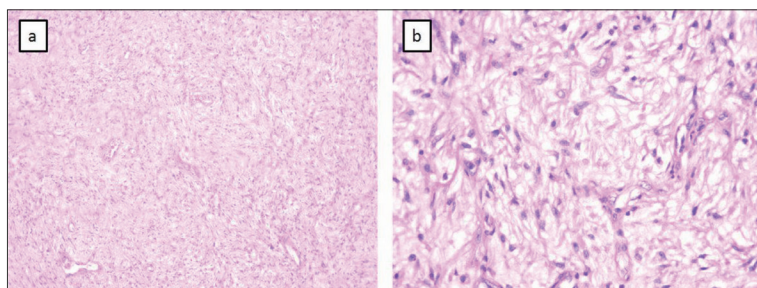


Figure 1. H&E staining, magnification: (a) $\times 40$, (b) $\times 400$

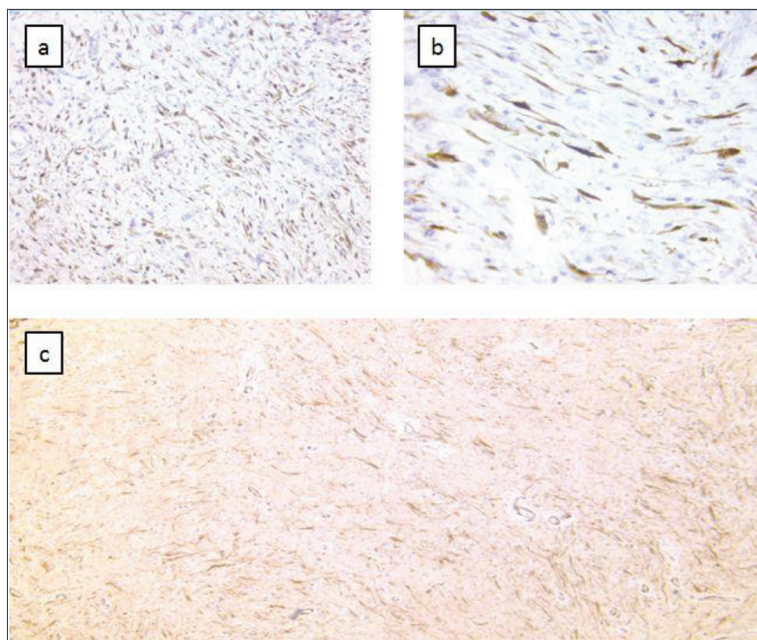


Figure 2. Immunohistochemical staining: (a) CDK4 $\times 400$; (b) p16 $\times 400$; (c) alpha-SMA $\times 100$

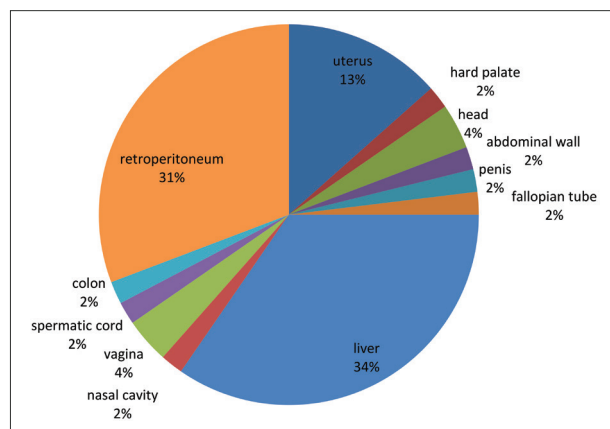


Figure 3. Extrarenal localization of AML according to Minja et al. [3]

DISCUSSION

AML are rare benign neoplasms that usually occur in the kidneys, and account for 1% of all renal masses. Extrarenal localization of AML is exceedingly uncommon [4]. After kidneys, the liver and the skin are the next most common sites of AML origin. Minja et al. [3] conducted a literature review in 2012 and found only 52 cases of AML with extrarenal localization. Summarized findings of the Minja

et al. [3] review are given in Figure 3. The liver localization was the most common (18 cases), followed by the uterus (seven cases), and retroperitoneum (four cases). Out of all presented cases, only one patient had a spermatic cord AML (3), i.e. in 1989 this case was described by Castillenti and Bertin [5]. According to our knowledge, our case is the second AML located in the spermatic cord.

AML are previously thought to be hamartomatous lesions. It is now known that AML arise from the perivascular epithelioid cells (PEC) and belong to a family of tumors named "PEComas." These tumors show phenotypic (smooth muscle, epithelioid, and lipid-rich histology), and immunohistochemical coexpression of myogenic (smooth muscle actin) and melanocytic (HMB-45, melan A, microphthalmia transcription factor, tyrosinase) modulation. In other words, pathohistological findings of AML typically tend to have triphasic features: myoid spindle cells, islands of fat tissue, and dysmorphic blood vessels that have thick walls and do not have elastic lamina [6, 7]. In AML immunohistochemical studies show positive staining for various markers such as MART1/Melan-A, muscle-specific actin (HHF35), HBM45, calponin, NKI-C3. Also, AML tend to be negative for renin and keratin [6, 8]. In our case, histopathological and immunohistochemical examination revealed typical AML. On the other hand,

scrotal region tumors are mostly testicular germ cell tumors, which are associated with an increase in serum tumor markers. Since in our case the tumor grew from the spermatic cord, before obtaining definitive diagnosis by histopathology, our assumption was that germ cell tumor is the probable diagnosis. However, the tumor markers were within the normal range. Since AML represents a rare entity which can be clinically present in many guises, a pathohistological and especially an immunohistochemical examination are the gold standard in the definitive diagnosis of AML.

Extrarenal retroperitoneal AML may present in a variety of ways, such as incidental radiological finding, abdominal pain, loin and back pain, feeling of fullness in the abdomen, diffuse pain and bleeding, hematuria, vomiting, constipation, weight loss, abdominal mass [6]. Pain in the right groin, high fever, and a local finding indicative of incarcerated inguinoscrotal hernia were present in our patient. Thus, AML of extrarenal localization can appear in many possible scenarios and diagnosis prior to obtaining a pathohistological finding is almost impossible.

According to Minja et al. [3], CT scan is the commonest used radiologic technique in the investigation of AML. Also, brain CT is recommended in patients with AMS, because about 40% of them have CT features of tuberos sclerosis [6]. High proportion of fat content, which is

found in the majority of AML, produces a characteristic pattern on CT scan. Variants of AML with poor fat content (about 5% of cases) or cystic AML, as well as atypical (epithelioid or monophasic) AML may present diagnostic challenges on radiological studies, and in such cases, it is very difficult to distinguish an AML from a renal cell carcinoma. This is also case in the patients with tuberous sclerosis coexistence, where up to one third of patients do not demonstrate macroscopic fat on CT. Also, calcifications are rare in AML [9]. MR imaging is excellent at evaluating lesions containing fat tissue, and two main sequences are used. First, fat saturated sequences demonstrate high signal intensity on non-fat-saturated sequences and loss of signal following saturation of fat. The second technique is to use in-phase and out-of-phase imaging which generates "India ink artifact" at the interface between fat and non-fat components. This can occur either at the interface between the AML and surrounding tissue or between fat and other components of the tumor [10]. Also, AML are hypervascular lesions demonstrating often characteristic findings on angiography images: a sharply marginated hypervascular lesion with a dense arterial network, with tortuous vessels (arterial phase), spiral "onion peel" appearance of peripheral vessels (venous phase), absent arteriovenous shunting, and intraumoral aneurysms [11]. In our case preoperative diagnosis was not performed because of the patient's general state and pernicious local finding, so patient was immediately taken to operating room. However, postoperatively we performed whole-body CT including brain CT scan, and all findings were normal.

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Ангиомиолипом сперматичне врпце погрешно дијагностикован као ингвиноскротална кила

Горан Александрић¹, Вук Алексић², Перица Јоцкић³, Зорана Бокун⁴

¹Клиничко-болнички центар Земун, Служба хирургије, Београд, Србија;

²Клиничко-болнички центар Земун, Служба неурохирургије, Београд, Србија;

³Клиничко-болнички центар Земун, Служба урологије, Београд, Србија;

⁴Клиничко-болнички центар Земун, Служба патологије, Београд, Србија

САЖЕТАК

Увод Ангиомиолиполи представљају туморе мезенхимног порекла састављене од абнормалних крвних судова дебелих зидова, глатких мишићних ћелија и зрих масних ћелија. Најчешће настају у бубрезима, а друге локализације су изузетно ретке. Приказујемо случај ангиомиолиполима сперматичне врпце погрешно дијагностикованог као укљештена ингвиноскротална кила; по нашем сазнању, ово је други описани случај ангиомиолиполима ове локализације.

Приказ болесника Приказујемо случај мушкарца старог 63 године који се јавио у нашу установу због повишене телесне температуре и отежаног хода услед бола и отока у десној препони. Према клиничком налазу и лабораторијским претрагама претпостављена дијагноза била је укљештена ингвиноскротална кила и болесник је хитно оперисан. Експлорацијом ингвиналног канала уочена је туморска маса димензија 9 × 9 cm порекла сперматичне врпце, због чега

је учињена радикална ингвинална орхиектомија са уклањањем целе туморске масе. Хистопатолошки и имунохистохемијски налаз су указали на ангиомиолипому сперматичне врпце. Постоперативни ток је протекао уредно.

Закључак Иако ретки, ангиомиолиполи сперматичне врпце морају бити укључени у диференцијалну дијагнозу тумефакција у ингвиноскроталној регији. Такође сматрамо да би обављање допунских дијагностичких процедура (ултразвучни преглед или компјутеризована томографија) било значајно пре оперативног захвата, јер се могу наћи различити патолошки супстрати. После постављања дефинитивне дијагнозе ангиомиолиполима потребна је даља дијагностика, а посебно компјутеризована томографија мозга, због могуће коегзистенције ангиомиолиполима и туберозне склерозе.

Кључне речи: ангиомиолиполи; екстрауренални тумори; тумор сперматичне врпце

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

18F-FDG PET/CT “hepatic superscan” in incomplete Carney triad

Ljiljana Zivgarević, Nebojša Kozarević, Svetlana Žunić

Clinical Center of Serbia, Center of Nuclear Medicine, National PET Center, Belgrade, Serbia

**SUMMARY**

Introduction Carney triad is a rare non-hereditary condition characterized by gastrointestinal stromal tumors – intramural mesenchymal tumors of the gastrointestinal tract with neuronal or neural crest cell origin, pulmonary chondromas, and extra-adrenal paragangliomas. The term incomplete Carney triad more precisely refers to the occurrence of at least two of these tumor types. Carney triad named after J. Aidan Carney is considered to be a specific type of multiple endocrine neoplasia. Less than 30 cases of complete and less than 100 cases of incomplete Carney triad have been reported worldwide. Carney triad primarily affects young women (mean age of onset of 20 years).

Case outline A 35-year-old female patient had an initial presentation at the National PET Center, Clinical Center of Serbia, after the gastrectomy, with multiple hepatic metastases as well as bilateral pulmonary chondromas. 18F-FDG PET/CT scan revealed the following: 1) intense 18F-FDG uptake in the liver metastatic lesions, with reduced physiological activity in the brain and heart, bowel, and renal tracer uptakes commonly known as FDG hepatic superscan; 2) multiple irregular-shaped lesions, mostly calcified in bilateral pulmonary parenchyma; 3) a nodular lesion in the left adrenal gland with accumulation of 18F-FDG in its anterior part.

Conclusion The present study describes a hepatic superscan in a patient with incomplete Carney triad, including gastrointestinal stromal tumors and pulmonary bilateral chondromas, as well as a tumor in the left adrenal gland.

Keywords: GIST; 18F-FDG PET/CT; hepatic superscan; Carney triad; tartrate-resistant acid phosphatase

INTRODUCTION

Carney triad was first described by Carney et al. [1] in 1977. This medical entity [the triad of paragangliomas, gastrointestinal stromal tumors (GISTs) and pulmonary chondromas] named Carney triad was latter distinguished from the dyad of paragangliomas and gastric stromal sarcomas (Carney-Stratakis syndrome) [2]. Carney triad belongs to the group of rare diseases [3, 4]. GISTs are generally Kit (CD117)-positive, mesenchymal tumors of the gastrointestinal tract [5].

The molecular basis of GIST is important for the understanding of GIST biology [6].

GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract with malignant potential. They can be associated with synchronous tumors of different histogenesis, although uncommonly [7]. In some cases, these tumors can be neuroendocrine in origin [8].

According to the publication of Ignjatović [9], about 55% of GISTs had malignant behavior. Correct diagnosis of GIST was based on immunohistochemical studies and biological behavior upon the clinicopathological parameters in 90% of the cases [9].

We report the visualization of an incomplete Carney triad in 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography – computed tomography (PET/CT) study in GIST postoperative phase and try to understand the

anticipated coexpression of tartrate-resistant acid phosphatase in different organs, as they are liver and lungs.

CASE REPORT

A 35-year-old female patient had an initial presentation at the National PET Center, Clinical Center of Serbia. Her medical history revealed a GIST diagnosed in 1989 and followed up with surgery (subtotal gastrectomy at the age of eight years, as well as total gastrectomy at the age of 23 years). The disease worsened in spite of surgery and chemotherapy and a recent clinical examination showed multiple hepatic metastases and bilateral pulmonary chondromas.

After the patient's fasting six hours before the PET/CT study, and the median cubital vein cannulation, injection dose of 200 MBq 18F-FDG was applied, followed by a 90-minute data acquisition. 18F-FDG PET/CT examination on a 64-slice hybrid PET/CT scanner (Biograph; Siemens Medical Solutions USA, Inc., Malvern, PA, USA) was performed 90 minutes after tracer application. A three-dimensional PET scan (three minutes per bed position) and low-dose non-enhanced CT scan was acquired from the base of the skull to the mid-thigh. Multidetector CT was acquired with 120 kV and with automatic, real-time dose modulation amperage [CareDose4D (Siemens Healthcare GmbH,

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Correspondence to:

Ljiljana ZIVGAREVIĆ
Clinical Center of Serbia
National PET Center
Višegradska 26
11000 Belgrade, Serbia
ljzivgarevic@gmail.com

Erlangen, Germany], with the baseline being 45 mA) (slice thickness of 5 mm, the pitch of 1.5, and a rotation time of 0.5 s). CT, PET (attenuation-corrected), and combined PET/CT images were displayed for analysis on a single Multimodality Workplace (Siemens Healthcare GmbH).

The study revealed elevated right semi-diaphragm with heart dislocation to the left hemithorax (Figure 1).

There are multiple irregular-shaped lesions in bilateral pulmonary parenchyma, mostly calcified, partially consisting of a soft component, without increased uptake of 18F-FDG: 1) a single calcified (616 HU) lesion with a 13 × 12 × 16 mm diameter (AP × LL × KK) in the apical segment of the upper lobe of the right lung; 2) calcified (814 HU) lesion, soft tissue (57 HU), lesion diameter 36 × 33 × 33 mm (AP × LL × KK), perivascular paratracheal right at the Th3/Th4 level; 3) a single calcified lesion (540 HU), soft tissue (44 HU), lesion diameter 25 × 25 × 41 mm (AP × LL × KK) in the anterior segment of the upper lobe of the right lung; 4) a single calcified lesion (831 HU), soft tissue (71 HU), lesion diameter 35 × 30 × 23 mm (AP × LL × KK) in a lateral segment of the middle lobe of the right lung; 5) a single calcified lesion (652 HU), soft tissue (57 HU), lesion diameter 20 × 18 × 18 mm (AP × LL × KK) in the anterobasal segment of the low lobe of the left lung (Figure 2).

Augmented liver 20 × 24 × 27 cm (AP × LL × KK) contained multiple single and confluent hypodense lesions with intense uptake of 18F-FDG (SUVmax 27) and lesions without any uptake of 18F-FDG reflecting areas of necrosis in the “hepatic superscan” (Figure 1c, Figure 3).

There was a nodular lesion 30 × 12 mm in size (AP × LL) with intense accumulation of 18F-FDG (SUVmax 21) near the medial contour of the anterior part of the spleen (Figure 4).

The right kidney was dislocated caudally (level L3/L5) (Figure 3B). There was a nodular lesion diameter 31 × 16 × 21 mm (AP × LL × KK) in the left adrenal gland with accumulation 18F-FDG (SUVmax 3.1), in the anterior part of the nodular lesion (Figure 5).

Diffuse intense 18F-FDG uptake in the liver on PET, with reduced physiological activity in the brain and heart, bowel, and renal tracer uptakes is commonly known as FDG hepatic superscan (Figure 1c) [10, 11].

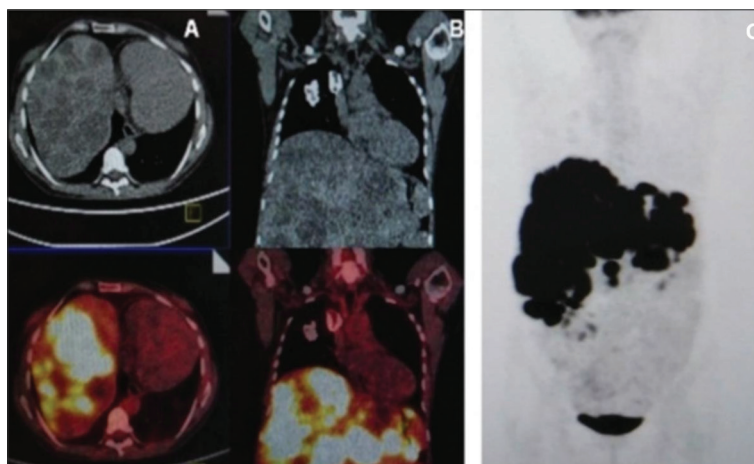


Figure 1. A – axial CT, fused PET/CT; B – coronal CT, fused PET/CT; C – (maximum intensity projection) PET images of elevated right semi-diaphragm with heart dislocation to the left hemithorax

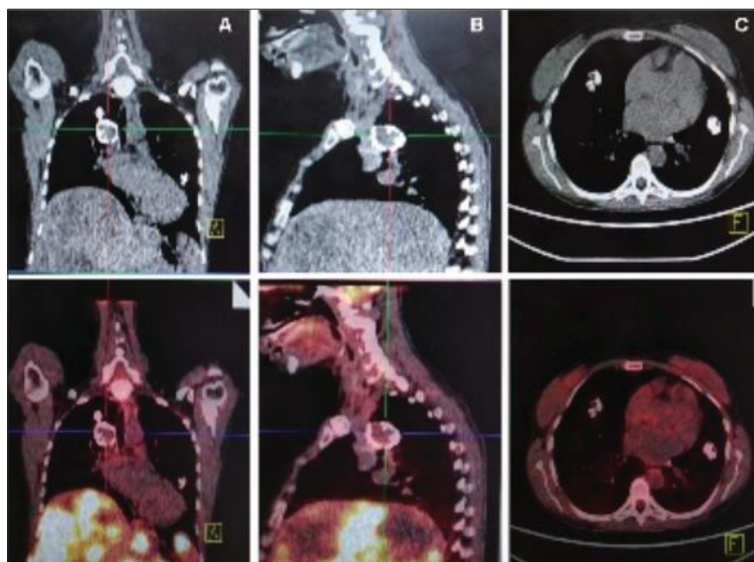


Figure 2. A – coronal, B – sagittal, C – axial CT, fused PET/CT (mediastinal window) images of bilateral pulmonary chondromas

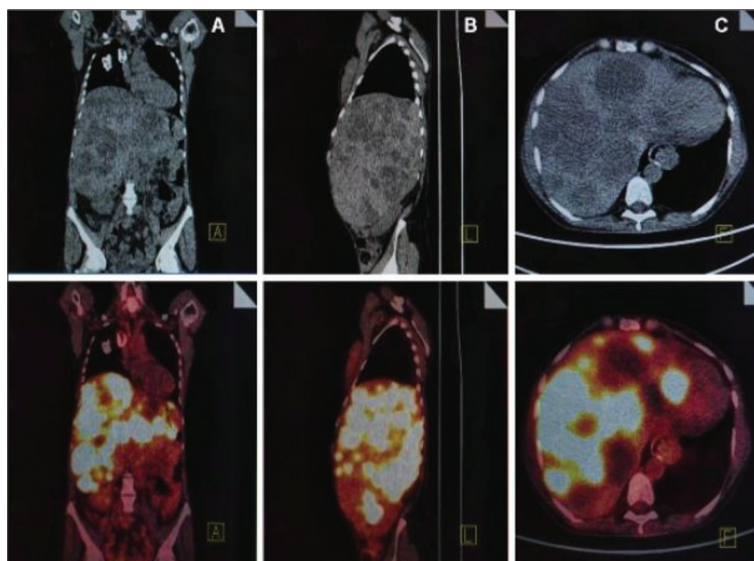


Figure 3. A – Coronal, B – Sagittal, C – Axial CT, fused PET/CT images of multiple single and confluent hypodense lesions with intense uptake of 18F-FDG; lesions without any uptake of 18F-FDG show areas of necrosis in the hepatic superscan image

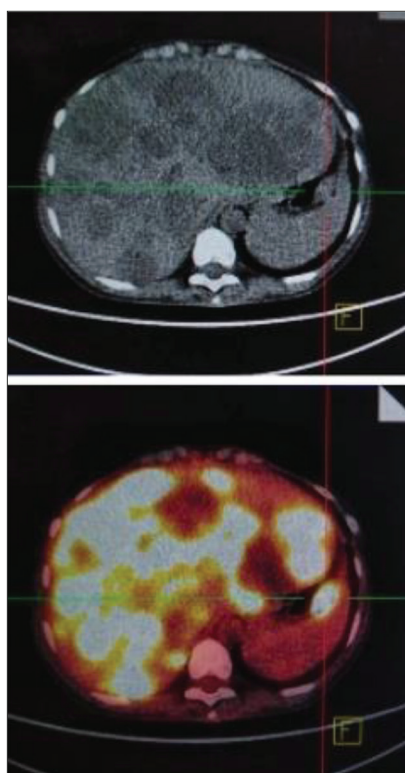


Figure 4. Axial CT, fused PET/CT images of the nodular lesion near the medial contour of the anterior part of the spleen with intense uptake of 18F-FDG

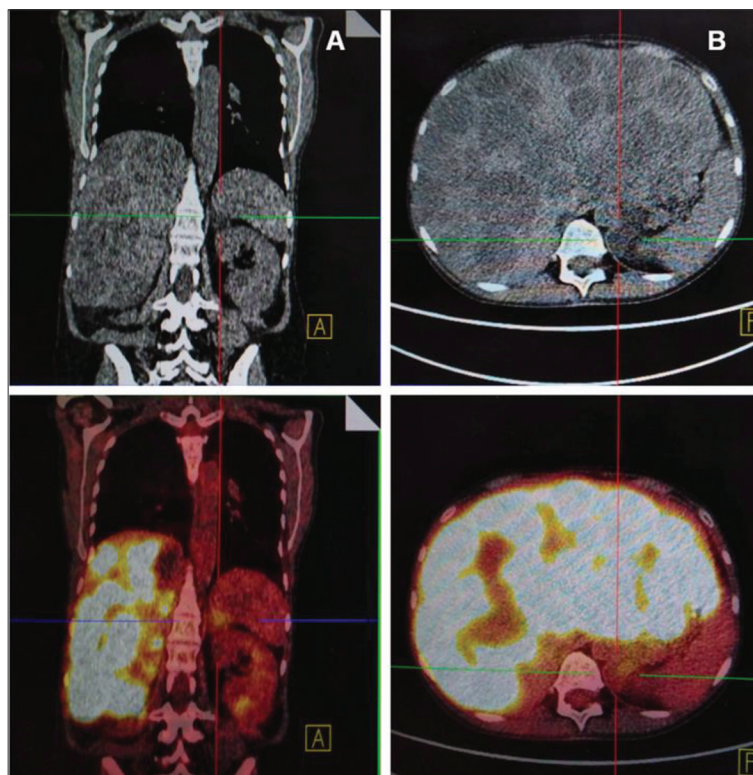


Figure 5. A – Coronal, B – Axial CT, fused PET/CT images of the nodular lesion in the left adrenal gland with accumulation of 18F-FDG in the anterior part of the nodular lesion

DISCUSSION

Multiple neoplasia syndromes are often considered with the presentation of multiple rare primary tumors in young patients. It is important to recognize the possibility of other primary tumors when associated neoplasms are detected [12]. The term Carney triad refers to the occurrence of at least two of the following tumor types: GIST, pulmonary chondroma, extra-adrenal paraganglioma. In a small percentage of affected patients, adrenocortical adenoma (a benign tumor of the adrenal gland) or esophageal leiomyoma (a benign tumor of the esophagus) may also occur [13]. The Carney triad is an extremely rare syndrome, with fewer than 30 cases reported with all three tumors present, and fewer than 100 incomplete cases having two of the three tumor types present [13]. According to Carney in 1999, chondromas developed in 76% of patients [13].

The present report describes the patient with incomplete Carney triad, including GIST and pulmonary bilateral pulmonary chondromas, as well as the tumor in the left adrenal gland. This is a demonstration of the 18F-FDG PET/CT utility in diagnosis / differential diagnosis in some of the rare diseases. The hepatic superscan was demonstrated in the reported case of an incomplete Carney triad.

The multiorgan (liver, lungs) molecular coexpression of tartrate-resistant acid phosphatase (TRAP) in immunocytes

belonging to monocyte/macrophage lineage should be anticipated as of importance in the pathogenesis of this clinical case. Physiologically, TRAP is primarily a cytochemical marker of macrophages, osteoclasts, and dendritic cells [14]. Under normal circumstances, TRAP is highly expressed by osteoclasts, activated macrophages, neurons, and by the porcine endometrium during pregnancy [15, 16]. In newborn rats, TRAP is also detectable in the spleen, thymus, liver, kidneys, skin, lung, and heart at low levels. TRAP expression is increased in certain pathological conditions. These include leukemic reticuloendotheliosis (hairy cell leukemia), Gaucher's disease, HIV-induced encephalopathy, osteoclastoma and osteoporosis, and metabolic bone diseases (available at https://en.wikipedia.org/wiki/Tartrate-resistant_acid_phosphatase).

TRAP is a glycosylated monomeric metalloprotein enzyme expressed in mammals and characteristic for its expression in activated osteoclasts and macrophages and was proposed as a driver of metastasis and was associated with clinically relevant parameters of cancer progression and cancer aggressiveness [17, 18].

The coexistence of an adrenal tumor with incomplete Carney triad indicates possible neuroendocrine origin and inclusion in multiple endocrine neoplasia syndromes.

Conflict of interest: None declared.

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Суперскен јетре 18F-FDG PET/CT у некомплетној Карнијевој тријади

Љиљана Зивгаревић, Небојша Козаревић, Светлана Жунић

Клинички центар Србије, Центар за нуклеарну медицину, Национални ПЕТ центар, Београд, Србија

САЖЕТАК

Увод Карнијева тријада је ретко ненаследно обољење које се карактерише присуством гастроинтестиналног стромалног тумора – интрамурални мезенхимални тумори гастроинтестиналног тракта порекла неуралног гребена, присуством хондрома у плућном ткиву и екстраадrenalних параганглиома. Прецизније, медицински ентитет под називом некомплетна Карнијева тријада односи се на присутност најмање два од наведених типова тумора. Карнијева тријада је добила назив по Ј. Ејдану Карнију и сматра се специфичним типом вишеструке ендокрине неоплазије. Досад је публиковано мање од 30 случајева комплетне и мање од 100 случајева некомплетне Карнијеве тријаде. Карнијева тријада се најчешће појављује код млађих особа женског пола (просечне животне доби око 20 година).

Приказ болесника Болесница старости 35 година упућена је на испитивање у Национални ПЕТ центар Клиничког центра Србије, после гастректомије, са налазом бројних

метастаза у јетри и обостраним плућним хондромима. Студијом 18F-FDG PET/CT доказано је присуство следећег:

1. интензивно везивање 18F-FDG у бројним метастазама у јетри, са редукованим везивањем у мозгу, срцу, цревима и бубрезима, што одговара опису суперскена јетре FDG; 2. вишеструке лезије неправилног облика, највећим делом калцификоване, са мањим уделом мекоткивне компоненте, обострано у плућном паренхиму; 3. нодуларне лезије у левој надбубрежној жлезди, која у свом предњем делу појачано накупља 18-FDG.

Закључак Овај приказ описује налаз суперскена јетре код болеснице са некомплетном Карнијевом тријадом, која у конкретном случају укључује желудачни гастроинтестинални стромални тумор и обостране хондроме у плућима, као и присуство тумора у левој надбубрежној жлезди.

Кључне речи: ГИСТ; 18F-FDG PET/CT; суперскен јетре; Карнијева тријада; кисела фосфатаза резистентна на тартрат

HISTORY OF MEDICINE / ИСТОРИЈА МЕДИЦИНЕ

Jovan Apostolović, MD, the first Serbian medical doctor – life and work achievements

Zoran Gajić^{1,2}, Vladimir Sakač^{2,3}, Boris Golubović^{1,2}, Ksenija Bošković^{1,2}¹University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;²Clinical Centre of Vojvodina, Novi Sad, Serbia;³Scientific Society for the History of Health Culture of Vojvodina, Novi Sad, Serbia**SUMMARY**

Jovan Apostolović was born between 1730 and 1735, in Buda and died in 1770 in Novi Sad. He was the first Serbian physician who acquired the title of a medical doctor with his doctoral thesis. After his graduation from the Halle Medical School in 1757, he defended his doctoral thesis there, titled "How Emotions Affect the Human Body". This thesis, considering the time of its publication, was the first in the history of medicine that studied psychosomatics taking into consideration the influence of emotions on human organism. Upon his arrival to Novi Sad, in 1759, Apostolović had founded his medical practice as an only graduate physician in the town. When, after its outbreak in Belgrade, Srem and Banat, the plague threatened to spread to the Novi Sad area, he was appointed the town's doctor in 1763, but was resolved from this position in 1765, since the Magistrate was not able to handle the pressure from the barbers, catholic priests and German population of the town. After losing this position, he continued with his medical practice in Novi Sad, till 1770 when he died of tuberculosis.

Keywords: Buda; doctoral thesis; 18th century; psychosomatic; emotions

INTRODUCTION

Jovan Apostolović was the first Serb to hold a doctorate in medicine and the first Serb with a university degree. There are no reliable historical data about the exact year of his birth, but it is known that he was born in Buda, between 1730 and 1735 [1–5]. At the time of his birth, Serbs living in Buda outnumbered the Hungarian population, since there had been Serbian merchants, craftsmen, clergy and a handful of Serbian intellectuals living in Buda even before the Great Migration of the Serbs (Figure 1) [6]. Jovan received a traditional, Orthodox Christian

upbringing. Eager to learn, he started his education in his hometown of Buda, at a lower gymnasium, the so-called Latin School [1, 2, 5, 7], and with the support of his teacher, Damjan Ignjatović, he continued his secondary education in Pressburg (today's Bratislava), where he graduated from the Lyceum, a Protestant-Evangelical gymnasium, in 1754 [1, 5, 7, 8]. It is no coincidence that Apostolović continued his education in Pressburg, rather than Pest. The community in Pressburg was Protestant, which means it was home to more progressive and liberal thought than Catholic environments like Pest or Vienna. The time Jovan Apostolović



Figure 1. 18th century Buda

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Correspondence to:

Ksenija BOŠKOVIĆ
University of Novi Sad
Faculty of Medicine
Hajduk Veljkova 3
21000 Novi Sad, Serbia
boskovicksenija@gmail.com



Figure 2. 18th century Halle

spent at the Lyceum in Pressburg contributed greatly to his social and intellectual development [5].

Medical studies in Halle

After graduating from the Lyceum in Pressburg, Jovan Apostolović continued his education as a student at the Faculty of Medicine, in the Prussian Protestant city of Halle, on May 18, 1754 (Figure 2) [7]. Halle was a large and highly populated city for its time, due to the great number of schools; in 1782, Dositej Obradović called it “the seat of the muses and divine sciences.” Apostolović went to Halle to undertake his medical studies because this faculty of medicine was founded as early as 1694, Halle was a prestigious university town, but it is also certain that he was influenced by his Protestant professors in Pressburg. Nevertheless, the principal reason he did not choose Vienna, which is only 80 km away from Pressburg, are perhaps in the fact that the University of Vienna was Catholic and that a Protestant city like Halle undoubtedly held a greater appeal for Apostolović. In addition, the medical faculty in Vienna lacked botanical gardens, chemistry laboratories, and clinics since it was only starting to gain recognition [1, 7]. In 1749, Maria Theresa entrusted the reform of the faculty to Gerard van Swieten, who had studied under Herman Boerhaave, a professor at the faculty of medicine in Leiden, the Netherlands [1, 9, 10].

Jovan Apostolović studied medicine in Halle for approximately three and a half years (1754–1757), and records about this period of his education are scant. However, it is known that he was an exceptional student, and that he was taught, among others, by three distinguished professors. Johann Juncker was a prominent German physician and chemist who played a major role in transforming Halle into an internationally recognized center for practical medical training and clinical teaching [1, 11]. Friedrich Hoffmann, the son of Friedrich Hoffman Senior, was a German physician and chemist, one of the founders of the medical faculty in Halle, famous for introducing a series of transformative medicines into German medical practice [1, 12]. He was also taught by Andreas Elias Büchner, who authored a number of volumes on physiology, pathology, and pharmacology [1, 13].

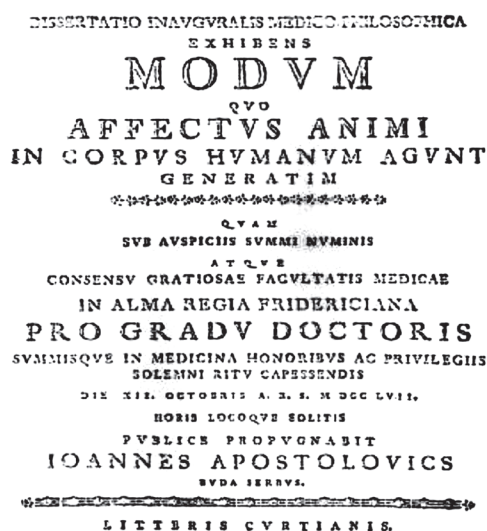


Figure 3. Front cover of Apostolović's Doctoral Thesis

DOCTORAL THESIS

On October 20, 1757, in Halle, Jovan Apostolović defended his doctoral thesis entitled “How Emotions Affect the Human Body” (Lat. *Dissertatio inauguralis medicophilosophica exhibens modum quo affectus animi in corpus Humanum agunt generatim*), thus becoming the first medical doctor among Serbs, and the first who has researched the influence of emotions on the body in such a modern way [1, 2, 7, 14]. It is interesting that the date stated in the document is October 12, therefore we can deduce that the defense of the thesis was postponed until October 20 [1].



Figure 4. 18th century Novi Sad

Jovan Apostolović's doctoral thesis was written in Latin, while on its cover (Figure 3) Apostolović signed his name as *Buda Serbus* (A Serb from Buda). What follows is a whole page of eulogy dedicated to the Viennese Medical School reformer, Gerard van Swieten [1, 7]. Apostolović may have dedicated his dissertation to Gerard van Swieten because van Swieten was a highly influential person, but also as a kind of apology for not having studied in Vienna at the Medical School there. Medical studies in Vienna took five years, which was two years more than in Halle, which might have influenced his choice [1, 7]. In the four pages of the foreword, Apostolović states that he "might be the first and the only one belonging to the glorious Serbian people who dedicated his spirit to medical science." He also expresses his hopes that "my people, famous for their destiny and their arms, would become famous for their literature and science that would contribute to the spiritual and bodily health. Maybe they will start the process of enlightening themselves, which would represent a struggle, not by a sword, but by art, for the benefit of their sweet homeland" [1].

Jovan Apostolović's doctoral thesis, with the title "How Emotions Affect the Human Body" is comprised of 40 pages divided into 65 paragraphs. Its content encompasses the basic elements of psychology, supported by the medical foundation of the time, with definitions and interpretations of the notions such as sensation, perception, and neural tone. Some of the interesting statements during Apostolović's lifetime claimed that "the thinking process stops when a pressure affects the brain," that "the nerves are hollow and filled with liquid," that "when the flow of the liquid is obstructed, due to pressure, the thinking process ceases to exist, which happens in cases of vertigo, when a person endures a great sorrow, or in similar intensive emotional states," as well as that "thoughts can be changed if the liquid in the nerves is changed with some noble wine, diet, or opiates" [1].

In his dissertation Apostolović claims that the neural liquid has the ability to think, and that the movement of the liquid through some parts of the brain produces thoughts; namely, that somewhere in the brain there is a kind of a spirit whose power is activated with the movements of neural liquid towards the creation of thoughts. Apostolović

opts for the last proposition, stating that that spirit creates the thoughts; the spirit is different from the body, its place is in the brain and he calls it a soul. Furthermore, he offers definitions and interpretations of the notions of sensation, perception and their origin through senses. He claims that nerves possess tone which depends on the "strain of certain small fibers" and that the nerves create pressure on the liquid in all directions, so that even the walls of the brain are strained, and that is how the neural tone is created." He tried to establish a relation between the philosophy and the medicine of his era, and to explain the notion of soul through human physiology. Krstić comments: "It would be very difficult today to follow everything Apostolović had written. It would be even more difficult to detect precisely all the source from which he drew" [1, 5]. It is a fact that in his work he cited and quoted from the famous names of his time, more than sixty of them. Apart from renowned scientist and medical experts of the 18th century, Jovan Apostolović also quoted lines of the Roman poet Ovid; he cites from Roman philosopher and poet Lucretius, refers to one of the greatest Greek philosophers, Aristotle, and many other notable scientists and thinkers [1, 5]. In order to understand this approach, it is important to stress the fact that in the 18th century physiology was still a speculative branch [1]. Although his thesis bears only a historical significance today, in the history of Serbian psychopathology it is seen as a first work in psychosomatic medicine, a field that barely existed anywhere in the world [1, 15]. One copy of Apostolović's dissertation is kept at the University Library in Budapest, while the other is kept at the British Museum in London [2].

THE LAST ELEVEN YEARS SPENT IN NOVI SAD

There is no reliable written evidence about where Jovan Apostolović spent the two years after he finished his studies, but it is probable that he returned to Buda and practiced as a doctor there [1, 2, 7]. Invited by the economically and nationally empowered Serbian civil community, he moved to Novi Sad in 1759 (Figure 4), where he continued working as a private practitioner. Although Novi Sad was a leading town in Serbia in Austria-Hungary, it did not have a single qualified doctor until the arrival of Jovan Apostolović [1]. People were uneducated about

their health, while lesser surgeries, tooth extractions, setting, and immobilization of broken bones were done by self-taught healers and barber surgeons [14]. Despite the fact that the bishop, Mojsej Putnik, referenced Jovan Apostolović for the post of the town doctor, the Hungarian Court Chamber did not give the necessary consent. The lack of approval was partially caused by the attitude of the Magistrate whose 12 senators governed the town, and who were greatly influenced by the barbers, mostly of Germanic origin [4, 5]. When the plague that was decimating Belgrade, Srem and part of Banat arrived at the end of 1762, the Novi Sad Magistrate held a meeting with the town councilors about the measures that needed to be taken to stop the contagion from spreading [1, 7]. On January 13, 1763, Jovan Apostolović was chosen for the post of the town doctor (*publicus civitatus medicus*), with the annuity of 300 forints. His degree was read aloud – and thus publically presented – at the session of the Magistrate, with the explanation that Jovan Apostolović deserved the greatest accolades [1]. His strict preventative and quarantine measures managed to save Novi Sad from tragedy threatened by the plague [1, 4]. Soon after the of contagion risk was gone, some town government representatives expressed their opinion that Jovan Apostolović's salary was too high, and that it should be cut to 200 forints a year, at the meeting with the Magistrate held on April 28, 1763. This is why Apostolović announced his resignation. The town councilors believed that the town did not need a doctor, and that the money spent on his salary could be invested into lumber or oxen trade. When the Magistrate was renewed on May 10, 1765, Jovan Apostolović was relieved of duty as the town doctor, two and a half years after his appointment [1, 4]. This verdict of dismissal was certainly also influenced by his religion and nationality, as well as the backward attitude towards health at the time, but also by the power that the barbers, catholic clergy and Germanic citizens had over the Magistrate [4, 5, 7]. Jovan Apostolović continued working as a private practitioner of medicine in Novi Sad until his untimely death in 1770, caused by tuberculosis [1, 2, 7] (Figure 5).

DISCUSSION AND CONCLUSION

Taking into consideration that the doctoral thesis of Jovan Apostolović was written in the 18th century, it is quite understandable that this work was to a considerable extent based on philosophical and speculative aspects.

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Figure 5. Sculpture of Jovan Apostolović in front of the building of Pasteur Institute in Novi Sad; work of B. Jokanović donated by the author

Apostolović's attempt to use the physiological phenomena of "neural tone," and the imbalanced "movement of nerve liquid" as a proof of connection between body and mind did not contribute much to the clinical, diagnostic or therapeutic aspects of psychiatry, but it was certainly an important step in stretching the boundaries of knowledge which was, at the time, largely influenced by idealist philosophy and religion.

Even though the importance of this dissertation is mostly national, cultural and historical, the insistence of Jovan Apostolović that the mind and body are a dynamically connected certainly makes him a founder of psychosomatic medicine, despite the fact that nowhere in his dissertation does he use the term 'psychosomatic'.

Conflict of interest: None declared.

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Др Јован Апостоловић, први Србин доктор медицине – живот и дело

Зоран Гајић^{1,2}, Владимир Сакач^{2,3}, Борис Голубовић^{1,2}, Ксенија Бошковић^{1,2}

¹Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;

²Клинички центар Војводине, Нови Сад, Србија;

³Научно друштво за историју здравствене културе Војводине, Нови Сад, Србија

САЖЕТАК

Јован Апостоловић је рођен између 1730. и 1735. године у Будиму, а преминуо је 1770. године у Новом Саду. Био је први српски школовани доктор медицине. По завршетку студија медицине у Халеу, у истом граду је 1757. године одбранио докторску дисертацију под називом „Начин на који уопште осећања делују на људско тело“, којом је први у историји српске медицине изучавао психосоматику, разматрајући утицај осећања на људски организам. По доласку у Нови Сад, 1759. године, обављао је приватну лекарску праксу као једини школовани лекар у граду. Због велике опасности да

се куга која се ширила на подручју Београда, Срема и Баната прошири и на Нови Сад, изабран је 1763. године за градског лекара, а те дужности је одлуком Магистрата разрешен 1765. године, и то услед утицаја и притисака тадашњих бербера, католичког клера и германског становништва на Магистрат. После разрешења наставио је да ради као приватни лекар у Новом Саду, све до 1770. године, када је умро од туберкулозе.

Кључне речи: Будим; дисертација; XVIII век; психосоматска медицина; осећања



ИСТОРИЈА МЕДИЦИНЕ / HISTORY OF MEDICINE

Др Јован Мијушковић, претеча кардиохирургије у Србији

Душан Велимировић

Научно друштво Србије, Одељење медицинско-биолошких наука, Београд, Србија

САЖЕТАК

Рани почеци кардиохирургије у Србији одвијали су се непосредно по завршетку Другог светског рата, када је прве операције на „затвореном срцу“ на Другој хируршкој клиници у Београду, 1946–47. године обавио проф. др Војислав Стојановић, као и генерал-пуковник, академик проф. др Изидор Папо педесетих година на Војномедицинској академији, такође у Београду.

Операције на „отвореном срцу“, уз примену машине за екстракорпоралну циркулацију, у Србији су почели да раде 1960. године такође пионири српске кардиохирургије В. Стојановић и И. Папо. Прве и најстарије хируршке интервенције на срцу рађене су знатно пре појаве кардиохирургије као хируршке дисциплине. Ове интервенције на „затвореном срцу“ извођене су после повреда срца и рађене су из нужде, као животно спасавајуће.

У раду је посебно дат приказ прве хируршке успешно збринуте повреде срца у Србији, настале после рањавања револверским пројектилом, урађене од стране др Јована Мијушковића, 7. априла 1928. године на хируршком одељењу болнице у Ваљеву. У раду је дат приказ из богате стручне биографије др Јована Мијушковића, који је после завршених студија медицине у Бечу, 1917. године, вршио бројне одговорне функције у здравству Србије у периоду од 1919. до 1944. године, и то као управник и шеф хируршких одељења болница у Туприји, Ваљеву, шеф хирургије Градске болнице у Београду, професор Медицинског факултета у Београду, министар здравља, све до трагичне погибије, 1944. године.

Кључне речи: кардиохирургија; историја; Србија

УВОД

Кардиохирургија је релативно млада хируршка дисциплина, која се постепено развијала током двадесетог века, да би у његовој другој половини, практично после завршетка Другог светског рата, доживела пун захват и процват [1].

Кардиохирургија у Србији настала је, такође, непосредно по завршетку Другог светског рата и имала је ране почетке у поређењу с рађањем и појавом кардиохирургије у свету. Прве операције на срцу, пре проналаска и примене машине за екстракорпоралну циркулацију („операције на затвореном срцу“) рађене су у периоду 1946–47. на Другој хируршкој клиници Медицинског факултета Универзитета у Београду, која се сматра колевком српске кардиохирургије. Пионир кардиохирургије у Србији, и један међу првим протоганистима у Европи, био је оснивач и први управник Друге хируршке клинике у Београду, професор др Војислав Стојановић [2].

Педесетих година операције на „затвореном срцу“ радиле су се и на Одељењу за грудну хирургију Клинике за хируршке болести Војномедицинске академије (ВМА) у Београду под руководством генерал-пуковника, академика, професора др Изидора Папа [2].

Савремена кардиохирургија настала је проналаском, применом и сталним уса-

вршавањем машине за екстракорпоралну циркулацију, која је омогућила рад на заустављеном, мирном и сувом срцу, што је у великој мери повећало сигурност, прецизност и индикације хируршког рада.

У Србији је прву операцију на „отвореном срцу“ (сутура ASD) урадио професор Стојановић на Другој хируршкој клиници 1960. године, а исте године професор Папо је на Војномедицинској академији хируршки кориговао VSD [2].

У аналима српске хирургије забележено је да је прву успешну операцију збрињавања повреде срца урадио 1928. године, на Хируршком одељењу болнице у Ваљеву, хирург др Јован Мијушковић (1886–1944) [3–7].

Циљ рада је да се са кардиохируршког аспекта прикаже прва операција срца урађена у Србији, 1928. године, знатно раније него што је кардиохирургија настала као хируршка дисциплина. Та прва операција срца због повреде револверским пројектилом, рађена у општој болници, на „затвореном“ или куцајућем срцу, без минималних услова за извођење кардиохируршког захвата, од стране општег хирурга, у условима локалне анестезије, и поред бројних компликација завршила се успешно по болесника, коме је спашен живот. Узимајући у обзир време и околности у којима је рађен овај први хируршки захват на срцу, представљао је несумњив медицински подвиг, значајан у историји кардиохирургије у Србији.

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Correspondence to:

Душан ВЕЛИМИРОВИЋ
Владимира Томановића 11
Београд 11000
prof.velimirovic@gmail.com

ХИРУРШКО ЗБРИЊАВАЊЕ ПОВРЕДА СРЦА КАО ПРЕТЕЧА НАСТАНКА И РАЗВОЈА КАРДИОХИРУРГИЈЕ

Прве кардиохируршке операције, рађене четрдесетих и педесетих година, пре ере екстракорпоралног крвотока (ЕКК), биле су операције на „затвореном срцу“. Операције на затвореном, куцајућем срцу, у врло ограниченим техничким условима и код ограничених кардиопатолошких стања, најчешће су имале вредност палијативног хируршког лечења. Поред свих ограничења и недостатака, ова врста кардиохирургије је, у тој почетној фази развоја, ипак доносила значајна побољшања једном броју болесника. Операције на затвореном, куцајућем срцу, као претеча савремене кардиохирургије на отвореном и заустављеном срцу, иако су рађене у малом, тј. ограниченом броју кардиохируршких центара, представљале су снажан подстицај развоју савремене кардиохирургије, чија ера је започела после 1953. године, када је Џон Гибон у САД урадио прву операцију на „отвореном срцу“ уз помоћ машине „срце-плућа“. Проналазак и примена екстракорпоралне циркулације, која је омогућила операције на сувом, заустављеном и отвореном срцу, сматра се једним од највећих медицинских достигнућа друге половине 20. века, чиме је омогућен даљи развој савремене кардиохирургије [1].

Међу оперативним захватима на „затвореном срцу“, који су били претеча савремене кардиохирургије, најстарије хируршке интервенције извођене су после повреда срца и рађене су из нужде, као животно спасавајуће (*life-saving*).

Сматра се да је прву операцију на срцу урадио Лудвиг Рен (*Ludwig Rehn*) из Франкфурта 1896. године, када је хируршки збринуо убудну рану леве коморе, с три шави, користећи малу интестиналну иглу и свилени конач. Прву успешну репарацију убудне ране срца у САД урадио је Хил (*L. L. Hill*) из Алабаме 1902. године. Једну од својих операција повреде десне коморе, збринуте кетгутским шавом, др Хил је урадио у кући повређеног пацијента, у импровизованим условима, на кухињском столу и уз светлост керозинске лампе. Прву велику серију успешно збринутих траума и рана срца објавио је Харкен (*Harken*), ратни хирург америчке армије за време Другог светског рата [1].

ПРВО УСПЕШНО ХИРУРШКО ЗБРИЊАВАЊЕ ПОВРЕДЕ СРЦА У СРБИЈИ

Детаљан опис првог успешног хируршког збрињавања повреде срца у Србији (и у Краљевини Југославији) аутор др Јован Мијушковић изнео је у свом раду „Један успео шав на срцу“, који је објављен у „Српском архиву“ [3].

Према подацима из рада др Мијушковића, „до сада је извршено, уколико је то познато у целој светској литератури, око 300 шавова на срцу. Морталитет износи око 65%, али овде треба приметити, да се успели случајеви ређе публикују, од неуспелих случајева, па се може рећи, да је проценат смрти већи“ [3].

Пацијент др Мијушковића био је старости 15 година и био је рањен револверским пројектилом у пределу леве предње стране грудног коша и у болницу је примљен десет часова после рањавања. Дијагноза је постављена на основу физикалног и рендгенолошког прегледа, којим је констатовано присуство течности у перикарду, као и присуство пројектила у сенци срца, који се кретао синхроно са његовим покретима. Операција је рађена у локалној анестезији, а грудни кош је отворен медијастиналним прозором по Ротерој методу. После отварања перикарда евакуисано је око један литар тамне крви. Констатована је повреда у близини врха десне коморе, са улазном раном од пројектила величине кукурузног зрна, која није крварила. Компресијом десне коморе на месту повреде евакуисан је коагулум, са пројектилом, из њене шупљине, што је последично проузроковало крварење у млазу. Дигиталном компресијом контролисано је крварење из срца, а повреда од пројектила збринута је са четири дубока, повратна, појединачна шави, коришћењем танке цревне игле [3]. Перикард је затворен ретким појединачним свиленим шавовима. Постоперативни опоравак био је тежак, спор и компликован пнеумонијом и плеуритисом, али на крају је повређени отпуштен кући као успешно излечен [3].

На крају текста др Мијушковић закључује: „Са успехом, ја сам задовољан. Мислим да је ово први успели случај на срцу у нашој држави. Операцију сам вршио под врло тешким околностима... Успех приписујем и брзини са којом сам завршио целу операцију, која није трајала више од 35 минута, а и локалној анестезији коју је овај дечко храбро издржао“ [3] (Слика 1).

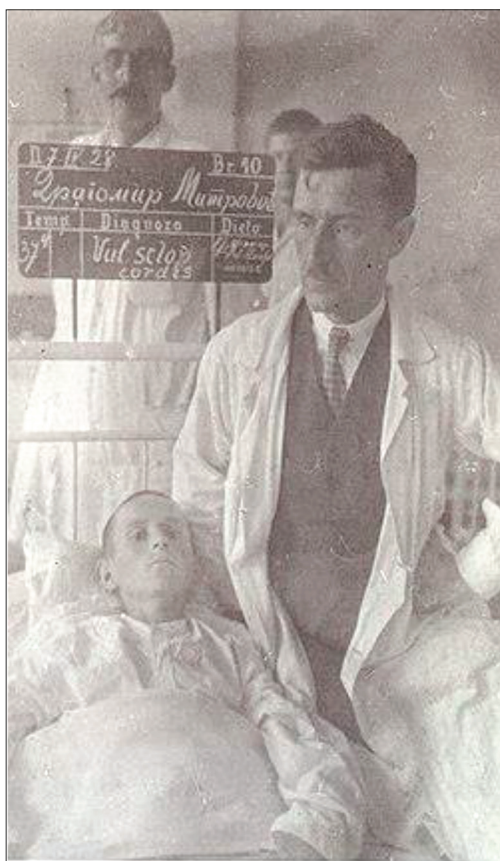
КРАТКА БИОГРАФИЈА ДР ЈОВАНА МИЈУШКОВИЋА (1886–1944)

Др Јован Мијушковић рођен је 1886. у Нишу. Основну школу и гимназију завршио је у Београду, а студије медицине у Бечу, где је промовисан за доктора медицине 1917. године. Као студент, шест година био је председник бечког студентског друштва „Зора“ и уредник истоименог листа, који је заступао идеје југословенске радикалне националне омладине у српско-хрватским областима које су се тада налазиле у оквиру Аустроугарске монархије. Пред светски рат 1914. лист је угашен, многи сарадници затворени, као и сам др Мијушковић, који је у затвору провео годину дана, а потом је интерниран у српски заробљенички логор у Великом Међеру, у Мађарској [4, 6, 8].

По ослобађању враћа се у Србију, где ради на више различитих места и градова, вршећи различите функције. У периоду од 1919. до 1923. радио је као лекар срезова рачанског, ваљевског и тамнавског.

Године 1923. враћа се у Беч на специјализацију хирургије, где проводи годину и по дана, а специјализацију завршава у Београду, на клиници код професора Костића.

Од октобра 1925. године врши функцију шефа хирургије и управника болнице у Ћуприји, а од јуна 1926.



Слика 1. Др Јован Мијушковић са болесником после прве успешне операције повреде срца у Србији (1928)
Figure 1. Dr. Jovan Mijušković with patient after the first successful heart wound surgery in Serbia (1928)

до половине 1932. исте функције обавља у болници у Ваљеву [4, 5].

Године 1933. постављен је за шефа санитета Министарства саобраћаја, а 1936. године постаје већник Општине града Београда [4, 5, 6, 9, 10].

За хонорарног наставника на Медицинском факултету у Београду за предмет Историја медицине изабран је 1936. године [4, 9, 10, 11].

Министар здравља у влади Милана Недића постао је 1941. године, а за шефа хируршке службе Градске болнице у Београду постављен је крајем 1942. године. По ослобађању Београда 1944 године, ухапшен је и стрељан од стране партизана као „непријатељ народа“ [4].

Током своје професионалне каријере, као шеф хируршке службе Ваљевске болнице знатно је повећао обим и квалитет хируршког рада. У периоду од 1927. до 1931. број оперативних захвата се кретао од 343 до 378 годишње [4, 5].

Поред редовног хируршког рада, др Мијушковић публикује и стручне радове из различитих области хирургије, у страним и домаћим стручним часописима и у дневним листовима, понајвише у „Правди“. Бавио се историјом медицине и на Народном универзитету држао је различита тематска предавања: историја медицине Месопотамије, Египта, медицина пре и после Хипократа, медицина александријског доба, ислама и Арабљана [9].

Др Мијушковић је био политички ангажован и припадао је Радикалној странци [10]. Био је и председник клуба већника Градског поглаварства Југословенске радикалне заједнице и председник исте заједнице за Срез тамнавски.

Као министар здравља, целу Србију је за време окупације опасао санитетским кордоном, спречивши ширење заразних болести које су тада харале суседним земљама [8, 10].

Према наводима историчара С. Ђирковића, др Јован Мијушковић је ухапшен 23. октобра 1944. и одлуком Војног суда осуђен на смрт под оптужбом да је „одано служио окупатору и позивао народ на борбу против НОП-а“ и да се посветио „раду на обнови земље“ [6].

Дневни лист „Политика“ је 7. новембра 1944. године објавио списак стрељаних, на коме се налазило име др Јована Мијушковића, који је стрељан „као сарадник окупатора јер је организовао санитетски кордон кроз који су морале да прођу избеглице које су после пропасти Југославије прелазиле у Србију. На тај начин је чувао немачке војнике од могуће епидемије“ [10]. То је била једина „кривица“ због које су га комунисти стрељали! [7].

У српској историографији влада Милана Недића различито је називана – од „колаборационистичке“, „квислиншке“, „марионетске“, па до „влада народног спаса“ [10, 12].

Између осталог, тврди се да „је у питању ‘водећи српски квислинг’ и ‘самозвани отац Србије одраније опседнут немачком војном снагом’, који је прихватањем избеглица стварао мит о себи као спасиоцу, а у основи их искоришћавајући за манипулацију ‘у оквиру политике служења окупатору’, данас се стигло до тврдњи (у најгорем случају) да је у питању ‘најконтроверзнија’ личност српске историје“ [12].

Можда је део историје у Србији од 1941. до 1944. најбоље назвао историчар Сима Ђирковић назвавши га „зобрањеном епохом“ [6].

Не улазећи у историјске контроверзе, различита тумачења догађања у Србији током Другог светског рата и немачке окупације земље, што и није тема овога рада, чињеница је да су политички ангажман др Мијушковића, његов положај министра здравља у влади Милана Недића, и припадност политици и покрету који је изгубио рат, нажалост, утицали на његову трагичну судбину.

Име др Јована Мијушковића налази се на списку наставника Медицинског факултета Универзитета у Београду који су удаљени са посла и из наставе у периоду 1944–1953. и који су 2001. године рехабилитовани одлуком Наставно-научног већа истог факултета.

ПРЕГЛЕД ДЕЛА ПУБЛИКОВАНИХ РАДОВА ДР ЈОВАНА МИЈУШКОВИЋА

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У овом раду приказан је део библиографије др Јована Мијушковића, која је тематски врло хетерогена и односи се на различите области хирургије: абдоминална хирургија, ендокрина хирургија, гинекологија, радиотерапија, кардиохирургија. Овај приказ радова има за циљ да покаже захтеве времена и стадијум тадашњег развоја хирургије, који је подразумевао врло широк опус хируршког рада. Тада нису постојале специјалистичке хируршке дисциплине и општи хирурзи су морали да овладају хируршким вештинама које су покривале бројне и различите делове хируршке патологије. Развојем хирургије, нарочито после Другог светског рата, и рађањем нових хируршких дисциплина обим хируршког рада се сужавао и хируршки рад одвија се данас доминантно у оквиру нових специјализација и супсценијализација.

ДИСКУСИЈА

Подаци који се могу наћи у литератури о др Јовану Мијушковићу су оскудни, углавном су дати у лексикографској форми и највећим делом баве се политичком и социјалном активношћу др Мијушковића. Међутим, у скоро свим кратким биографским текстовима посебно је назначена прва операција хируршког збрињавања повреде срца, коју је др Мијушковић урадио у Ваљеву 1928. године. Погрешно је ова операција представљена у литератури као „операција на отвореном срцу“. Ова терминолошка грешка је разумљива пошто ниједан од објављених текстова није изашао из руку кардиохирурга.

Др Илија Трипковић, хирург Ваљевске болнице, чијом иницијативом је у Ваљеву 2002. године основана невладина организација „Фондација др Јован Мијушковић“ [7], написао је 1993. године текст „Др Јован Мијушковић, зачетник кардиохирургије у

Србији“, који садржи обимније податке из биографије и професионалне каријере др Мијушковића, са цитатом његовог оригиналног текста о првој операцији срца, коју је урадио 1928. године [4].

Увидом у ауторски рад др Мијушковића „Један успео шав на срцу“ [3] може се схватити сва тежина ове операције, која је рађена у условима који су потпуно непримерени данашњој кардиохирургији [3].

У периодима пре проналаска и примене машине за ЕКК операције повреде срца рађене су на куцајућем срцу са великим али прихватљивим ризиком пошто се радило о животно спасавајућим процедурама. И у данашње време у кардиохируршким центрима поједине повреде срца могу да се раде без машине за ЕКК, што зависи од величине повреде, врсте оружја, повреде осталих структура срца и других органа и ткива итд., али је неопходно да се у случају немогућности збрињавања повреде срца она одмах ради у условима вантелесног крвотока, тј. на отвореном срцу. У општим болницама, које немају кардиохирургију и машину за вантелесни крвоток, и данас се у случајевима животне угрожености повређеног и немогућности транспорта повреде срца збрињавају на куцајућем срцу од стране општинских хирурга. Услови у којима се те операције раде у овим болницама нису оптимални, већег су ризика, али су оправдане и одвијају се у далеко бољим условима од оних у којима су рађене пионирске операције на срцу током почетка XX века.

Величина хируршког подвига др Мијушковића и његова храброст да се упусти у спасавање живота младом рањенику, који је стигао у болницу 10 сати после рањавања, добијају на значају када се сагледају услови у којима је операција рађена.

Радити операцију повреде срца у условима локалне анестезије, са отварањем грудног коша без електричног стернотоме, а применити медијастинални „прозор“ са ресекцијом два ребра, немогућност примене инвазивног хемодинамског мониторинга, као и одговарајућих инфузионих раствора, лекова, адекватног хируршког инструментаријума и шавног материјала, и без машине за вантелесни крвоток у приправности, била је храбра и оправдана одлука предузета из неопходности спасавања живота повређеном пацијенту.

Опис хируршке технике, са маневром асистента и компресијом повређене десне коморе између кажипрста и палца леве руке оператора, и шивење ране дубоким, појединачним, наизменичним, свиленим шавовима, указују на коректну хируршку технику.

ЗАКЉУЧАК

Неоспорно да је операција успешног хируршког збрињавања пројектилне ране срца од стране др Јована Мијушковића, урађена у Ваљеву 1928. године, подвиг настао у времену пре рађања кардиохирургије и може се сматрати подухватом значајним у аналина српске хирургије и, посебно, претечом кардиохирургије у Србији.

Сплет историјских догађаја у Србији током Другог светског рата, политичка делатност др Мијушковића, његова активност као министра здравља у влади Милана Недића и, на крају, пресуда да буде стрељан „као непријатељ народа“, учинили су да његова богата професионална каријера и подвиг првог успешног хируршког збрињавања повреде срца у Србији и Југославији остају дуго времена табу тема, прикривена његовом трагичном судбином непосредно после завршетка Другог светског рата.

Рехабилитација др Јована Мијушковића од стране Наставно-научног већа Медицинског факултета

Универзитета у Београду из 2001. године омогућила је реафирмацију његове професионалне хируршке каријере и историјског места претече српске кардиохирургије.

ЗАХВАЛНИЦА

Аутор се захваљује проф. др Бошку Ђукановићу на уступању делова историјско-архивских података и литературе која је коришћена у припреми овога рада.

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Dr Jovan Mijušković, precursor of cardiac surgery in Serbia

Dušan Velimirović

Scientific Society of Serbia, Department for Medico-Biological Sciences, Belgrade, Serbia

SUMMARY

The beginnings of cardiac surgery in Serbia date back to the aftermath of World War II, when the first “closed heart surgery” was performed in Belgrade. It was done by Professor Vojislav Stojanović at the Second Surgical Clinic, and shortly afterwards, during the 1950s, by Professor Izidor Papo at the Medical Military Academy, also in Belgrade. “Open heart surgery,” using heart-lung machine, was introduced in Serbia in 1960, and performed by the same cardiac surgery pioneers.

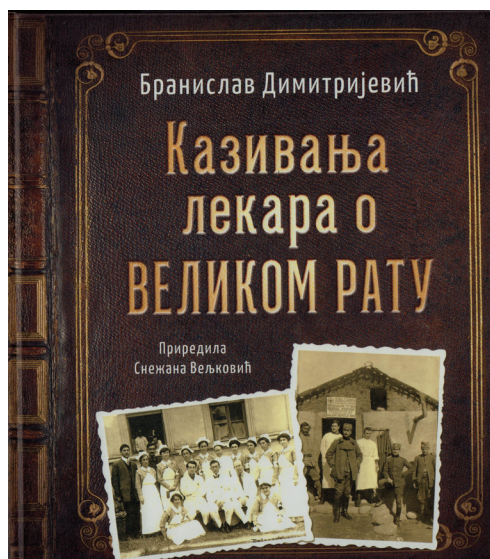
Some of the very first heart operations in the world had been done before cardiac surgery was even officially recognized as a surgical discipline. Therefore, they were performed only as lifesaving procedures in patients with heart wounds.

This article describes the first successful surgical treatment of heart wound in Serbia. It was a penetrating revolver wound, and the operation took place on April 7, 1928, at Valjevo City hospital, performed by Dr. Jovan Mijušković, who had received his degree from the School of Medicine in Vienna in 1917, and over the years worked as director and chief of surgical departments in various hospitals – Čuprija, Valjevo, as well as in the City Hospital in Belgrade. He was elected Professor of History of Medicine at Belgrade School of Medicine in 1936. In 1941 he was appointed Minister of Health in the pre-war Serbian Government. Sadly, upon liberation of Belgrade in 1944, this surgical pioneer was arrested and executed.

Keywords: cardiac surgery; history; Serbia

ПРИКАЗ КЊИГЕ / BOOK REVIEW

Казивања лекара о Великом рату (Doctors' testimonies of the Great War)



Приредила: Снежана Вељковић
Аутор: Бранислав Димитријевић
Издавач: Лагуна, 2019.
Обим књије: 554 стр.
ISBN: 978-86-521-2810-5

Књига „Казивања лекара о Великом рату“ припремана је неколико година, у време када се у свету обележавала стогодишњица Првог светског рата. По замисли аутора Бране Димитријевића (1939–2015), професора Стоматолошког факултета у Београду, историчара медицине и књижевника, осим поглавља која је лично написао, књига садржи и истраживачке радове чији су аутори историчари медицине Снежана Вељковић, Лука Николић, Зоран Ваџић и Милче Чанковић Кадијевић. Базирана је на необјављеним и објављеним изворима и богатој домаћој и иностраној литератури – дневничким забелешкама и сећањима учесника рата и на резултатима истраживања савременика, међу којима се издвајају радови доајена у области историје српског војног санитета Александра Недока. Хронолошки и тематски концептирана у оквиру 53 поглавља, ово је потресна прича о борби српских и иностраних лекара и болничара са епидемијама заразних болести, несташицама санитетског материјала и лекова, проблемима евакуације болесних и рањених бораца, о српској Голготи – преласку преко Албаније, о страшном страдању српске младости – регрута, о раду санитета на Солунском фронту и његовим стручним успесима у немогућим условима, о санитетским базама у Африци,

о стању здравствене службе непосредно по ослобођењу земље...

Али „Казивања“ су и својеврстан споменик – споменик лекарицама, медицинарима и болничарима преминулим на својим дужностима и споменик напорима њихових преживелих сабораца који су оставили сведочења о најтрагичнијем времену новије српске историје. Споменик је и самом аутору Брани Димитријевићу, који је прикупљање тих сведочанстава осећао као своју мисију, те у овој књизи написао: „Оног тренутка када сам растумачио Петровићев ратни дневник 1916–1918, и кад сам се спрам Петровића, његове храбрости, одлучности, високог не само професионалног него и личног морала... лично осетио као најобичније зрнце песка, почела је можда моја герилна, мој унутрашњи препород... Ако је Петровић могао оно... зар ја не могу да бар обновим сећање на његово дело...“ [реч је о књизи „У контејнеру – записи српског ратног хирурга 1916–1918“, која је доживела два издања – прво 2001. године (Београд, „Апостроф“) и друго 2004. године (Београд, „Водич за родитеље“); др Михаило Петровић (1863–1934), отац српске ратне хирургије, био је санитетски генерал и професор Ратне хирургије на Медицинском факултету Универзитета у Београду, у време Првог

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светског рата творац и хирург-консултант чувене Прве пољске хируршке болнице II армије у Драгомацима, на Солунском фронту (1916–1918)].

Димитријевић је књигу посветио *οἰηчесῖву*. Нажалост, није доживео њено публикување. То што је она, иако остала у рукопису, ипак угледала светлост дана чини је такође и симболом – симболом заједништва и сарадње чланова Секције за историју медицине Српског лекарског друштва, коју је управо Брана Димитријевић својим радним еланом и ауторитетом реорганизовао 2009. године, после дводеценијског прекида њеног рада. Његова секција је одлучила да рукопис публикује, приређивања се прихватила Снежана Вељковић, а својим саветима и проналажењем илустративног материјала помогли су бројни чланови.

Снежана Вељковић је професор судске медицине Медицинског факултета у Београду у пензији, и историчар медицине и књижевник. Аутор је књига „Хроника судске медицине у Београду“, „Хроника Медицинског факултета“, „Господин који није знао санскрит“ и два историјско-медицинска романа. У својим књигама и научним радовима бавила се темама Првог светског рата. Њен рад одликују изванредан истраживачки дар, стрпљење у трагању за сведочанствима прошлости

која се налазе у архивима, у литератури – штампаној и оној у електронском облику која значајним делом није била позната домаћој стручној јавности, и изнад свега – умеће јасног и узбудљивог приповедања. Захваљујући управо књижевном дару који је одликовао аутора „Казивања“ Брану Димитријевића, а такође одликује приређивача Снежану Вељковић, књига је уобличена у хомогену целину и чита се у даху.

„Казивања“ су ризница записа и гласова – учесника Великог рата – српских и страних лекара, болничарки и болничара, официра и војника, страних новинара и пријатеља српског народа у љутој невољи, али и некадашњих и данашњих историчара и историчара медицине. Гласови из прошлости и гласови из данашњег времена у њој се преплићу, допуњују и причају причу која, надамо се, никада више неће бити заборављена. За незаборав „Казивања лекара о Великом рату“ посебно је важно то што је књигу објавила „Лагуна“, издавачка кућа са угледом и широком читалачком публиком.

Јелена Јовановић-Симић
Музеј науке и технике, Београд, Србија
jelena2767@gmail.com

PERSONAL VIEW ARTICLE / ЛИЧНИ СТАВ

How to publish your scientific work

Stephen W. Carmichael, Susan L. Stoddard

Emeritus Center, Mayo Clinic, Rochester, Minnesota, USA



In order for your scientific endeavors to impact patients outside your home institution it is valuable for your results to be published in a peer reviewed journal. Peer reviewed journals generally have a broader distribution than non-peer reviewed journals and they are more highly regarded in the medical and scientific fields. Therefore, publication of scientific results in a peer reviewed journal has a greater potential to broadly impact patient care and lower morbidity. To assess the influence of a peer reviewed journal, consider the Impact Factor[®] of the journal, which is a quantitative measure of how frequently published articles from that journal are cited in the scientific literature. A higher Impact Factor[®] suggests the influence of that journal is greater.

There are two important criteria for manuscript acceptance. The information must have clinical relevance and it should be novel. To demonstrate clinical relevance, the results of your study should directly influence an improved diagnostic method, procedure or aspect of patient care. Novel information is new information that has not been previously published. This concept was summarized by Abraham Lincoln, an American president, in 1863: "I know of nothing so pleasant to the mind as the discovery of anything which is at once new and valuable." In order to determine if your work is novel, conduct a thorough search of the scientific literature. Center your search on journals where related studies are published. In reviewing the various journals, you are likely to identify the journal that is best suited to publish your study.

As you are preparing to write the first draft of your manuscript, keep your readers in mind. Will they find the material interesting? Will they be able to apply the information directly to clinical practice, to anatomy education or, possibly, to both?

Once you have selected the journal where you plan to submit your manuscript, find the instructions for authors, sometimes called the

"guidelines for authors." It is critical to conform to the general guidelines, paying particular attention to the format for bibliographic references. Using the proper format for references early on in the process makes manuscript preparation much easier and more efficient.

Since anatomy and imaging techniques broadly used in everyday clinical practice are visual sciences, the illustrations in your manuscript need to be of the highest possible quality. Photographs need to have optimal resolution and sufficient file size; graphics should be created by a professional medical illustrator. Most graphics are a straightforward rendering of the relevant anatomy, but occasionally the illustrator needs a deeper understanding of the topic. This is particularly important when one is trying to introduce a new anatomical concept.

Some journals allow the author to suggest reviewers. During your literature search, note who is doing research relevant to your study and well-designed studies that are similar to yours. Authors of these articles may be appropriate to review your manuscript. Some journals also allow you to specify who should *not* review your manuscript. Is there anyone in your field who would benefit from your research not being published? Do you have a scientific rival? This is not common for people early in their careers, but rather tends to come into play with some well-established scientists.

If you plan to use human specimens in your study, it is mandatory to have obtained proper permission from your Institutional Review Board (IRB) before you begin. Clearly state in your manuscript that such permission was obtained. If you used cadaveric material, it is appropriate to express gratitude to the donors who have contributed to your will body program or body donation program.

Various responses are possible after your manuscript has been submitted and reviewed. A few manuscripts are accepted without revision, although this is unusual. More commonly,

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Correspondence to:

Stephen W. CARMICHAEL
Emeritus Center, Plummer Building 10N
Mayo Clinic
Rochester, MN 55902
U.S.A.
carmichael.stephen@mayo.edu

a manuscript is conditionally accepted pending major or minor revisions. The distinction between major and minor revisions is frequently difficult to define. Unfortunately, manuscripts are also rejected after review or rejected without review (i.e. “expedited rejection”). Expedited rejection is most likely to occur when the editor(s) believe your topic is not within the scope of that journal.

If your manuscript is accepted pending revisions, take the reviewers’ opinions seriously; one assumes that the reviewers want to improve your manuscript. This is sometimes challenging because individual reviews can be conflicting, and what may be clear to you may not be clear to the reviewers. Whenever possible, make modifications the reviewers suggest. If it is not possible to address their concerns, clearly state your reasoning for not doing so. For example, a reviewer may suggest a larger sample size for your study, but for practical reasons this simply might not be possible. Perhaps there are very limited specimens or collection of the specimens is financially prohibitive. Clearly address these issues in your response.

If your revised manuscript is rejected, you could consider submitting it to another journal. Your literature search would have involved many journals and another

one may be where you could successfully submit your revised manuscript.

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PREVIOUS PRESENTATION

This manuscript is based on an oral presentation given by Stephen Carmichael at the 19th Congress of the IFAA, London, August 9, 2019. An abstract, “How to publish your clinically related anatomical research” was submitted.

Conflict of interest: None declared.

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публикавање. Радови објављени у СА се не хонораришу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 pt). Све четири маргине подесити на 25 mm, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 mm, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лежиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користи-

ти кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ⁹⁹Tc, IL-6, O₂, B₁₂, CD8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншким декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME*; <http://www.wame.org>) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/ аутоплагијаризам преко *SCIndex Assistant – Cross Check (iThenticate)*. Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH* (<http://www.nlm.nih.gov/mesh>).

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или син-

тагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публикавање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. $12,5 \pm 3,8$). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса ($^{\circ}\text{C}$), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.

Видео-радови могу трајати 5–7 минута и бити у формату *avi*, *mp4(flv)*. У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table-Insert-Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у СА се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватити за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији члан-

ка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).

Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi*, *mp4(flv)*. Уз видео доставити посебно слику која би била илустрација видео-приказа у е-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе носе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распооређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикана. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикана и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексан у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (<http://www.icmje.org>), чији формат користе U.S. National Library of Medicine и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници http://www.nlm.nih.gov/bsd/uniform_requirements.html. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (SUBMISSION LETTER). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (<http://www.srpskiarhiv.rs>).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокујно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који

плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокујно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сnose део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: <http://www.srpskiarhiv.rs>

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11000 Београд

Србија

Телефони: (+381 11) 409-2776, 409-4479

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Editorial Office

Kraljice Natalije 1

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Serbia

Phones: (+381 11) 409-2776, 409-4479

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