SRP ARH CELOK LEK

ISSN 0370-8179 (PRINT)
ISSN 2406-0895 (ONLINE)

COBISS.SR-ID 3378434
UDC 61(497.11)

СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

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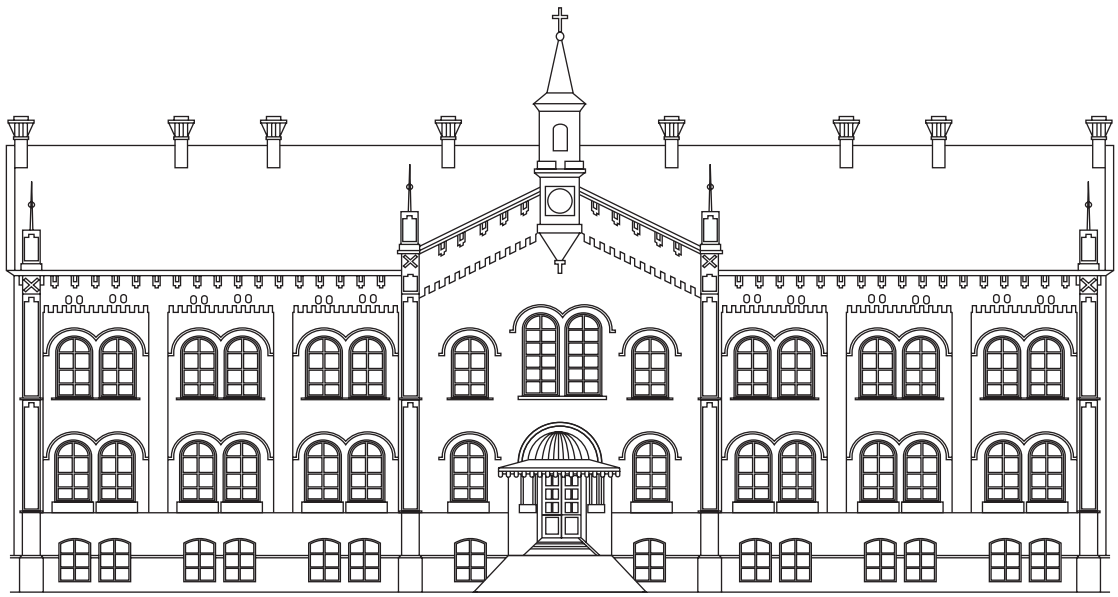

SERBIAN ARCHIVES
OF MEDICINE

JOURNAL OF THE SERBIAN MEDICAL SOCIETY

VOLUME 152 · NOVEMBER–DECEMBER 2024 · ISSUE 11–12

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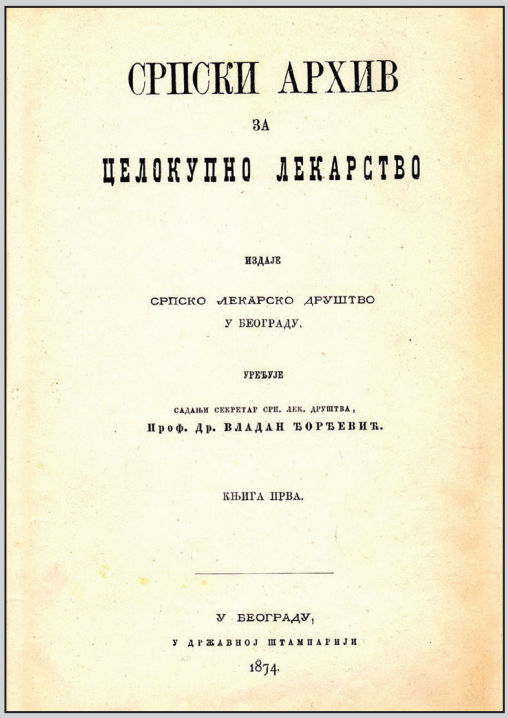

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ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

ИЗДАЈЕ

СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

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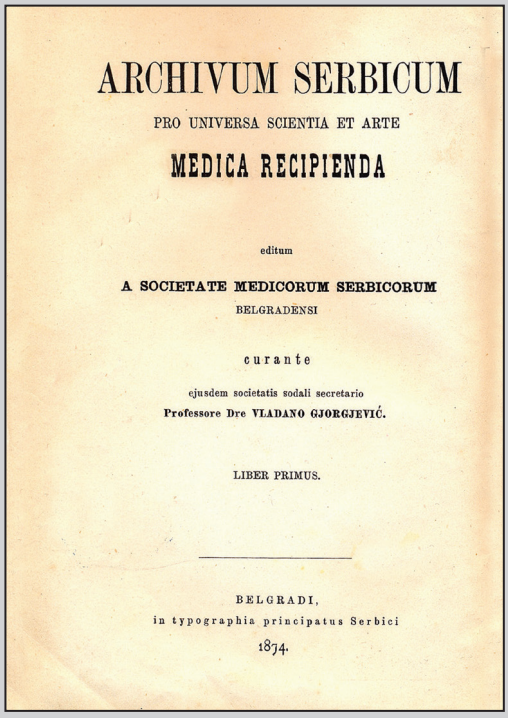
У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



ARCHIVUM SERBICUM

PRO UNIVERSA SCIENTIA ET ARTE

MEDICA RECIPIENDA

editum

A SOCIETATE MEDICORUM SERBICORUM

BELGRADENSI

curante

ejusdem societatis sodali secretario

Professore Dre VLADANO GJORGJEVIĆ.

LIBER PRIMUS.

BELGRADI,

in typographia principatus Serbici

1874.

The title page of the first journal volume in Latin

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Srp Arh Celok Lek
ISSN 0370-8179
UDC 61(497.11)
COBISS.SR-ID 3378434
Српски архив за целокупно лекарство
Званичан часопис Српског лекарског друштва
Излази шест пута годишње

ГОДИШТЕ 152 НОВЕМБАР–ДЕЦЕМБАР 2024. СВЕСКА 11–12

Часопис „Српски архив за целокупно лекарство" је индексиран у базама: Science Citation Index Expanded, Journal Citation Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journals, DOI Serbia.

Оснивач, власник и издавач
Српско лекарско друштво
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Председник
Проф. др Милан А. Недељковић
Интернет страна: http://www.sld.org.rs

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355-1009094-22

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Цена претплате за календарску годину је 3.000,00 динара за појединце, 6.000,00 динара за установе и 100 евра за читаоце ван Србије. Цена појединачног примерка из текуће године је 600,00 динара, а свеске из претходних година 300,00 динара.

Штампање „Српског архива за целокупно лекарство" током 2024. године помогло је Министарство науке, технолошког развоја и иновација Републике Србије.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Отворен приступ
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Штампано у Србији

Редакција
Технички уредник: Јасмина Живковић
Лектор за српски језик: Дивна Продановић
Лектори за енглески језик: Мирко Рајић, Ана Којић
Корице: *MaxNova Creative*

Штампа: ЈП „Службени гласник", Београд

Тираж: 850 примерака

Serbian Archives of Medicine

VOLUME 152 NOVEMBER–DECEMBER 2024 ISSUE 11–12

The journal "Srpski arhiv za celokupno lekarstvo" (Serbian Archives of Medicine) is indexed in: Science Citation Index Expanded, Journal Citation Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journals, DOI Serbia.

EDITORIAL OFFICE
Technical editor: Jasmina Živković
Serbian language editor: Divna Prodanović
English language editors: Mirko Rajić, Ana Kojić
Cover & Logo: MaxNova Creative

Printed by: JP "Službeni glasnik", Belgrade

Circulation: 850 copies

Srp Arh Celok Lek
ISSN 0370-8179
UDC 61(497.11)
COBISS.SR-ID 3378434
Serbian Archives of Medicine
Official Journal of the Serbian Medical Society
Published six times per year

FOUNDER, OWNER & PUBLISHER
Serbian Medical Society
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Website: www.srpskiarhiv.rs

SUBSCRIPTION AND DISTRIBUTION
Serbian Medical Society
Džordža Vašingtona 19, 11000 Belgrade
Serbia
Phone: +381(0)11 3245-149
Bank accounts: 205-8041-21 and
355-1009094-22

Full-text articles are available at website: www.srpskiarhiv.rs

Calendar year subscription prices are as follows: 3,000 dinars for individuals, 6,000 dinars for institutions, and 100 euros for readers outside Serbia. The price of a current year issue is 600 dinars, and of issues from previous years 300 dinars.

The publishing of the Serbian Archives of Medicine during 2024 is supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Open Access
(CC BY-NC)

Printed in Serbia

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DOI: https://doi.org/10.2298/SARH231221089I
UDC: 615.456

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The laboratory investigation of the capillarity of various dental solutions at three temperature levels

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SUMMARY

Introduction/Objective Many oblong micro-spaces of less than 500 μm exist within oral cavity, such as dentine canalicular spaces, gaps, recesses, gingival sulcus etc. Since these spaces are susceptible to food and pathogenic microbe's accumulation, most dental solutions should be able to penetrate into those micro-spaces exhibiting therapeutic effects. The aim of this study was to evaluate and compare the effect of capillarity of commonly used dental solutions at three temperature levels.

Methods The following solutions were examined: ethanol (EA), sodium hypochlorite (SH), hydrogen peroxide (HP), chlorhexidine, saline, citric acid, ethylenediaminetetraacetic acid (EDTA), and distilled water. The samples were exposed to the temperature of 20°C, 38°C, and 50°C measuring capillary by glass tube of 400 μ diameter. The capillary effects of the solutions were recorded on the graduated capillary tube (mm) and data were statistically processed.

Results Seventy-percent EA showed the highest raise of capillarity (20–50°C; 8.8 ± 1.1) and 2.5% SH (2.1 ± 1.5) and 3% HP (2.1 ± 1.6) showed the lowest. The highest capillarity at 50°C was showed by 17% EDTA (40.1 ± 1.4) while 4% SH showed the lowest capillarity (25.9 ± 2.1) ($p < 0.05$).

Conclusion The level of capillarity of dental irrigating solutions was enhanced with temperature increase in all solutions, but not to the same extent.

Keywords: irrigation; sodium hypochlorite; chlorhexidine; EDTA; surface free energy

INTRODUCTION

Capillarity is defined as a liquid's property to move along (penetrate) the narrow tubular spaces against the force of gravity or voids of a porous material, and depends on the liquid's nature and surface tension [1]. Considering the nature of the liquid and its density, the formula of capillary action is as follows:

$$h = 2\gamma\cos\alpha / \rho g d$$

where h is height of the liquid column, γ – liquid–air surface tension, ρ – the liquid density, d – radius of the capillary tube, g – gravity acceleration, and α – contact angle between the liquid column and the capillary wall. The h value depends on the liquid–air surface tension being proportional to this value. The narrower the capillary tube, the more pronounced the capillarity is, especially when $d < 1$ mm and when it does not show the phenomenon of connected vessels. A capillary immersed in liquid shows a concave meniscus. Actually, adhesion occurs between fluid and the capillary wall pulling the liquid up until there is sufficient liquid for gravitational forces to overcome these intermolecular (adhesive) forces.

Knowing this, dentinal tubules could be considered a capillary model due to their natural diameter (2–10 microns) that becomes wider and more passable after citric endodontic solutions treatment [2]. Marginal restoration gap, gingival crevice, periodontal pockets, interdental niches, canalicular pulpal oblong spaces, etc. can be considered capillary spaces where dental plaque/microbe might freely enter. For this reason, there were studies related to the capillary penetration of dental disinfectants. For example, Cunningham et al. [3] have been investigating dentine capillarity focusing on depth of endodontic irrigants penetrations since 1973. Adding of the ethanol (EA) to the sodium hypochlorite (SH), they found that small surface tension of EA permits deeper flow than SH in the capillary tube. Since then, many studies appeared related to the dynamics of fluids used in everyday dental practice such as analgesics, solvents, demineralizers, sealers, etc. Such liquids present superior capability to reach aforementioned narrow spaces, if warmed up. Also, papers appeared regarding the influence of liquid concentration and temperature to the antimicrobial and capillarity effect, which are mostly proved with SH solutions [4, 5]. Sirtes et al. [6] worked with 1%, 3%, and 5% SH at 20°C, 45°C, and 60°C against microbes and found the highest temperature much more effective than other two, indicating an increase in diffusivity with temperature rise. Some authors

Received • Примљено: December 21, 2023
Revised • Ревизија: November 26, 2024
Accepted • Прихваћено: November 26, 2024
Online first: November 28, 2024

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even advocate the use of gelatinous NaOCl preheated by ultrasonic streaming, resulting in high-quality capillarity of that disinfectant [7]. Hydrogen peroxide (HP) is nowadays a very frequent additive to dental solutions/pastes, predominantly as a weak disinfectant, but potent surfactant (bleacher) at 30% concentration [8]. It exposed the rise of capillarity between 20°C and 37°C in one study and thus the possibility of penetration through treated substrate [9]. Moreover, strong combination of sporicidal and bactericidal effects of HP (3–23.6%) was noted in combination with 25% peracetic acid [10]. Chlorhexidine digluconate (CHX), with appropriate low surface tension (high capillarity) is the useful mean in endodontics, periodontology and as a cleanser for orthodontic braces and fixed restorations. Bearing that in mind, it is important to mention the work of González et al. [11], who found the temperature rise (37–40°C) upon ultrasonic irrigation of CHX meaningful for endodontic treatment.

Concerning aforementioned, the aim of this study was to investigate and compare the power of capillarity of various dental solutions of different concentrations, at three temperature levels.

METHODS

Materials

The study involved the following solutions: 96% and 70% EA; 4%, 2.5%, and 0.5% SH; 30% HP; 2%, 0.2% (a), and 0.2% (b) CHX; saline solution (SS); 10% citric acid (CA); 17% and 2% ethylenediaminetetraacetic acid (EDTA) and distilled water (DW), forming a total of 14 experimental groups, derived or used as of original manufactured preparations: EA (Etanol 96%, Zorka Pharma, Šabac, Serbia); 5.25% SH (Sodium hypochlorite, Cerkamed, Poland); HP (Vodonik peroksid 30%, Zorka Pharm, Šabac, Serbia); CHX (Curasept 2%, Septodont, France); 0.2% CHX(a) (Lacalut active mouth wash, Hamburg, Germany); 0.2% CHX(b) (Curasept mouth wash, Curadent, Milan, Italy); SS (Natrii chloride infundibule, Hemofarm, Vršac, Serbia); CA (Citric acid 10%, Cerkamed, Poland); EDTA (Ethylenediaminetetraacetic acid 17%, Cerkamed, Poland); EDTA (Kavipran – 2% ethylenediaminetetraacetic acid, Galenika, Belgrade, Serbia); DW (Aqua destilata, Hemofarm, Vršac, Serbia).

Instruments and measurement method

Graduated glass capillary tube 400 μm in diameter (LingYan Engineering Co. Ltd, China) was used for capillarity experiments and orthodontic ruler (raster of 0.5 mm) and magnifying glass (4 ×) were employed for the measurements of the solutions level (Figure 1).

The temperature levels of 20, 38, and 50°C were assembled by alcohol thermometer in the stable ambient laboratory conditions (t = 20°C, 65% humidity). Each sample solution was poured into Erlenmeyer vessel at the level of 22 mm. Capillary glass tube was then plunged into the vessel perpendicular to the vessel bottom. Immediately upon solution rise, the tube was sealed by thumb and the level of meniscus was recorded by a red water-resistant marker. Capillarity value was measured from the tip of the glass tube to the red marker point by an orthodontic ruler and a magnifying glass (± 0.25 mm error). The span value (Δl) was calculated as the difference between capillarity values (h) among all three temperature points (i.e.: Δl_1 = h50 - h20, Δl_2 = h50 - h38, Δl_3 = h38 - h20), for all solutions. Measuring was repeated three times for every experimental solution at all three temperature points.

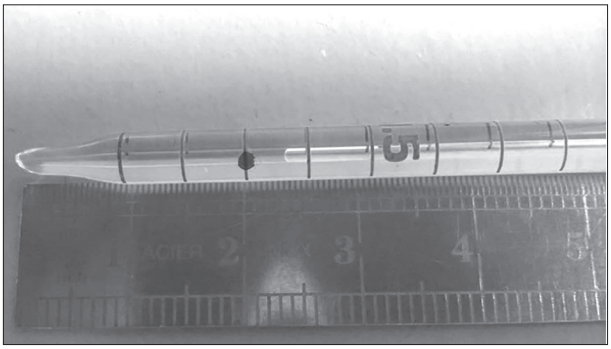

Figure 1. Graduated glass capillary tube with a diameter of 400 μm adjacent to an orthodontic ruler

Statistical analysis

The obtained values were submitted to statistical analysis using SPSS Statistics, Version 17.0 (SPSS Inc., Chicago, IL, USA).

Normality of data was checked using the Kolmogorov–Smirnov test, then one-way ANOVA test (with repeated measures and multiple-comparisons Bonferroni tests) was utilized for within-group and between-group comparison, considering the following parameters: solution and temperature. The statistical significance was set at $p < 0.05$.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine, as well as ethical standards of institutions for each author involved.

RESULTS

The obtained capillarity values of studied solutions are presented in Figures 2 and 3. Summary of between-group statistical analysis is presented in Table 1.

All heated solutions expressed increase in capillarity, but 96% EA, 70% EA, 2% CHX, 0.2% CHX(a), 0.2% CHX(b), and 10% CA showed statistically significant rise, especially when heated from 20°C to 50°C ($p < 0.05$). The highest capillary value span was recorded for 70% EA (8.8 ± 1.1 mm), while the lowest one was noted for both 2.5% SH and 3% HP (2.1 ± 1.5; 2.1 ± 1.6 mm, respectively).

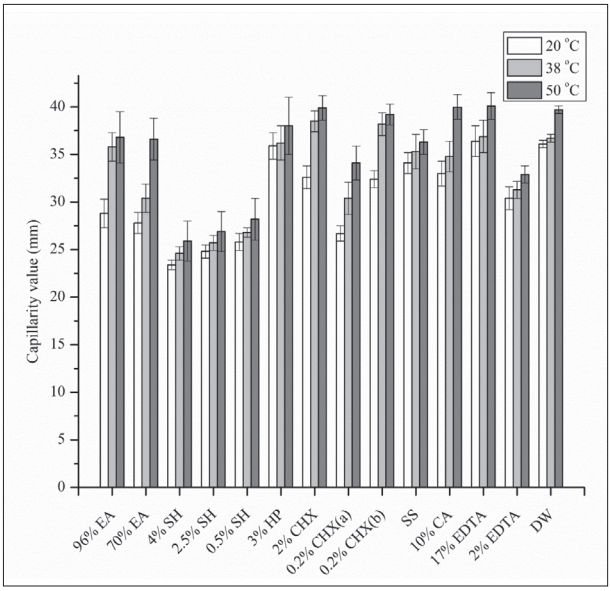

Figure 2. The obtained results of capillarity values (mean ± SD) for investigated solution at three temperature levels;

EA – ethyl alcohol; SH – sodium hypochlorite; HP – hydrogen peroxide; CHX – chlorhexidine; SS – saline solution; CA – citric acid; EDTA – ethylenediaminetetraacetic acid; DW – distilled water;
respective values (mean ± SD) distributed in the cells; plotted in computer software OriginPro 8.5

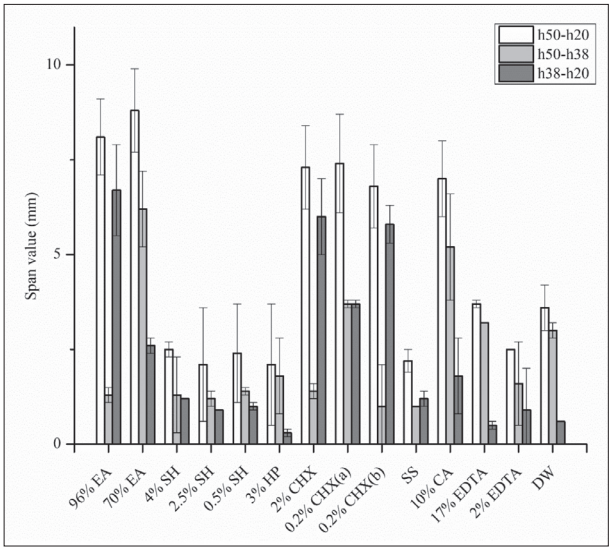

Figure 3. The span values of tested solutions' capillarity (mean ± SD). h50–h20, difference in capillarity values between temperatures of 50°C and 20°C; h50–h38, difference in capillarity values between temperatures of 50°C and 38°C; h38–h20, difference in capillarity values between temperatures of 38°C and 20°C;

EA – ethyl alcohol; SH – sodium hypochlorite; HP – hydrogen peroxide; CHX – chlorhexidine; SS – saline solution; CA – citric acid; EDTA – ethylenediaminetetraacetic acid; DW – distilled water;
respective values (mean ± SD) distributed in the cells; plotted in computer software OriginPro 8.5

DISCUSSION

Bearing in mind that the capillary effect in the oral cavity can be both beneficial (spreading of medicamentous solutions into capillary spaces) and detrimental (undesirable attraction of unwanted pathogenic substances into tissue spaces), the goal of this work was to examine various solutions' capillarity, especially at the maximum bearable temperature of the oral cavity (~ 50°C) [12].

The rise of concentration of studied solutions did not follow correspondently the rise in capillary height for the temperature span of 20–50°C. Namely, with concentration decrease of EA solutions, length span increased. The opposite situation was found for SH and EDTA solutions. The correlation between solution concentration and span value was not found for CHX samples. Commercial preparations of CHX showed different capillarity values, where explanation might be due to different addition of corrigens and stabilizing agents such as polyethylene glycol (PEG), propylene glycol, castor oil, etc. Aforementioned indicates that the very nature of the dissolved substance in investigated samples might cause the uneven distribution of capillary values.

Considering the change of capillarity values at investigated solutions for temperature spans of both 20–38°C and 38–50°C, it is to note similar situations; i.e. sometimes, the rise of water partition in the samples resulted in the fall of capillarity span, or the opposite.

The studied solutions resulted in different extent of capillarity rise at all samples due to enhanced velocity of solution molecules and less friction along the glass walls of the capillary tube. Different values of capillarity at different solutions could be explained by their nature. Moreover, the water partition of the samples with different substances did not influence the obtained values at the same way: somewhere water enhanced, and somewhere it lessened the capillary power, although DW *per se* resulted in very high values of capillarity for all three temperature levels (36.1 – 36.7 – 39.7 mm). Those discrepancies in capillarity change were in some cases statistically significant and in other cases they were not. Additional explanation might be in specifical bonding between water and solvate substances (EA, SH, CHX). In addition, very low capillarity rise for the 20–50°C temperature span for all SH concentrations, 2% EDTA, 3% HP, and SS indicates that they should not be heated, although there are no literature results if such small capillary rise could significantly influence the elimination of pathogens.

The present study is the first report in the literature of the capillarity values of different dental solutions and therefore there are no other studies to compare with. There are many studies about rheological and similar properties of the solutions to apply in dentistry, correlating the nature of solution and tooth tissues. Those solutions' features were presented through the different physical values: viscosity [13], surface tension – surface free energy [14], contact angle [15], wetting [16, 17], as well as temperature dependence to contact angle [18]. Regarding before mentioned, the results of those studies represented through the various physical units should be adequately converted thus allowing the results' comparison. Considering the equation for capillarity determination, it will be interesting to discuss the capillarity value (height of the solution column) in correlation to the parameters that could have influence on it, such as surface tension (γ), wetting angle (α), and density (ρ) of the liquid. For instance, the value of surface tension

Table 1. Summary of between-group statistical analysis results at three temperature levels

Solutions		p-value		
(I) Group	(II) Group	(I vs. II) at 20°C	(I vs. II) at 38°C	(I vs. II) at 50°C
96% EA	70% EA	0.006	0.000	1.000
	4% SH	0.000	0.000	0.000
	2% SH	0.000	0.000	0.000
	0.5% SH	0.000	0.000	0.000
	3% HP	0.000	0.368	0.076
	2% CHX	0.001	0.000	0.000
	0.2% CHX(a)	0.000	0.002	0.000
	0.2% CHX(b)	0.000	0.000	0.000
	SS	0.000	1.000	1.000
	10% CA	0.000	1.000	0.000
	17% EDTA	0.000	0.027	1.000
	0.2% EDTA	0.000	0.006	0.000
	DW	0.000	0.059	0.000
70% EA	4% SH	0.000	0.000	0.000
	2% SH	0.000	0.000	0.000
	0.5% SH	0.000	0.000	0.000
	3% HP	0.000	0.000	0.003
	2% CHX	0.000	0.000	0.000
	0.2% CHX(a)	0.047	1.000	0.000
	0.2% CHX(b)	0.000	0.000	0.000
	SS	0.000	0.000	1.000
	10% CA	0.000	0.000	0.000
	17% EDTA	0.000	0.000	1.000
	0.2% EDTA	0.000	1.000	0.000
	DW	0.000	0.000	0.000
4% SH	2% SH	0.000	1.000	0.619
	0.5% SH	0.000	0.032	0.000
	3% HP	0.000	0.000	0.000
	2% CHX	0.000	0.000	0.000
	0.2% CHX(a)	0.000	0.000	0.000
	0.2% CHX(b)	0.047	0.000	0.000
	SS	0.000	0.000	0.000
	10% CA	0.000	0.000	0.000
	17% EDTA	0.000	0.000	0.000
	0.2% EDTA	0.000	0.000	0.000
	DW	0.000	0.000	0.000
2% SH	0.5% SH	0.002	1.000	0.060
	3% HP	0.000	0.000	0.000
	2% CHX	0.000	0.000	0.000
	0.2% CHX(a)	0.000	0.000	0.000
	0.2% CHX(b)	0.000	0.000	0.000
	SS	0.000	0.000	0.000
	10% CA	0.000	0.000	0.000
	17% EDTA	0.000	0.000	0.000
	0.2% EDTA	0.000	0.000	0.000
	DW	0.000	0.000	0.000
0.5% SH	3% HP	0.000	0.000	0.000
	2% CHX	0.000	0.000	0.000
	0.2% CHX(a)	0.514	0.000	0.000
	0.2% CHX(b)	0.000	0.000	0.000
	SS	0.000	0.000	0.000
	10% CA	0.000	0.000	0.000
	17% EDTA	0.000	0.000	0.000
	0.2% EDTA	0.000	0.000	0.000
	DW	0.000	0.000	0.000
3% HP	2% CHX	0.000	0.193	0.004
	0.2% CHX(a)	0.000	0.000	0.014
	0.2% CHX(b)	0.000	1.000	0.564
	SS	0.000	1.000	0.000
	10% CA	0.000	1.000	0.000
	17% EDTA	1.000	1.000	0.908
	0.2% EDTA	0.000	0.000	0.000
	DW	1.000	1.000	0.001
2% CHX	0.2% CHX(a)	0.000	0.000	1.000
	0.2% CHX(b)	0.000	1.000	1.000
	SS	0.000	0.001	0.000
	10% CA	0.000	0.000	1.000
	17% EDTA	0.000	1.000	0.000
	0.2% EDTA	1.000	0.000	0.000
	DW	0.000	0.984	1.000
0.2% CHX(a)	0.2% CHX(b)	0.000	0.000	1.000
	SS	0.000	0.000	0.000
	10% CA	0.000	0.000	1.000
	17% EDTA	0.000	0.000	0.000
	0.2% EDTA	0.000	1.000	0.000
	DW	0.000	0.000	1.000
0.2% CHX(b)	SS	0.000	0.016	0.000
	10% CA	0.635	0.001	0.387
	17% EDTA	0.000	1.000	0.000
	0.2% EDTA	0.000	0.000	0.000
	DW	0.000	1.000	1.000
SS	10% CA	0.001	1.000	0.000
	17% EDTA	0.000	1.000	0.736
	0.2% EDTA	0.000	0.000	0.000
	DW	0.000	1.000	0.000
10% CA	17% EDTA	0.000	0.260	0.000
	0.2% EDTA	0.000	0.000	0.000
	DW	0.000	0.517	1.000
17% EDTA	0.2% EDTA	0.000	0.000	0.000
	DW	1.000	1.000	0.000
0.2% EDTA	DW	0.000	0.000	0.000

EA – ethyl alcohol; SH – sodium hypochlorite; HP – hydrogen peroxide; CHX – chlorhexidine; SS – saline solution; CA – citric acid; EDTA – ethylenediaminetetraacetic acid; DW – distilled water; one-way ANOVA and multiple comparisons Bonferroni test, $p < 0.05$

is in reverse proportion to the capillary power of the liquid, while wetting is directly proportional to the capillary power and in reverse relation to the contact angle value. In this way Lopes et al. [17] applied the measurements of the contact angle and the surface tension of irrigants, calculating the wettability of the studied solutions using Young's equation.

Khattab et al. [19] investigated the density, viscosity, and surface tension of water + ethanol mixtures from 293 to 323 K. They made mathematical conversion of density, viscosity, and surface tension of binary mixture of water + ethanol at 293, 298, 303, 308, 313, 318, and 323 K and compared the data with the available literature data. This study shows that the Jouyban–Acree model can correlate/

predict physicochemical properties of mixtures of solvents at different temperatures with acceptable error in calculations. Thus, positive correlation was confirmed between contact angle (wetting) and capillarity values [19]. The addition of active substances for surface tension lessening into the CHX solutions gives positive effect, but it does not influence the superior pulp tissue dissolution and better lubricant in root canal [14]. In that way, surfactant can enter the minor lacunar spaces even narrower than 0.5 mm (capillary space). PEG, usually employed as a surfactant, acts as hydrophilic molecule attracting water molecules and inducing more capillarity, and might be used as the experimental additive-surfactant where coarse aggregate solutions affect the permeability of the substrate [20].

It is interesting to mention a study by Rossi-Fedele and Guastalli [14] using pendant drop method to evaluate the effect of an alcohol-based caries detector (Kurakay; Kuraray Co., Ltd., Tokyo, Japan) on the surface tension of a conventional SH solution at 20°C by optical recording with a commercially available apparatus. In this manner, the addition of Kurakay significantly reduced the surface tension of SH [14].

The capillary potential can be most clearly understood at 50°C, where the greater significant difference among investigated solution was found, compared to those obtained at 20°C and 38°C. In fact, the differences between 20°C and 38°C were not significant in most solutions. The explanation that the increase of temperature provoked higher capillary power lies in the fact that all dissolved molecules then become more mobile going along the glass wall of the capillary tube. The high value of EDTA molar mass (338.2 g/mol) might be the reason for low speed of its molecules even when warmed. Hence, there would be no clinical benefit of using warmed EDTA irrigant.

EA solutions along the increase of active ingredient (70–96% ethanol) showed the increase of capillarity at all three temperature levels (28 – 30 – 37; 29 – 36 – 37 mm, respectively). The greatest increase of capillary column (h50–h20 span) was found for 70% EA (8.8 mm), presumably making it a better antimicrobial solution compared to 96% EA (8 mm). The utilization of 96% EA in our study can be justified by its use in dentistry as a dehydrator, although less antiseptic than 70% EA. One review reported the antimicrobial effect of alcohol solution with the addition of CHX in surgical procedures [21].

In contrast to EA, SH solutions with an increase of chlorine concentration (0.5 – 2.5 – 4% SH) exhibited simultaneously the weakening of their capillary power although statistically insignificant at all temperature points (0.5% : 26 – 24 – 23; 2.5%: 27 – 26 – 24; 4%: 28 – 27 – 26 mm). Hence, the utilization of higher concentration SH irrigants (5.25% and 6%) would result in the similar way. Guerisoli et al. [22] indicated the rise of viscosity, i.e., the lessening of the capillarity effect of SH 0.986–1.110 times by the increase of its concentration (0.5–4%), which is in numerical accordance with the results of our study. Sirtes et al. [6] found that the temperature rise of SH samples (5.25%, 2.5%, and 1%, 20–40°C and 60°C) do not exhibit significant antimicrobial effect on *Enterococcus faecalis*.

Regarding the newer data on the chemical nature of surfactants, some authors found amphiphiles with longer hydrocarbon chains more surface-active than solutions with shorter hydrocarbon chains, which could be applicable to the capillarity energy. Namely, the fluorine ions in the fluorocarbon chain serve as a caries-protective agent, exhibiting a stronger hydrophobic effect than the hydrocarbon chain alone [23]. Observing the affinity of certain substances for water, Ekholm et al. [24] found by structural analysis that at the surface, the linear-structured alcohol preferred an orientation with the hydrophobic tail pointing out from the surface, whereas the hydroxyl group remains immersed in the water. This phenomenon, regarding the alcohol solutions, is likely transferable to other small molecules with similar structures but other functional groups [24]. In addition to previously mentioned, microbial-derived biosurfactants present the interesting concept in modern dentistry with a potential for future utilization [25].

It is also necessary to search for a suitable *in vivo* model for testing the capillarity of dental solutions, which would be significantly more accurate than the *in vitro* patterns. Also, the question of finding a suitable surfactant to be added to the dental solution in order to improve capillary strength and other fluid properties still remains open.

CONCLUSION

The greatest capillarity power among investigated solutions was found for 17% EDTA, and the lowest one for SH solutions. The increase of solution concentration considerably influenced the capillarity of EDTA, while different concentrations of SH and CHX showed approximately the same values of capillarity. Finally, the capillarity of the investigated solutions significantly increased with the temperature rise, approving the warming of dental solutions up to 50°C for clinical use in dentistry.

Clinical significance

The obtained results indicate the importance of warming the aforementioned solutions for clinical practice, even for the solutions where capillarity was weak, due to their certain penetrability and antimicrobial effect on the substrate to be conditioned. The nature of the surface along with liquid movability can be an important factor for capillary power, bearing in mind the roughness of the clinical surface where liquid moves (enamel, dentine, root cement, periodontal tissue, composite restauration, ceramic surface, etc.).

Conflict of interest: None declared.

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Лабораторијско испитивање капиларитета различитих стоматолошких раствора на три температурна нивоа

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САЖЕТАК

Увод/Циљ Дугуљасти микропростори ужи од 500 *μm* присутни су у усној дупљи у виду тубуларних простора дентина, пулпопериодонталних каналића, гингивног сулкуса, зјапа рестаурације итд. Како су ови простори изложени задржавању хране и патогена, већина денталних раствора требало би лако да продре у њих и делује терапеутски. Из тог разлога је циљ ове студије био да се процени ефекат капиларности често коришћених денталних раствора на три температурна нивоа.

Методе Испитивани су раствори етанола, натријум-хипохлорита, водоник-пероксида, хлорхексидина, физиолошког раствора, лимунске киселине, етилен-диамино-тетраацетатне киселине и дестиловане воде, на 20, 38 и 50° *C*, у капиларној цеви промера 400 *μm*. Висина капиларног стуба је забележена на градуисаној капиларној цеви (*mm*), а подаци су статистички обрађени.

Резултати Највећи пораст капиларности (20–50° *C*) показао је 70% етанол (8,8 ± 1,1), а најнижи 2,5% натријум-хипохлорит (2,1 ± 1,5) и 3% водоник-пероксид (2,1 ± 1,6). Највиша капиларност добијена је на 50° *C* за 17% етилен-диамино-тетраацетатну киселину (40,1 ± 1,4), а најнижа за 4% натријум-хипохлорит (25,9 ± 2,1) ($p < 0,05$).

Закључак Ниво капиларности свих денталних раствора расте са порастом температуре, али у различитом степену.

Кључне речи: иригација; натријум-хипохлорит; хлорхексидин; етилен-диамино-тетраацетатна киселина; слободна површинска енергија

DOI: https://doi.org/10.2298/SARH241018087P
UDC: 616.314-002-08

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Variability in the integration of minimum intervention principles in caries management among dental students

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SUMMARY

Introduction/Objective The aim of the study was to assess the knowledge and attitudes of dental students and young dentists towards caries management and principles of minimum intervention cariology.

Methods Students filled in the online questionnaire that included: 1) attitudes and knowledge about the use of caries risk (CR) assessment tools in clinical practice; 2) treatment plans in clinical case scenarios of smooth surface and occlusal caries in relation to CR; 3) impact of different diagnostic procedures on the management of dentin caries, tooth preparation and preferred restoration techniques and materials.

Results The majority of students thought that CR should influence the treatment plan. Oral hygiene was considered the most important CR factor. More invasive treatment was chosen in high CR patients. The most important criterion for caries removal was dentin hardness. The majority of students would completely remove soft dentine in deep caries lesions, either in one-step or two-step preparation technique. Composite was the most frequently selected restorative material.

Conclusion Conventional approach to caries management is still widely accepted among students and young dentists. Their knowledge of minimum intervention dentistry is limited. Periodic assessment of implemented curriculum and teachers' calibration could serve as resources for improving the teaching process.

Keywords: dental students; knowledge; cariology; minimum intervention

INTRODUCTION

Operative treatment of dental caries traditionally involved removal of all infected tissues and their replacement with a restoration [1]. For many decades, teaching operative dentistry was based on demonstrating techniques for complete caries removal. The most recent understanding of caries pathophysiology, advancement in the field of remineralization agents, and the accessibility to adhesive materials, changed the conventional caries management towards minimum intervention (MI) oral care [2]. However, many dental practitioners consider MI procedures as temporary aid in caries treatment [3, 4].

School of Dental Medicine of the University of Belgrade is the oldest dental school in the Western Balkans region. The Curriculum in Cariology for undergraduate students shares similar learning outcomes with European Core Curriculum in Cariology [5]. Students are introduced to the fundamental mechanisms of dental caries in pre-clinical courses, such as General and Oral Biochemistry, and Microbiology and Immunology. As students progress to the final undergraduate year, they gain knowledge about various aspects of caries prevention and management. Theory and practice are integrated into the course of Preventive Dentistry, Restorative Odontology, Pediatric Dentistry, Public Health, and elective courses. The courses are designed to equip students with knowledge on both traditional and contemporary aspects of delivering oral health care. Curriculum sets general learning objectives, but the presentation of information, expertise, and resources may vary among faculty members. This variation can be either beneficial or counterproductive for future graduates. Understanding MI can be complex and overwhelming for students, especially at the beginning of their education.

The aim of the study was to assess the knowledge and attitudes of dental students and young dentists towards caries management and principles of MI cariology.

METHODS

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee (document 36/10). The following groups of undergraduate students were invited to fill in the online questionnaire: fourth-year students who completed the Preventive Dentistry course and

Received • Примљено: October 16, 2024
Revised • Ревизија: November 18, 2024
Accepted • Прихваћено: November 19, 2024
Online first: November 22, 2024

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participated in the clinical course of Restorative Dentistry; fifth-year students who passed Restorative Dentistry and were currently practicing Pediatric Dentistry, and sixth-year students who finished the aforementioned courses. Additionally, students enrolled in the internship program were invited to participate in survey.

The questionnaire was based on the ones previously used to evaluate attitudes towards caries risk (CR) assessment (CRA) [6, 7], enamel [6, 7], and dentin [8] caries treatment, and cavity restoration [9]. Two bilingual researchers experienced in conducting surveys translated the selected questions from the aforementioned questionnaires from English to Serbian. An independent bilingual researcher conducted the back-translation to English with only a few discrepancies. Research team reviewed translations and reached consensus on the final version. The questionnaire was pilot-tested by 45 undergraduate students (15 students from each study year). Students completed the questionnaire, provided their feedback, and confirmed understanding of all the questions.

Besides demographics, the questionnaire included three parts. Questions in the first part were related to attitudes and knowledge about the use of CRA in clinical practice, and the impact of different CR factors. The second part analyzed the choice of caries treatment for smooth and occlusal surfaces according to CR in clinical case scenarios. The third part aimed to assess students` understanding of how different diagnostic procedures influence dentin caries treatment, their attitudes towards caries removal criteria and methods, and preferred cavity restoration techniques.

Students were invited through the website of the Belgrade School of Dental Medicine, and social media. Google Forms was used as the platform to create the online questionnaire and collect data. E-mail verification was used to prevent the multiple participation. In a short note preceding the questionnaire, students were informed on the research purpose, and that their participation was voluntary and anonymous. Completing the questionnaire and submitting of the answers were considered to be the consent to participate in the survey. Students were allowed to select multiple answers and write explanations to further clarify their opinions. The survey was opened for six weeks.

Statistical analysis was performed using IBM SPSS Statistics 20.0 (IBM, Armonk, N.Y., USA). Data were first descriptively analyzed. The groups were compared using Fisher's exact test, with statistical significance set at $p < 0.05$. In order to account for multiple comparisons, the Bonferroni correction was applied, and statistical significance was determined using a Bonferroni-corrected significance level.

The article was written in accordance with the ethical standards of the institutions and the journal.

RESULTS

A total of 221 questionnaires were completed resulting in an average response rate of 41%. Specifically, 35% of the fourth-year, 32% of the fifth-year, 48% of the sixth-year undergraduate students, and 64% of graduate students participated.

Caries risk assessment

Most of the participants (96%) believed that a patient's CR should influence the treatment plan, but only 41% performed the CRA in their clinical practice (Table 1). The CRA was not consistently implemented because teaching staff did not enforce it (39%). Some students lacked the knowledge of how to perform CRA (21%), while others did not have time to do it (21%), and 11% considered the CRA unnecessary. Oral hygiene, patient's motivation and diet were considered to be the top three factors for determining CR.

Table 1. Attitudes towards caries risk assessment

Variable	4th-year students	5th-year students	6th-year students	DDS	Total
Do you perform CRA?					
Yes (%)	30	46	43	44	41
No (%)	70	54	57	56	59
Should CRA influence the treatment plan?					
Yes (%)	95	98	97	97	97
No (%)	5	2	3	3	3
How well are you informed about CRA?					
Well (%)	23	37	25	9	25
Partially (%)	36	22	23	38	28
Insufficiently (%)	41	41	52	53	47

CRA – caries risk assessment;
DDS – doctors of dental surgery

Enamel caries

Selected options for the treatment of smooth and occlusal surfaces are presented in Table 2.

For the white spot lesion, students chose more invasive treatment for high CR compared to low CR patients. No differences in the selected treatment options were found between undergraduate students of different study years (except for obvious cavity in high CR patients), between students and young dentists, or between male and female students.

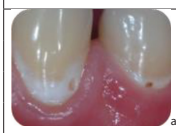
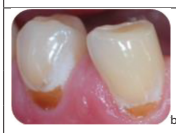
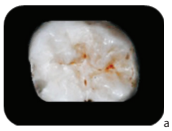
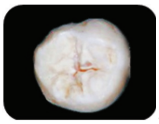
The upward trend in selecting more invasive treatment for occlusal caries was noticed in both low and high CR patients. A small number of students stated that they would need additional diagnostic tools in the decision-making process.

Dentin caries

A thorough anamnesis was considered crucial for the proper diagnosis of dentin caries, followed by radiographic findings and vitality testing.

Seventy-six percent of respondents would perform tooth preparation using rotary instruments. Rotary in combination with hand instruments in pulp proximity were the preferred method of caries removal for 23%, mainly senior students (Table 3).

Table 2. Treatment options for enamel lesion according to the caries risk (%)

Treatment options		Low CR					High CR				
		4th-year students	5th-year students	6th-year students	DDS	Total	4th-year students	5th-year students	6th-year students	DDS	Total
 a	O	30	24	32	28	29	4	0	4	72	13
	REM	64	76	68	72	69.5	53	57	71	28	57
	REST	2	-	-	-	0.5	39	41	25	-	29
	NA	4	-	-	-	1	4	2	-	-	1
 a	O	7	4	8	3	6	2	-	3	-	1
	REM	45	52	63	66	56	12	13	20	9	15
	REST	36	39	29	28	33	77	88	74	91	80
	NA	12	5	-	3	5	9	2	3	-	4
 b, c	O	2	2	3	-	2	3	-	4	-	2
	REM	7	11	11	16	11	2	2	3	-	2
	REST	86	87	83	84	85	86	98	93	100	94
	NA	5	-	3		2	9	-	-	-	2
 a	O	21	19	7	28	17	2	9	1	-	3
	REM	20	11	18	9	15	11	7	12	19	11
	FS	54	70	75	63	66.5	62	69	62	62	65
	REST	2	-	-	-	0.5	20	15	25	19	20
	NA	3	-	-	-	1	5	-	-	-	1
 a,b	O	12.5	11	14	22	14	-	6	-	-	1
	REM	11	7	12	9	10	7	9	5	9	7
	FS	32	52	34	53	41	25	26	6	22	18
	REST	32	26	39	16	31	57	59	89	69	71
	NA	12.5	4	1	-	4	11	-	-	-	3
 a,d	O	9	11	-	13	7	-	4	-	-	1
	REM	7	4	9	6	7	3	2	2.5	6	3
	FS	27	20	16	31	22	9	7	2.5	3	5
	REST	52	65	72	50	62	77	87	95	91	88
	NA	5	-	2	-	2	11	-	-	-	3
	O	3	2	2.5	-	2	3	-	-	-	1
	REM	2	2	2.5	-	2	2	-	2.5	-	1
	FS	7	2	2.5	3	4	2	-	-	-	0.5
	REST	85	94	92.5	94	91	90	100	95	100	95.5
	NA	3	-	-	3	1	3	-	2.5	-	2

CR – caries risk; O – observation; REM – remineralization; FS – fissure sealing; REST – restoration; NA – do not know; DDS – doctors of dental surgery;
[a]p = 0.000 (Fisher's exact test) between low and high caries risk;
[b]p < 0.0125 (Fisher's exact test, Bonferroni-corrected p-value) for the treatment choice in high caries risk patients among students of different study years;
[c]p < 0.0125 (Fisher's exact test, Bonferroni-corrected p-value) between low and high caries risk;
[d]p < 0.0125 (Fisher's exact test, Bonferroni-corrected p-value) for the treatment choice in low caries risk patients among students of different study years

Dentin hardness was reported as the most important criterion for assessing the endpoint of caries removal. Even in deep cavities, the vast majority (99%) would excavate all softened dentin, and finished the preparation in either leathery or hard dentin. Half of the respondents did not consider the color of dentin a relevant criterion. Eighty-one percent of students believed that all microorganisms should be removed from the cavity, otherwise caries might progress (Table 3). Senior students tended to prefer conservative treatment compared to their younger peers.

Treatment choices for clinical scenario involving an asymptomatic tooth with dentin caries were usually removal into leathery or hard dentin (Table 3). In deep asymptomatic caries lesions, 86% of students opted for complete caries removal. Stepwise excavation was the preferred option for incomplete dentin removal (Table 4).

Students were indecisive when choosing calcium hydroxide treatment duration for deep caries (Figure 1).

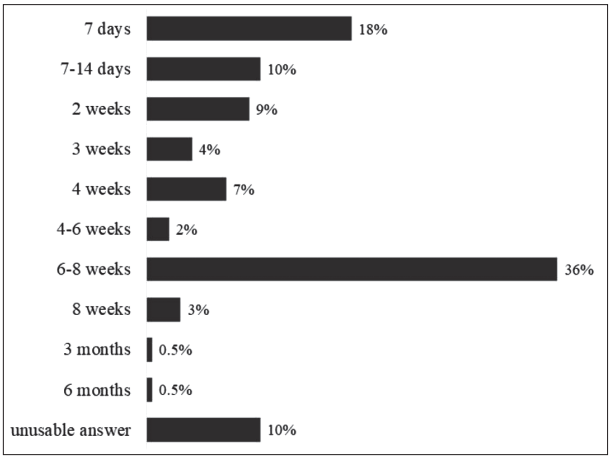
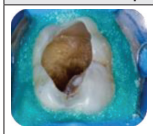
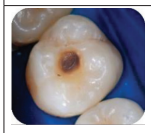
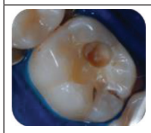


Figure 1. Duration of calcium hydroxide treatment

Table 3. Attitudes towards caries excavation (%)

Variable	4th-year students	5th-year students	6th-year students	DDS	Total
Preferred caries removal method[a]					
Rotary instruments	87	80	67	72	76
Hand instruments	4	-	1	-	1
Combination	9	20	32	28	23
Hardness					
Soft dentin should be removed	98	100	97	100	98.6
Leathery dentin should be removed	2	-	-	-	0.4
Irrelevant	-	-	3	-	1
Color[b]					
Normal dentin	75	28	36	41	44
Stained dentin	2	7	6	-	5
Irrelevant	23	65	58	59	51
Microorganisms[c]					
All bacteria need to be removed, otherwise caries might progress	95	89	71	72	81
Some bacteria may be left beneath a tightly sealed restoration	5	9	28	28	18
Depends on restorative strategy	-	2	1	-	1
Carious dentin[c]					
Carious dentin should always be removed completely, otherwise it might influence the pulp vitality	84	65	52	88	68
Carious dentin in close proximity to the pulp should be left to avoid pulp exposure	14	30	46	12	29
Depends on restorative strategy	2	5	2	-	3
Border of the preparation[c]					
	7	9	13	22	12
	70	41	29	53	46
	21	42	52	25	38
More tissue should be removed (all dentin with changed color)	-	4	1	-	1
Cannot decide without probing	2	4	5	-	3

DDS – doctors of dental surgery;
[a]$p < 0.0125$ (Fisher's exact test, Bonferroni-corrected p-value) between students of different study years;
[b]$p = 0.000$ (Fisher's exact test) between students of different study years;
[c]$p < 0.001$ (Fisher's exact test) between students of different study years

Glass-ionomer (47%) and zinc phosphate cement (44%) were usually chosen as temporary restorations.

Most students would opt to place a liner/base under a permanent restoration of deep cavity. Composite was the most frequently selected material for permanent restoration (Table 4).

DISCUSSION

The field of MI dentistry and advancements in biomaterials have been continuously expanding. It is important for undergraduate dental students to be exposed to and gain experience with new technologies and techniques. However, many professionals and dental educators resist successful implementation of MI across the oral healthcare sector. Students' answers might reflect the way they were educated.

There was no consensus among students regarding caries diagnostics, non-restorative and restorative management. Often, students are overwhelmed with information and faced with numerous possibilities, yet they lack the specific tools needed to define the appropriate approach to caries management. Various methodological tactics, instructional strategies, practical applications, and teachers' attitudes could potentially lead to confusion or overconfidence among students. The insecurities often become apparent during final exams and later in graduate programs.

Individual treatment plan should rely on the patient's CR. Dentists must be able to identify the components of the disease and create appropriate treatment plan. General dentists usually perform CRA, but often without specific forms and clear rules [6, 7, 10]. The present study revealed that students felt insufficiently informed about CRA. The CR factors and assessment methods are taught meticulously in the course of Preventive Dentistry during the second study year. It seems that CRA demonstration and practice are neglected during the fourth study year in the Restorative Dentistry course. In the fifth study year, CRA is presented as obligatory during clinical practice in Pediatric Dentistry. The inconsistencies in the educational process limit students' ability to determine the correct approach. Students are left uncertain whether CRA is a necessity in the diagnostic process or just an occasionally employed tool. Similarly, French students expressed confusion regarding the necessity of CRA [11]. Some stated that CRA was not adequately demonstrated (31%), while others admitted having insufficient knowledge (23.5%). CRA was not important for 11% of Serbian students and for 2% of their French peers. Serbian and French students agreed on the hierarchy of CRA factors. Nasseripour et al. [12] highlighted the importance of addressing the lack of knowledge and motivation to perform the CRA not only among students but, more importantly, also among educators in the future cariology curricula.

Early intervention was more likely to be chosen in patients with high CR. Although non-invasive caries

Table 4. Restoration of a deep caries lesion (%)

Variable	4th-year students	5th-year students	6th-year students	DDS	Total
Restoration of deep caries lesion[a]					
complete removal of carious dentine + temporary restoration + definitive restoration in next visit	53	31	38	34	40
complete removal of carious dentine + definitive restoration	34	46	53	50	46
partial removal to soft dentine + temporary restoration + definitive restoration in next visit	11	17	5	16	11
partial removal to soft dentine + definitive restoration	2	6	1	-	2
depends on a case scenario	-	-	3	-	1
Materials for indirect pulp capping					
$Ca(OH_2)$-based liner	73	70	72	66	71
MTA	22	26	23	28	24
Biodentine	5	4	4	6	4.5
No liner	-	-	1	-	0.5
Materials for permanent restoration[b,c]					
GIC	37	17	18	6	21
Composite	30	78	69	53	59
"Sandwich" technique	29	5	13	35	18
Amalgam	4	-	-	6	2

GIC – glass-ionomer cement, MTA – mineral trioxide aggregate;
[a]$p < 0.0167$ (Fisher's exact test, Bonferroni-corrected p-value) between students of different study years;
[b]$p = 0.000$ (Fisher's exact test) between students of different study years;
[c]$p < 0.0167$ (Fisher's exact test, Bonferroni-corrected p-value) between undergraduate and postgraduate students

management is recommended for non-cavitated smooth surface lesions [13], one third of students would perform invasive treatment in high-CR patients. This finding might provoke two possible explanations. The first one suggests a lack of knowledge about caries development, and the concept of non-invasive caries management. The second is that students might be uncertain about their knowledge and experience with non-invasive procedures, so they chose "safer" invasive treatment to avoid errors.

Recent literature suggests that resin infiltration might be a suitable option for esthetically concealing white spot lesions with a greater masking effect than remineralization techniques [14]. It is only recently that the resin infiltration technique has become a part of the cariology curriculum at the Belgrade School of Dental Medicine. For that reason, it was not offered as an option for the smooth surface treatment in the questionnaire.

For "suspicious" non-cavitated fissures that could have benefit from fissure sealing [13], the majority of students chose restorative treatment. Booth et al. [15] reported that high CR led to early restorative intervention of non-cavitated occlusal lesions. Similarly, French students tend to perform operative treatment for "suspicious" occlusal surfaces [16], due to the fear of existing caries progression under the sealant [11].

The most often selected cavity preparation technique was rotary instruments. Senior undergraduate students were in favor of a less invasive approach to caries removal in comparison to the younger ones. Gasqui et al. [17] reported frequent use of hand instruments in the close proximity of pulp among French students, who also chose chemo-mechanical caries removal and polymer/ceramic burs. Although dental professionals in Serbia are familiar with novel cavity preparation techniques, they do not routinely use them. Limited availability and relatively high price hinder widespread implementation of these methods.

In the present study, dentin hardness was accentuated as the most important criterion for caries removal. When students analyzed the clinical scenario of a deep caries lesion, the majority selected the picture that reflected to either 'firm' or 'leathery' dentin. As shown in literature, the majority of dental practitioners preferred removal of all soft dentine, either in the one-step or two-step preparation technique [18, 19]. Growing evidence support selective caries removal to soft dentine in deep cavities, in order to protect pulpal health [20]. However, many dentists are reluctant to perform such treatment and leave caries behind [18].

Dentin color and moisture are recognized as additional clinical judgment criteria for caries removal [20]. The color was not significant for caries removal (51% of respondents). Conversely, 44% of students would perform a cavity preparation to reach dentin with 'normal' color. Similar results were reported in a group of French students [17]. Although the concept of extensive cavity preparation to remove bacteria is outdated [20], 81% of students believe that all cariogenic microorganisms need to be removed. The same attitude was present in 39% of French students [17].

Students demonstrated a lack of understanding for the management of deep caries lesions, in relation to the duration of treatment with calcium hydroxide. The source of their misconception could be that they learn from teachers who have different opinions on the subject. As shown in previous studies [9, 21], most of students would choose to place the liner material under permanent restoration, probably due to the traditional belief that pulp should be protected in order to heal after exposure to cariogenic agents [9].

Composite material was the most popular choice for restoring deep cavity lesions, which is consistent with previous findings [22]. The adequate restoration material should seal the lesion, and resist fracture. Bonding of composite material to caries-affected dentine, which has reduced mineral content, increased porosity and altered collagen structure, is less successful than to the sound dentine [23]. This could lead to the fracturing of the restoration. New generations of glass-ionomer and glass-hybrid cements may be able to tightly seal dentine, while providing the necessary strength for the restoration [24]. It seems that students should be more informed about advantages and limits of contemporary restorative materials.

The potential limitation of the present study could be the response rate. However, the proper response rate for online surveys in the research papers has not been determined yet, and average online survey response rate in education-related fields is 44.1% [25]. Additionally, the survey was conducted in one dental school. Nevertheless, School of Dental Medicine in Belgrade is the largest school that educates approximately 60% of all dental students in the country. The present study demonstrates students` understanding of cariology, but more importantly, it provides answers to questions regarding the way teachers educate and communicate. Results provide evidence of variations in the content being taught with a mixture of modern and traditional concept. It appears that MI approach has not been adequately translated into clinical teaching. The ability to adopt the MI philosophy is a learning curve because it necessitates a change in mindset and perspective, and seeing beyond simple tooth restoration. The problem of cariology being taught in separate departments/clinics, each with its own methodology, has been emphasized in numerous dental schools worldwide [26]. The results of this study could help identify gaps in current teaching and practices and assist in tailoring a new educational process in the field of cariology.

CONCLUSION

Conventional approach to caries management is still widely accepted among students and young dentists. Their knowledge of MI dentistry is limited. A strong cariology curriculum and adoption of evidence-based strategies for the management of dental caries is mandatory in dental education system. Maintaining the high level of caries management competency of faculty members through active training and calibration should be a priority in educational process. Periodic assessment of implemented curriculum and teachers' calibration could serve as a resource and tools for improving the teaching process.

ACKNOWLEDGMENT

This work was supported by the Ministry of Science, Technological Development and Innovation (Grant 451-03-65/2024-03/200129), and the Ministry of Health (Document 000039234 2024 11900 009 001 401 119) of the Republic of Serbia.

Conflict of interest: None declared.

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Разлике у усвајању принципа минималне интервенције у кариологији међу студентима стоматологије

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САЖЕТАК

Увод/Циљ Циљ рада је био да се испитају знање и ставови студената и младих доктора стоматологије о лечењу каријеса и принципима минималне интервенције у кариологији.

Методе Студенти су попуњавали електронски упитник који је обухватао: 1) ставове и знања о процени ризика за настанак каријеса (КР); 2) избор терапије каријеса глатких и оклузалних површина у зависности од КР; 3) избор дијагностичких процедура у лечењу каријеса дентина, техника препарације и материјала за рестаурацију зуба.

Резултати Већина студената сматра да би КР требало да утиче на план третмана. Орална хигијена је најзначајнији фактор КР. Код пацијентата са високим КР биран је инвазивнији приступ. Најважнији критеријум за уклањање каријеса је чврстоћа дентина. Већина студената сматра да би код дубоких каријесних лезија требало уклонити сав размекшани дентин, било једноседансно или двосеансно. Најчешће изабран рестауративни материјал је композит.

Закључак Међу студентима и младим докторима стоматологије још увек је широко заступљен конвенционални приступ лечењу каријеса. Њихово познавање принципа минималне интервенције у кариологији је ограничено. У циљу унапређења наставног процеса, потребна је периодична евалуација курикулума и калибрација наставника.

Кључне речи: студенти; знање; кариологија; минимална интервенција

DOI: https://doi.org/10.2298/SARH231123078V
UDC: 616.36-006.3-073

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prevalence and characteristics of hepatic hemangiomas assessed by ultrasound – a single center experience

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SUMMARY

Introduction/Objective Liver hemangioma is the most common benign tumor of the liver, with estimated prevalence of 2.5–4%. This study aimed to investigate the prevalence and clinical characteristics of hepatic hemangioma in one primary care center in Serbia.

Methods We conducted a cross-sectional study, which included patients examined in the Dr Simo Milošević Primary Care Center in Belgrade, Serbia (December 2017 – March 2020). Patients with suspected atypical changes, malignancies, viral hepatitis infections, and liver cirrhosis were excluded from the study.

Results A total of 567 patients were included in this study (men 42.5%). In 27 patients (4.76%) a diagnosis of hemangioma was made (male:female ratio: 1.1:1). The total number of hemangiomas detected was 48. Hemangiomas were most commonly found in the right liver lobe (32/48, 66.7%). In this study, hemangiomas were most commonly localized in the fourth liver segment (11/48, 22.9%). The mean diameter of the hemangioma was 13.8 mm. In the half of patients diagnosed with hemangioma, more than one hemangioma was detected (13/27, 48.1%).

Conclusion Hemangiomas of the liver are commonly multiple. No sex difference in hemangioma prevalence was noted. The right liver lobe is the most common hemangioma localization in this study cohort.

Keywords: liver hemangioma; ultrasonography; frequency

INTRODUCTION

The liver hemangioma is the most common benign tumor of the liver [1, 2]. Hemangiomas are the third most common liver lesion with a frequency of 3.6%, after focal fatty sparing of the liver with prevalence of 6.3% and liver cysts with prevalence of 5.8% [3]. The number of hemangiomas in patients has increased in recent years, most likely due to the increased number of medical examinations. Its incidence ranges 2.5–4% in ultrasound series.

In most studies hemangiomas were more frequent in female than in men, with ratio of 5:1 to 1.9:1. Hemangiomas were most common in patients 30–60 years old [4–9].

There are three types of liver hemangioma: cavernous, capillary, and anastomosing hemangiomas. The most frequent is cavernous hemangioma [10]. Ultrasound has proven to be a sovereign method for diagnosing hepatic hemangiomas with an assessment of sensitivity of 96.9% and specificity of 60.3% [11]. Most of the patients with liver hemangioma have no symptoms. Treatment is not necessary if the tumor is asymptomatic and patients are only followed up [12]. If the tumor size increases, it can cause symptoms such as abdominal discomfort, pain, distension, vomiting, poor appetite, pressure on the local structures and even serious complications such as tumor rupture or bleeding [13]. In that case, the surgery is a choice of treatment [14, 15, 16].

To date, there are lack of epidemiological data on the frequency of liver hemangiomas in our region. There are few available studies, done in Germany, Italy, Iran, China, and Chile [3, 4, 6, 9, 17].

This study is aimed at investigating the prevalence and clinical characteristics of hepatic hemangioma in one primary care center in Serbia. According to our knowledge, studies like this have not previously been conducted in this field in our region.

METHODS

Data for this cross-sectional study were collected during regular ultrasound examinations in the Dr. Simo Milošević Primary Care Center, Belgrade, Serbia, in the period from December 2017 to March 2020. Data were collected from a review database of two physicians who performed the real-time gray-scale sonography.

The study population includes patients older than 18 years old who underwent an abdominal ultrasound. Patients were referred for an ultrasound examination by a general practitioner as part of regular medical check-ups or because of abdominal pain, abdominal discomfort and due to regular control of the underlying disease.

Received • Примљено: November 23, 2023
Revised • Ревизија: September 11, 2024
Accepted • Прихваћено: September 16, 2024
Online first: September 18, 2024

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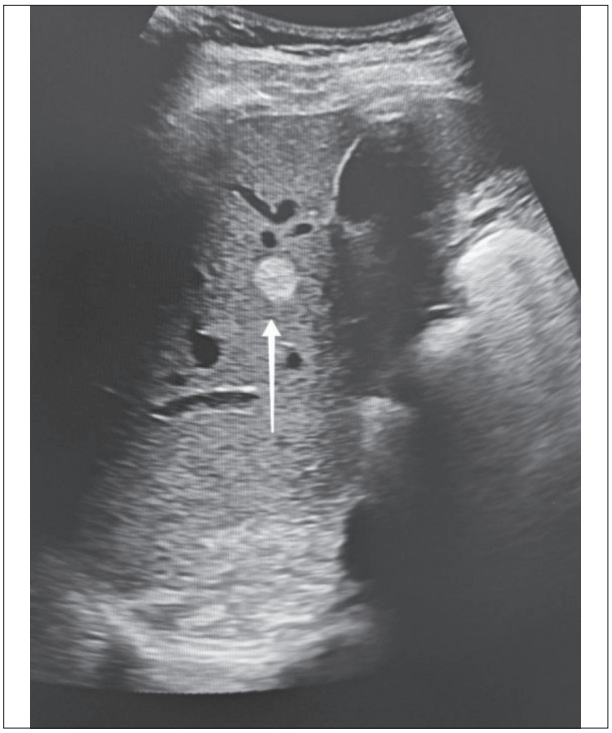

Figure 1. Ultrasound appearance of a typical hepatic hemangioma

Patients with suspected atypical changes, malignancies, viral hepatitis infections and liver cirrhosis who were diagnosed with liver lesions were excluded from the study.

During the examination, in addition to the basic abdominal ultrasound data, data on the size, location, and number of liver hemangiomas were also recored. The diagnosis of the hepatic hemangioma was determined using ultrasound parameters, which include homogenous hyperechoic mass with acoustic enhancement, sharp margins, and absence of halo sign [18] (Figure 1). Each case that was not typical was sent for further diagnosis and was excluded from the study.

The examination was done on SIEMENS ACUSON NX3 Elite and TOSHIBA Xario 100 xario devices.

The study is conducted in accordance with Good Clinical Practice guidelines (ICH-GCP), the Declaration of Helsinki and applicable local regulations. The study protocol was approved by the Institutional Ethics Review Board of the Dr. Simo Milošević Primary Care Center, Belgrade, Serbia. Patient consent was waived due to the retrospective nature of the study.

Statistical analysis

All collected data were statistically processed in IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA). For continuous variables, the mean and standard deviation were calculated, while categorical attributes were presented in absolute and relative frequencies. The Mann–Whitney U test was used to compare the mean size. Corrected p-values < 0.05 were considered statistically significant.

RESULTS

In this study, 567 patients met the criteria for inclusion, of whom 326 were female (57.5%), and 241 were men (42.5%). The mean age of patients was 61 ± 13 years. The number of patients diagnosed with hemangiomas was 27 (4.76%). Among patients with diagnosed hemangiomas, a total number of 48 individual hemangiomas were found. Out of this number, 13 (48.1%) patients were female and 14 (51.9%) were male, with a ratio of 1:1.1. Descriptive clinical characteristics of the group are described in Table 1.

Table 1. Demographic characteristics

Variables		N (%)	
Sex (N = 567)	Male	241 (42.5)	
	Female	326 (57.5)	
Age (N = 567)		Mean ±	
	Without hemangioma	62.02 ±	
	With hemangioma	57.0 ±	
Hemangioma localization (N = 48)		N (%)	
	Left lobe	16 (33.3)	
	Right lobe	32 (66.7)	
Patients with hemangioma (N = 27)		N (%)	
	Multiple hemangiomas	13 (48.1)	
	Single hemangioma	14 (51.9)	
Spleen size (N = 567)		Mean ±	p = 0.338
	Without hemangioma	97.8 ±	
	With hemangioma	95.7 ±	
Liver size (N = 567)		Mean ±	p = 0.044
	Without hemangioma	131.53 ±	
	With hemangioma	125.37 ±	

The mean age of patients diagnosed with hemangiomas was 57 ± 13 years old (range 30–88 years). Hemangiomas were most commonly diagnosed in patients aged 60–69 years (11, 40.7%). The distribution of other age groups with decreasing frequency was as follows: 50–59 years (7, 25.9%), 40–49 years (4, 14.8%), 30–39 years (3, 11.1%), 80–89 years (2, 7.4%).

The mean size of the hemangioma was 13.8 ± 8.2 mm. The largest hemangioma was 42 mm in diameter and the smallest one was 5 mm in diameter. There is no statistically significant difference between men and women in the mean values of hemangioma size ($p > 0.05$). The size of the hemangioma was missing in two patients. Only one hemangioma was larger than 40 mm, which classifies as the giant hemangioma. The distribution of hemangiomas according to their diameter is presented in detail in Table 2.

Table 2. Distribution of hemangiomas according to the greatest diameter

Size of hemangioma (mm)	Frequency n (%)
< 10	16 (34.8)
10–19	21 (45.6)
20–29	7 (15.2)
30–39	1 (2.2)
> 40	1 (2.2)

The most common hemangioma localization was the right liver lobe (n = 32, 66.7%). The distribution of hemangiomas by segments is presented in Figure 2.

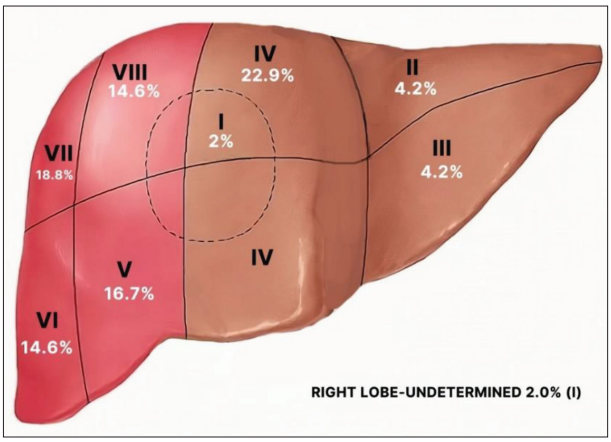

Figure 2. Distribution of hepatic hemangiomas based on the liver segments

Thirteen (48.1%) patients had two or more hemangiomas (nine male, four female). Out of 27 patients diagnosed with hemangioma, eight (29.62%) had previously known to have the liver hemangioma. Data were not available regarding the method used for the initial diagnosis. The patients were instructed and advised to have a follow-up visit in one year (n = 4, 14.81%), or were referred to the hepatologist for a further diagnostic work-up (n = 7, 25.92). Data regarding the follow-up plan was not available for the remaining patients (n = 8, 29.62%).

DISCUSSION

Cavernous hemangioma accounts for 55% of all benign liver tumors [1]. The most common symptoms associated with hepatic hemangioma are abdominal pain and discomfort [5]. There is limited data on the incidence of liver hemangiomas in the general population diagnosed by ultrasound. Our results indicate that the frequency of hemangiomas in our center diagnosed by ultrasound is 4.76%. This frequency is a similar as in previous published studies from Germany, Italy, and Iran, performed using ultrasound [3, 6, 9]. In a large retrospective cross-sectional study conducted by Mocchegiani et al. [9], the incidence of diagnosed hemangiomas was 2.5% in a population of 83,181 patients undergoing computed tomography (CT) and magnetic resonance imaging (MRI). In the study done by Horta et al. [17], among 1184 patients, 61 (5%) were found to have a hemangioma detected by CT. Liver hemangiomas were identified by ultrasound in 1640 of 45,319 patients (3.3%) in a German study [3]. A study by He et al. [19] indicates that the frequency of hepatic hemangioma in a population of 246,149 examined patients is 1.2%.

In our study, hemangiomas were found to be similar between men and women, with the ratio of male to female 1.1:1. Our study, along with several others, suggests that hemangiomas are not more common in females as previously believed, and their prevalence is nearly equal between the sexes [3, 9, 20]. According to Mocchegiani et al. [9], the prevalence of liver hemangiomas is 47.7% in women and 52.3% in men. Men's frequency in a study by Liu et al. [20] is 3.36%, while women's frequency is 2.89%. In a large study by Kaltenbach et al. [3], the sex distribution of hemangioma was nearly balanced, with 53.4% females and 46.6% males. This is most likely due to an increase in the number of males who get regular medical check-ups, as well as larger studies in this field.

The real number of hemangiomas in our population is presumably higher, because all atypical lesions were excluded from the study and sent for further diagnostics. In our study, the average age was 57 years old, hemangiomas were most often diagnosed in the group of patients aged 50–69 years, which is a slightly older group compared to previous studies. Recent data by Liu et al. [20] showed that hemangiomas were most often diagnosed in the group of patients aged 40–49 years. Also, in a study by Huang et al. [21], hemangiomas were most often diagnosed in the group of patients aged 41–60 years.

The most intensive growth of hemangiomas was observed in 30–39-year-olds, while after the age of 50 there is almost no increase [20]. In a multicentric study done by Tang et al. [4], 25% of hemangioma patients underwent treatment as a result of progressive hemangioma enlargement. Progressive growth of hemangiomas is considered to be more than 2 cm per year.

In our study, hemangiomas were most commonly diagnosed in the right liver lobe with percentage of 66.7%, which is consistent with findings in the previous studies [6]. Recent data by Yoon et al. [5], the frequency of hemangioma in the right lobe is 58%. In the study by He et al. [19], the most common localization was also in the right lobe with a frequency of 80.3%. In our study, the fourth liver segment was the most common localization (22.9%).

The most common hemangioma diameter ranged 10–19 mm. When a hemangioma is larger than 4 cm in diameter, it is referred to as a giant hemangioma [10]. Only one of our patients had a diameter of hemangioma over 40 mm (42 mm). The mean diameter of the hemangiomas was 13.8 mm, and there was no statistically significant difference between the sexes.

It was noticed that a large number of patients (48.1%) had two or more hemangiomas, and that it was more common in men than in women. Yoon et al. [5] found that 49% of patients had more than one liver hemangioma. This data suggests that if a hemangioma is diagnosed, the patient is quite likely to have more than one hemangioma.

By searching the available literature, there is no evidence for malignant transformation of liver hemangiomas. A case of cholangiocarcinoma growing within a giant hemangioma was described, but without proven malignant hemangioma transformation [22]. The differential diagnosis presents the biggest challenge to hepatic hemangioma diagnosis. Many primary tumors of the liver and secondary metastases can be differentially challenging [23]. If the hemangiomas are smaller, they may be completely fibrosed and mimicking the diagnosis of a malignant disease [24, 25].

There are some limitations to this study. Firstly, this is a single-center retrospective study and the sample size was small. Secondly, there was a lack of follow-up for patients diagnosed with hemangiomas or other atypical lesions.

CONCLUSION

This is a unique study on the frequency of hemangiomas in a primary care center in Serbia. Because the patients do not fall under any specific disease categories, we can consider them a cohort of the general population, which gives credibility to these results. Certain characteristics and specifics of our population could point out some characteristics of hemangiomas that would help doctors perform a more accurate diagnosis and further follow-up of these patients.

In our patients' cohort, hemangiomas were commonly multiple, and most commonly localized in the fourth liver segment. We did not detect any difference in hemangioma prevalence between the sexes. Patients who have discomfort or hemangiomas that grow more than 2 cm per year should consider further evaluation and surgical treatment. Hemangiomas with an uncharacteristic appearance on ultrasound should be referred for further diagnostics, primarily by MRI and CT.

Data availability statement: Data used in this research are available from the corresponding author (T.M.) upon reasonable request.

Conflicts of interest: None declared.

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Учесталост и карактеристике хемангиома јетре дијагностикованих ултразвуком – искуство једног центра

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САЖЕТАК

Увод/Циљ Хемангиоми су најчешћи бенигни тумори јетре са процењеном учесталошћу од 2,5 до 4%. Ова студија је имала за циљ да истражи преваленцу и клиничке карактеристике хемангиома на основу ултразвучног прегледа абдомена у једном дому здравља у Србији.

Метод Спровели смо студију пресека, која је укључивала болеснике прегледане у Дому здравља „Др Симо Милошевић" у Београду (Србија), у периоду од децембра 2017. до марта 2020. године. Болесници са суспектним атипичним променама, малигнитетима, вирусним хепатитисима и цирозом јетре нису укључивани у студију.

Резултати Студија је обухватила укупно 567 болесника (42,5% мушкараца). Код 27 болесника (4,76%) дијагностиковани су хемангиоми (однос мушкараца и жена износио је 1,1 : 1). Укупно је дијагностиковано 48 хемангиома. Најчешћа локализација хемангиома (32/48, 66,7%) била је у десном режњу јетре. Гледајући по сегментима, хемангиоми су најчешће били локализовани у четвртом сегменту (11/48, 22,9%). Просечна величина хемангиома била је 13,8 *mm*. Скоро половина болесника са дијагностикованим хемангиомом имала је више од једног хемангиома (13/27, 48,1%).

Закључак Хемангиоми јетре углавном нису појединачни. Није показана разлика у учесталости међу половима. Десни режањ јетре је био најчешћа локализација хемангиома у нашој студији.

Кључне речи: хемангиоми јетре; ултразвук; учесталост

DOI: https://doi.org/10.2298/SARH241029094Y
UDC: 616.594.1-089.843

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Hair transplant – initial experience with semiautomated extraction and preservation in follicular unit extraction

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SUMMARY

Introduction/Objective The most modern technique for follicular extraction in hair transplantation is the Follicular Unit Extraction (FUE) method, first described by Rassman et al. in 2002. With this method, individual intact follicular units are extracted "without visible scarring" and then implanted into the balding areas. A challenge with FUE is the lack of a single device that can adequately meet the requirements of different donor areas. The purpose of the present study is to share our initial experience with a new vacuum-automated FUE device with the ability to sterilely store follicles in an optimal environment in terms of temperature and humidity and to evaluate its capabilities to serve as a universal follicular unit extractor.

Methods Over a period of two years (2018–2020), 60 transplants were performed, of which 57 patients were male and three females, using this device for follicle extraction. Patients were divided into two groups: the first group with FUE vacuum-assisted extraction at 26.7% (n = 16), and the second group with forceps extraction at 73.3% (n = 44).

Results The mean graft numbers transplanted at the point of study were 2015 ± 507.2, and the mean graft numbers after 12 months were 1915.6 ± 480.6 (t = 10.33; p = 0.000). In both groups (at the point of the study and after 12 months), there was a statistically significant difference between the graft numbers transplanted and the age distribution, surgical technique, and donor area (p = 0.05). The younger group generally requires fewer grafts to be transplanted and has better skin quality, leading to a greater success rate.

Conclusion Our initial experience shows that with such a device, it becomes possible to achieve more than a thousand grafts in one day when working in different donor areas, which is minimally invasive for the patient and maximally ergonomic for the surgeon. Sterile storage of the follicles in an optimal environment is a prerequisite for increasing the viability of the transplanted follicles and achieving much better cosmetic results.

Keywords: FUE; automated extraction; hair transplantation

INTRODUCTION

Hair in every individual is associated with youth and vitality, and different hair styles shape our faces and unique personalities. Hair loss affects both men and women and it may impact psychosocial health and lead to emotional distress [1]. Androgenic alopecia (AA) is characterized by progressive androgen-related hair thinning and is the most common reason for seeking treatment. Nowadays, medical and surgical treatment options are available for stopping initial hair loss, and in advanced cases, new hair transplantation techniques are being developed [2]. In the early 1930s, the first autologous hair transplantation was performed in Japan by Okuda using punch grafts to harvest donor follicles and place them in the recipient area in openings made with smaller punches, but this technique received little attention worldwide. The hair transplantation technique became popular and received scientific success in the 1950s when Dr. Orentreich introduced large punch grafts 2–4 mm in size with 15–30 follicular units in each graft. He obtained the grafts from the posterior and lateral scalp in patients with AA and introduced the term "donor dominance," which refers to the fact that grafts maintain their original characteristics after they are placed in the recipient area [3]. Hair transplantation took an impressive leap in the early 1990s with the development of the Follicular Unit Transplantation (FUT) technique, which involves excising a linear strip of skin from the mid-occipital scalp. After that, each follicular unit is excised. This procedure leaves a long, thin scar, which is not appropriate for patients who like to have short hair [4]. Nowadays, the most commonly used technique is the Follicular unit extraction method (FUE), which was developed in the early 2000s. The technique is based on micropunches 0.8–1.0

Received • Примљено: October 29, 2024
Revised • Ревизија: December 5, 2024
Accepted • Прихваћено: December 12, 2024
Online first: December 16, 2024

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mm in size to directly dissect individual follicular units from the donor site, leaving a particularly small scar defect [5]. FUE provides incredible versatility in terms of graft placement and design, as well as consistent and natural cosmetic results [6].

METHODS

We performed a cross-sectional study in an independent clinic in Sofia, Bulgaria, between 2018 and 2021. It included 60 patients, of whom eight did not complete the final visit 12 months after surgery. All patients who were eligible for a hair transplant were included.

Before the procedure, patients underwent a primary evaluation for compatibility with the FUE method, including Norwood grade (refer to Figure 1), autoimmune diseases (Hashimoto's disease, anemia, syphilis, HIV, Hepatitis A/B/C), and testosterone levels.

Preoperative conservative treatment using platelet-rich plasma (PRP) every month for three months and a combination of topical and oral vitamin supplements was applied to almost all patients.

The procedure was performed under local anesthesia using ropivacaine and 2% lidocaine diluted with 0.9 saline. Trichoscopy with photo documentation is performed preoperatively in every patient. We start excising grafts from single or multiple donor areas (occipital scalp, beard, and body hair) with micropunches. In the case of thicker skin on the scalp or if the follicles are longer or the hair is curly, the vacuum may not be sufficient to extract the grafts without additional force, and we move to manual extraction using ophthalmic forceps. The hair follicles are stored in the device and kept moist and chilled to 4 °C. Once all the necessary grafts are taken, we move to the implantation phase. After repositioning the patient, the openings for the excised grafts are created using a 19- or 20-gauge needle. Follicles with one hair are divided from multiple ones when a hair line is needed. The PRP procedure is then performed, and the graft placement begins by using ophthalmic forceps. Once all the grafts are in place, the surface is cleaned with iodinated povidone 7.5/100 ml, and both the donor and recipient areas are sprayed with neomycin cutaneous spray. The donor area is then covered with a sterile bandage. The procedure time varies from three to 12 hours, depending on the number of harvested grafts (Figure 2).

After the surgery, the patient is told not to touch the implanted hair by no means. Every day for the next 10 days, the patient is asked to wash his hair by only placing foam from a bactericidal shampoo on it, leaving it for about two minutes, and washing it with a light force shower. After the initial 10 days, the post-op medication is stated as follows: six months of finasteride 1 mg, topical minoxidil 5%, oral vitamin supplements, hair regrowth shampoos depending on the patient's tolerance, and a PRP procedure once a month from the second to the sixth month after surgery, followed by twice a year after that.

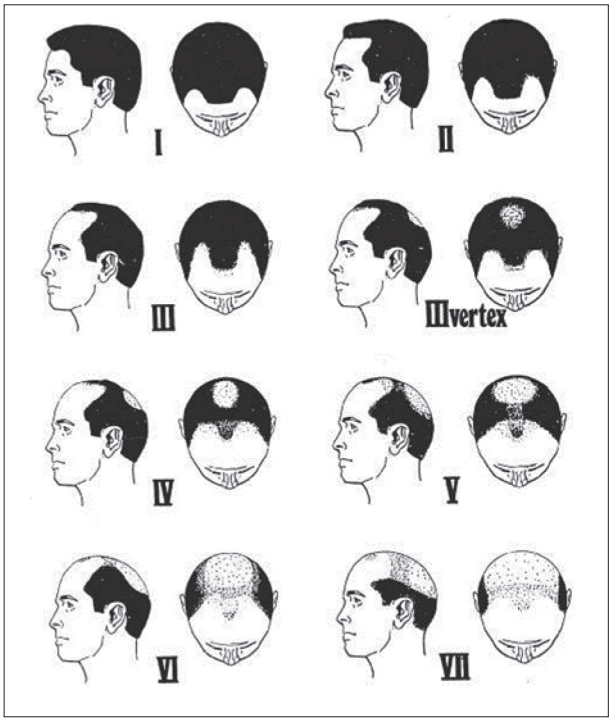

Figure 1. Hamilton–Norwood scale for male pattern balding

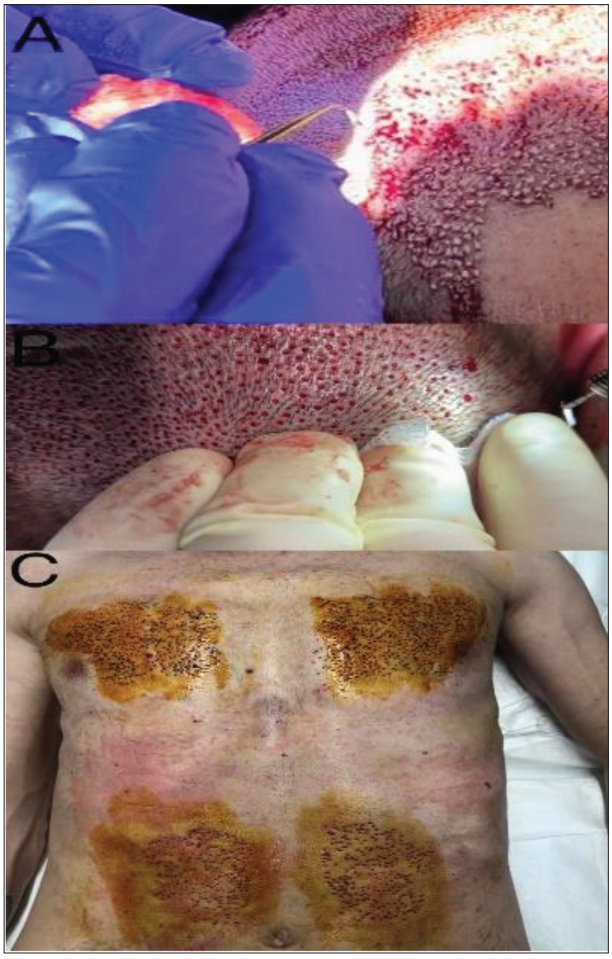

Figure 2. A – Follicle implantation; B – follicle extraction (occipital donor area); C – chest and abdomen after follicle extraction

Patient follow-up is performed between eight and 12 months after surgery for review by trichoscopy, and the hair count is compared to the pre-op photo documentation.

Our device is one of the most efficient harvesting systems available today, utilizing a light-weight handpiece with a cold illumination design, a bio-dome collection and storage system with a chiller, and a touch-screen computer to control its functions. This FUE technology minimizes procedure time, minimizes trauma to the grafts, and minimizes the amount of support staff needed. We believe that this device causes less trauma to the grafts from overhandling. It has a two-piece platform for easy transportation to be used in multiple locations, and has a greater viability of the grafts with its biodome technology that keeps the grafts cool and moist during the entire procedure until they are ready to be implanted. Keeping the grafts in these optimal conditions leads to a better overall survival rate and better results. With this semiautomated device we can control every aspect of the procedure, from temperature to graft count, illumination for better visibility, real-time graft extraction, and increased speed. Another advantage are the proprietary punches. The difference is that the punches we are using are 50% shorter and have a 26% smaller outside diameter, leaving a smaller footprint. They are available in both inner and outer bevels. It allows us to pull out grafts directly, which saves time and is less traumatic for the patient. The device allows for a reduction of 33% in procedure time over manual technique, which equates to less fatigue for the operator and less fatigue for the patient.

All statistical results were processed using the IBM SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY, USA) and their graphic presentation using Microsoft 365 (Microsoft, Redmond, WA, USA). All numeric variables were tested for normal distribution using the Kolmogorov–Smirnov test. Descriptive statistics, nonparametric tests, the t-test, the correlation test, the one-way analysis of variance (ANOVA), and the Bonferroni post-hoc test were used during statistical analyses. $p = 0.05$ was adopted for all tests to determine statistical significance.

All procedures strictly adhered to the ethical standards set forth by the institutional and national research committee, in line with the 1964 Helsinki Declaration and its subsequent revisions or equivalent ethical standards.

RESULTS

A total of 60 patients took part in the study. They were separated into two groups: the first group was performed with FUE vacuum-assisted extraction at 26.7% (n = 16), and the second group was performed using forceps for extraction at 73.3% (n = 44). Patients' median age was 42.3 ± 9.9. They were separated into two age groups (under 40 and 41–80). In total, 35% of patients had preoperative treatment with PRP and minoxidil, but there was no significant statistical difference in their final results ($p > 0.05$). Only 1.7% of patients did not receive postoperative conservative treatment due to a lack of compliance. A total of 13.3% did not complete the final visit 12 months after surgery. The only postoperative complication was folliculitis in four patients (6.7%). Patient demographic characteristics are presented in Table 1.

Table 1. Patient demographic characteristics

Profile characteristics	Overall, % (n)
Gender	
Male, % (n)	95% (57)
Female, % (n)	5% (3)
Age, years ± SD	42.3 ± 9.9
Age groups	
≤ 40 years, % (n)	45% (27)
≥ 41 years, % (n)	55% (33)
Comorbidity	
without Hashimoto's disease, % (n)	83.3% (50)
with Hashimoto's disease, % (n)	16.7% (10)
Previous procedures	
with, % (n) without, % (n)	93.3% (56)
with, % (n)	6.7% (4)
Donor Area	
Occipital scalp, % (n)	86.7% (52)
Occipital scalp + beard, % (n)	8.3% (5)
Occipital scalp + beard + body hair, % (n)	5% (3)

The average intraoperative time was 413.6 ± 127.2 minutes. There was a strong positive correlation ($r = 0.95$; $p = 0.000$) between the number of grafts transplanted and intraoperative time. Due to a more advanced stage of AA in the elder group, larger graft numbers were needed, leading to increased intraoperative time. There was a bigger time investment when harvesting follicles from different body areas, as it required further sedation and positioning of the patient. Using vacuum-assisted harvesting shortens the extraction time compared to the manual method (Table 2).

Table 2. The mean intraoperative time compared to study variables

Variables		n	mean	SD	F	p
Age groups	under 40	27	368.1	83.5	6.91	0.011
	between 41 and 80	33	450.9	144.9		
Surgical technique	FUE: vacuum	16	332.3	113.7	10.32	0.002
	FUE: forceps	44	443.2	119.8		
Donor area	Occipital scalp	52	374.6	79.4	54.82	0.000
	Occipital scalp and beard	5	618.4	5.9		
	Occipital scalp, beard, and body hair	3	750.0	50.0		

SD – standard deviation; F – analysis of variance;
FUE – follicular unit extraction

The mean graft numbers transplanted at the point of study were 2015 ± 507.2, and the mean graft numbers after 12 months were 1915.6 ± 480.6 ($t = 10.33$; $p = 0.000$). In both groups (at the point of the study and after 12 months), there was a statistically significant difference between the graft numbers transplanted and the age distribution, surgical technique, and donor area ($p = 0.05$). The younger group generally requires fewer grafts to be transplanted and has better skin quality, leading to a greater success rate (Figure 3). Hair follicles from the body and beard

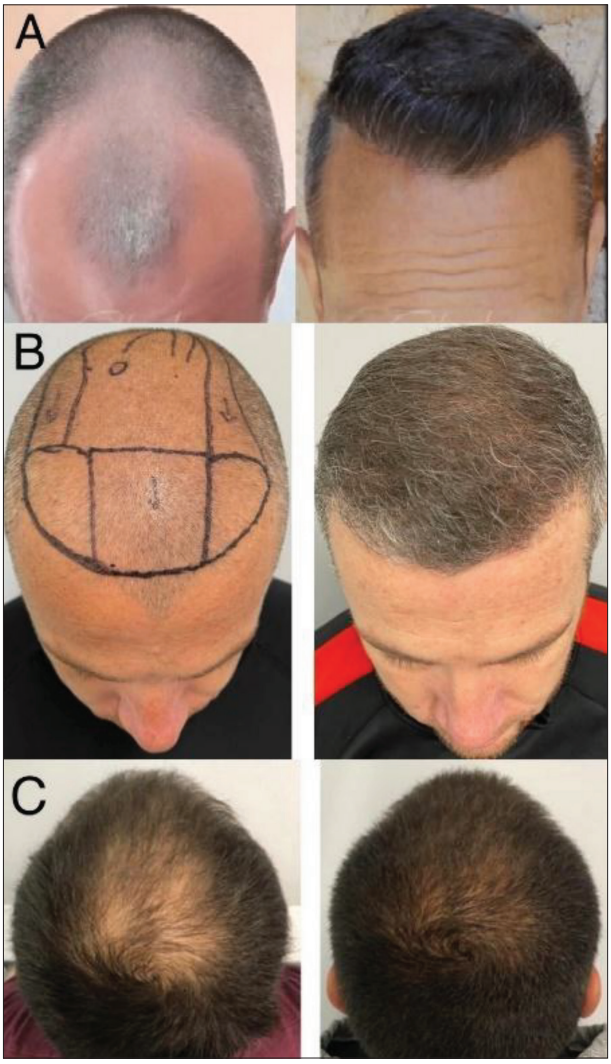

Figure 3. A – transplantation of 2400 follicle units; B – transplantation of 2000 follicle units; C – transplantation of 1000 follicle units

Table 3. Mean graft numbers transplanted after 12 months compared to study variables

Variables		n	mean	SD	F	p
Age groups	under 40	24	1774.6	382.2	4.07	0.049
	between 41 and 80	28	2036.4	528.3		
Surgical technique	FUE: vacuum	16	1511.3	545.9	15.83	0.000
	FUE: forceps	44	2050.4	376.0		
Donor area	Occipital scalp	52	1825.7	424.0	9.91	0.000
	Occipital scalp and beard	5	2485.3	114.7		
	Occipital scalp, beard, and body hair	3	2844.0	509.1		

SD – standard deviation; F – analysis of variance;
FUE – follicular unit extraction

have a higher difficulty of extraction, leading to a greater transection rate. The vacuum-assisted technique, although being the faster method, is less precise, leads to a greater transection rate, and is preferable for younger patients with a rich and healthy occipital donor area. 86.7% of patients were followed up for a period of 8–12 months after surgery. Most of the time, grafts enter the telogen phase for the first three months following transplantation before entering the anagen phase; this is why we cannot evaluate the results prior to at least the sixth and preferably after the 12th (Table 3).

DISCUSSION

AA is a progressive condition and the most common cause of hair transplantation. The severity of AA can be graded with the Hamilton–Norwood classification [7]. Nearly all of the patients benefit both from pharmacologic treatment and hair transplantation procedures, which ensure the best long-term results. The transplantation does not involve a net increase in new hair but rather the relocation of existing hair from the donor areas. Screening the patients is crucial in hair restoration surgeries, as the procedure is a long and taxing one with the need of a good post-surgery care from the patient, this is why a detailed pre-surgery interview is performed [8]. Some of the best conservative treatment options are: oral finasteride and topical minoxidil are the first-line treatment options for AA that have been approved by the United States Food and Drug Administration [9]. Finasteride can decrease the hair loss process in most men and can lead to partial regrowth in 66% of patients. For best results, finasteride needs to be used for at least six months. Topical minoxidil is used in both male and female patients; its direct mechanism of action is not yet understood, but its angiogenic and vasodilatory properties are suspected to have a positive influence. Its biggest side effect is unwanted hair growth on other hair bearing areas (face, hands, etc.). Dutasteride can be used off-label for patients who do not respond to finasteride. There are potential side effects that the patients should be notified about, including decreased libido, alterations to sperm, and erectile dysfunction. Topical finasteride is an option for patients who experience side effects from the oral drug or are reluctant to take it. The combination of oral finasteride and 5% topical minoxidil seems to achieve better results than monotherapy [10]. Other therapeutic options are PRP injections and low-level laser therapy (LLLT). There are clinical trials with PRP showing positive results; procedures are most commonly performed every 3–4 weeks, but more research is needed to determine the optimal regimen. In our study, we performed PRP preoperatively in 35% of our patients and postoperatively in 68.3%, with satisfying results and without any reported side effects. Other studies show that LLLT, based on the use of red light (wavelengths 635–678 nm), can improve hair density with little to no side effects. LLLT can be delivered with different devices like a helmet, cap, band, or comb. The protocols range from 10–30 minutes per session and 2–7 sessions per week. Combining different medical therapies from the ones listed above can have a synergistic effect, but more studies are needed to confirm the efficacy of the different treatment combinations. The use of at least two of the conservative treatment modalities before and after the hair transplantation is recommended. In our study, we considered the combination of PRP, minoxidil, and finasteride to be the best option for our patients because of its minimal side effects and excellent long-term results.

Nowadays, two types of hair transplantation techniques are used worldwide: harvesting donor grafts by elliptical excision of a horizontal strip (FUT) and removal of individual follicular groupings from the posterior scalp with a 0.75–1.2 mm punch device (FUE). Both techniques are associated with similar long-term results but with different intra- and post-operative complications. With FUT, there is a smaller risk of follicular transection, a shorter harvest time, the hair does not have to be trimmed, and the scar can be well hidden if the occipital hair is longer. The disadvantages of this method are a large visible scar when the hair is trimmed short, more work to prepare the grafts, the fact that body hair cannot be used, and a higher chance of nerve damage and bleeding. With the FUE technique, there is minimal graft preparation, body hair can be used, automated devices can be used to shorten the process, it is minimally invasive, and it is suitable for patients with thick scalps. On the other hand, this technique is associated with a greater risk of transection of the follicle, a longer harvest time and learning curve, a wider donor area, and the hair being preferably trimmed short [11].

FUE can be used for a variety of different indications, like body hair transplantation, camouflage of scars, and the treatment of secondary scarring alopecia caused by burns, skin tumors, or other types of trauma. FUE is the most versatile procedure in regards to cicatricial alopecia, as it can restore the natural anatomic structure [12]. By excising individual follicular units, surgeons have the option to repair hair defects on eyebrows and beards. The follicular survival rate is considerably high (above 75%), but the survival rates tend to vary in areas with significant scarring. The FUE procedure usually takes the surgical team between three and 10 hours, depending on the number of harvested grafts, ranging from 800 to 3600. In preparing for the procedure, standardization of photography of the hair and hairline is strongly recommended, with consistent lighting, patient positioning, and background. FUE allows the surgeon to obtain a large number of grafts with little to no visible scarring using a 0.75–1.2 mm punch device. FUE can be performed manually, with device assistance, or with a fully automated robotic device. FUE involves a longer learning curve compared to FUT because of the higher risk of transection of follicles and longer procedure times. Importantly, FUE also set the foundation for the incorporation of minimally invasive and automated technologies that lead to innovations on a regular basis [13].

Surgical complications from hair transplantation occur rarely, developing in approximately 2–3% of patients and often much less with experienced teams. Folliculitis and pustules occasionally develop and require treatment with topical or oral antibiotics. Neurosensory complications, including neuralgias, prolonged pain sensations, pruritus, or numbness, occur very rarely and generally resolve on their own in only a few days, almost always before the postoperative follow-up at eight to 12 months. Very rarely, patients experience abnormal scarring, or keloid formation in the donor or recipient sites, which is why a good history prior to the surgery is necessary. Some patients may experience a temporary effluvium throughout their scalp, including the donor area. Patient factors like adherence to postoperative instructions, preoperative and postoperative medical management of hair loss, smoking history, presence of actinic damage, and vascularity play a crucial role in treatment success. The results of our study show that 6.7% develop folliculitis, mostly due to a lack of proper aftercare, but no other complications were observed. According to most studies, patient follow-up should be performed at least after the sixth month or preferably between the eighth and 12th month. This is because grafts enter the telogen phase for the first three months following transplantation before entering the anagen phase [14].

CONCLUSION

AA is a progressive condition in both men and women and can seriously affect quality of life. Different conservative treatment options are available but none of them can achieve satisfactory long-term results. The hair transplantation techniques, including FUT and FUE, are the only chance for definitive treatment with long-lasting results. According to our study, semiautomated FUE using this system is the best hair transplant technique, which is associated with minimal invasiveness, shorter procedure times, greater comfort for the surgeon, and excellent cosmetic results.

Improving graft survivability before implantation is a major goal, and a variety of solutions have been proposed with almost no clinical results. The main limitation in meeting the patient's expectations is the amount of donor hair available, and thus, cloning of hair follicles will likely be the next leap in hair transplantation surgery over the next few decades. Many in vitro and animal model studies show the potential efficacy of the replication of hair follicles, but the challenges of translation into a useable in vivo model are vast, and the application of this technology is still a long way from its application in humans.

Despite this variety of conservative treatment options, an individual approach for every patient before and after transplantation is indicated for achieving the best long-term results.

Conflict of interest: None declared.

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Трансплантација косе – почетна искуства са полуаутоматизованом екстракцијом и очувањем у екстракцији фоликуларних јединица

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САЖЕТАК

Увод/Циљ Најсавременија техника за екстракцију фоликула у трансплантацији косе је екстракција фоликуларних јединица, метода коју су 2002. први описали Расман и сарадници. Овом методом се појединачне, нетакнуте фоликуларне јединице екстрахују „без видљивих ожиљака“, а затим се имплантирају у жељена подручја. Изазов са техником екстракције фоликуларних јединица је недостатак јединственог уређаја који може адекватно да испуни захтеве различитих донорских зона.

Циљ ове студије је да поделимо наше почетно искуство са новим вакуум-аутоматизованим уређајем за екстракцију фоликуларних јединица, који омогућава стерилно складиштење фоликула у оптималним условима температуре и влажности, и да проценимо његове могућности употребе као универзалног уређаја за екстракцију фоликула.

Методе Током двогодишњег периода (2018–2020) овим апаратом за екстракцију фоликула урађено је 60 трансплантација, од чега 57 код мушкараца и три код жена. Пацијенти су подељени у две групе. Прва група, у којој је рађена екстракција фоликуларних јединица помоћу вакуума, обухватала је 26,7% (n = 16) пацијената, а друга група, са екстракцијом форцепсом, обухватала је 73,3% (n = 44) пацијената.

Резултати Просечан број графтова трансплантираних у тренутку испитивања био је 2015 ± 507,2, а просечан број графтова после 12 месеци био је 1915,6 ± 480,6 (t = 10,33; p = 0,000). У обе групе (у тренутку испитивања и после 12 месеци) постојала је статистички значајна разлика између броја трансплантираних графтова и старосне дистрибуције, хируршке технике и донорске зоне (p = 0,05). Млађа група генерално захтева мање графтова за трансплантацију и има бољи квалитет коже, што доводи до веће стопе успеха.

Закључак Наше почетно искуство показује да је овим апаратом могуће урадити више од хиљаду графтова у једном дану у раду са различитим донорским зонама, што је минимално инвазивно за пацијента и максимално ергономско за хирурга. Стерилно складиштење фоликула у оптималним условима предуслов је за повећање виталности трансплантираних фоликула и постизање много бољих естетских резултата.

Кључне речи: екстракција фоликуларних јединица; аутоматизована екстракција; трансплантација косе

DOI: https://doi.org/10.2298/SARH240914088P
UDC: 617.735-053.32

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Examination of risk factors for the development of retinopathy in premature children

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SUMMARY

Introduction/Objective Retinopathy of prematurity (ROP) is a developmental vascular proliferative disorder in premature children's incompletely vascularized retina. Many factors slow down or prevent the normal development of retinal vascularization in premature babies. The aim of our study was to examine the risk factors in premature infants of gestational age (GA) of 25–36 weeks associated with the occurrence of severe ROP.

Methods The study was cross-sectional. The research included patients monitored by a screening program for ROP, i.e. prematurely born children with a body weight mass (BMW) ≤ 2000 g, and/or GA of ≤ 36 weeks.

Results Statistically significant differences were observed between the ROP and the control group in the mean values of GA, BWM at birth, Apgar score, and days of oxygen therapy. Also, frequencies of respiratory distress syndrome expression, broncho-pulmonary dysplasia, intraventricular hemorrhages, and requirement for mechanical ventilation were statistically significantly different between the two analyzed groups.

Conclusion Our work confirmed that low GA and low BWM are already accepted risk factors for ROP. The presence of perinatal asphyxia, the length of oxygen administration and assisted ventilation are significantly associated with the appearance of active forms of retinopathy. Sepsis and anemia were shown to be significantly associated with more severe forms of retinopathy, while hyperbilirubinemia was approximately present in both examined groups. More severe forms of intraventricular hemorrhages and necrotic enterocolitis are significantly more common in children with active retinopathy.

Keywords: retinopathy of prematurity; oxygen therapy; risk factors

INTRODUCTION

Retinopathy of prematurity (ROP) is a disease of the retina of prematurely born infants. It is a developmental vascular proliferative disorder in premature children's incompletely vascularized retina [1]. According to the International Classification for ROP (ICROP), the severity of the disease is described in five stages. Stage 1 is defined by the presence of the so-called demarcation line, stage 2 by the presence of the so-called ridge, and stage 3 by extraretinal fibrovascular proliferation. Stages 4 and 5 are severe conditions, the former characterized by sub-total retinal detachment and the latter by total retinal detachment [2]. The introduction of supplemental oxygen in the treatment of premature babies has been associated with the occurrence of more severe stages of this disease [1].

By introducing the monitoring of blood gas levels, it is possible to document and assess the need for oxygen better. Even with good oxygen monitoring, ROP persists, leading to examination of the influence of other factors involved in developing ROP and the possibility of other risk factors. A significant number of preterm infants require respiratory support and supplemental oxygen at birth [1, 3]. With the significant advances in neonatal care, the number of preterm infants with low gestational age (GA) and low body weight mass (BWM) has increased, resulting in a secondary epidemic of ROP [4].

Numerous factors slow down or prevent the normal development of retinal vascularization in premature babies. These are parameters of immaturity given at birth – gestational age and birth weight mass, as well as parameters of general health, treatment parameters and genetic factors [5, 6]. Dominant risk factors for the development of ROP are low GA (especially < 32 weeks), low BWM (< 1500 g, especially < 1250 g), sepsis, high concentrations of therapeutic oxygen, number of transfusions, damage to the central nervous system (CNS) [5, 6].

Therapeutic use of oxygen in the treatment of premature children is a significant risk factor for the occurrence of ROP, since high doses of oxygen lead to vasoobliteration of developing blood vessels. The transition to a room environment, which represents conditions of relative hypoxia, is accompanied by a vasoproliferative response and fibrosis [3, 7].

Other risk factors for the development of ROP are white race, heart disease, infections,

Received • Примљено: September 14, 2024
Revised • Ревизија: November 21, 2024
Accepted • Прихваћено: November 21, 2024
Online first: November 25, 2024

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multiple episodes of apnea, convulsions, respiratory distress, pneumonia, bradycardia, general health parameters (Apgar score – AS), intracranial bleeding, anemia, hyperbilirubinemia, and twin pregnancy [5, 8, 9]. Also, treatment parameters including the number of transfusions, use of surfactant, vitamin E, erythropoietin, and dexamethasone are important [5, 8, 9].

Current screening guidelines by the American Academy of Pediatrics, American Academy of Ophthalmology, and American Association for Pediatric Ophthalmology and Strabismus state that all infants ≤ 30 weeks GA or ≤ 1500 g BWM should be screened for ROP, as well as larger infants based on clinical course [10]. In our country, screening covers prematurely born children with a BMW of 2000 grams or less, and a GA of 36 weeks or less.

Our study aimed to examine the risk factors in premature infants of GA of 25–36 weeks associated with severe retinopathy of prematurity. Our results are useful in recognizing risk factors and prognosis, thereby improving preventive and management strategies.

METHODS

The study was cross-sectional, from January 1, 2011, to December 31, 2015, at the Institute of Gynecology and Obstetrics of the University Clinical Center of Serbia in Belgrade. The research included patients monitored by a screening program for retinopathy of prematurity, i.e. prematurely born children with a BWM ≤ 2000 g, and GA of ≤ 36 weeks. Neonatologists select preterm children for ophthalmic screening based on risk factors. This study was undertaken according to the tenets of the Helsinki Declaration, is part of a doctoral dissertation that was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade, record number 29/X-11.

The ophthalmological examination was performed in the intensive care units of the neonatology department. The examination was performed at the maximum wide pupil with an indirect binocular ophthalmoscope and a 20 D lens. An indentation was used to examine the peripheral parts of the retina. The ophthalmological examination determined the degree of ROP, based on which the premature children were divided into two groups. The classification of ROP was performed using the ICROP [2]. The first group consists of children without signs of retinopathy (normal findings) and children with forms of retinopathy that do not require therapy (ROPI and ROPII) – the control group, while the second group consists of children with an active form of the disease that requires therapy – the ROP group. The presence of risk factors was analyzed using medical records.

We examined post-natal risk factors: sex, GW, BWM at birth, mode of delivery (vaginal or cesarean section), children from multiple pregnancies, AS, intrauterine growth arrest, presence of anemia, hyperbilirubinemia, pneumonia, sepsis. We analyzed the need for oxygen therapy and mechanical ventilation (MV) as well as the presence of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). We also examined the presence of severe degrees (III and IV) of intraventricular hemorrhages (IVH) and necrotic enterocolitis (NEC).

Gas analyses and acid-base status were performed from a capillary blood sample from the heel, while blood count was performed from a capillary or venous blood sample. The criterion for anemia was a hemoglobin concentration of less than 90 mg/l. Ultrasound of the CNS was performed with a Logicum 3 Pro ultrasound device with a 7.5 MHz probe. Ultrasound findings of IVH are graded I–IV according to Papile [11]. Children with stages III and IV were included. The degree of RDS was assessed based on chest X-ray (grades I–V). The diagnosis of NEC was made according to Bell's classification [12]. Children who had stage I and II NEC and required medical treatment were included. Children with a more severe stage that required surgical treatment and transfer to another institution were excluded. Asphyxia was assessed based on the clinical picture, AS, and acid-base status, while sepsis was determined based on a positive blood culture, clinical picture, elevated C-reactive protein, leukocyte, platelet, and leukocyte formula values.

Statistics methods

The χ^2 test was used to test the significance of differences in nominal observational characteristics. Univariate and multivariate logistic regression analysis was used for association analysis. Multivariate modeling was done in two steps; in the first step, the Enter method was used. All predictors that were statistically significant in the univariate analysis were included in the analysis. Using the backward method with an entry criterion of $p = 0.05$ and an exclusion criterion of 0.01, predictors whose p-values in the model do not exceed 0.01 were obtained. Statistical analyses were performed using the SPSS statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA).

This study was conducted according to the guidelines of the Declaration of Helsinki, and is part of a doctoral dissertation, which was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade, record number 29/X-11.

Informed consent was obtained from all parents whose children participating in the study after receiving a full explanation of the study.

RESULTS

Our study included 239 premature-born children, of which 123 (51.5%) were female and 116 (48.5%) were male. The ROP group contained 113 children, while the control group contained 126 children. In the ROP group, the frequency of diagnoses was as follows: ROP3+ 51 children (21.3%), AP ROP 36 children (15.1%), and ROP 2+2A 26 children (10.9%). In the control group, 70 children had normal findings (29.3%), 44 children (18.4%) had ROP I, and 12 children (5%) had ROP II. Not a single child had stages 4 and 5 of the disease. Children from the ROP group

Table 1. Clinical data of two premature infant groups

Clinical characteristics	ROP group n = 113	Control group n = 126	p-values
Sex M/F	58/55	58/68	0.413
GA Weeks	29.96 ± 1.93	31.42 ± 1.93	< 0.001*
BWM (grams)	1236.73 ± 236.37	1400.40 ± 298.03	< 0.001*
Caesarean section	64 (56.6%)	73 (57.9%)	0.839
Multiple pregnancies	39 (34.5%)	33 (26.2%)	0.308
AS	4.73 ± 1.7	6.22 ± 1.61	< 0.001*
PA	85 (75.2%)	51 (40.5%)	< 0.001*
Intrauterine growth arrest	36 (31.9%)	47 (37.3%)	0.378
Days of oxygen therapy	24.28 ± 17.3	13.45 ± 10.68	< 0.001*
MV	58 (51.3%)	30 (23.8%)	< 0.001*
RDS	94 (83.2%)	69 (54.8%)	< 0.001*
BPD	28 (25%)	11 (8.7%)	0.001*
Pneumonia	48 (42.5%)	29 (23%)	0.001*
Sepsis	46 (40.7%)	31 (24.6%)	0.008*
Anemia	101 (89.4%)	82 (65.1)	< 0.001*
Hyperbilirubinemia	47 (41.6%)	58 (46%)	0.490
ICH	21 (18.6%)	11 (8.7%)	0.026*
NEC	19 (16.8%)	6 (4.8%)	0.003*

ROP – retinopathy of prematurity; GA – gestational age; BWM – birth weight mass; PA – perinatal asphyxia; MV – mechanical ventilation; RDS – respiratory distress syndrome; BPD – broncho-pulmonary dysplasia; ICH – intracranial hemorrhage; NEC – necrotic enterocolitis; AS – Apgar score

Table 2. Presentation of the week of gestation and body weight of the two examined groups

Parameters		ROP		Control		Results
		N	%	N	%	
GA (weeks)	< 30	51	45.1	19	15.1	$\chi^2 = 28.862$ p < 0.001
	30–32	48	42.5	67	53.2	
	> 32	14	12.4	40	31.7	
BWM (grams)	< 1000	18	15.9	8	6.3	$\chi^2 = 15.190$ p < 0.001
	1000–1500	83	73.5	82	65.1	
	> 1500	12	10.6	36	28.6	

ROP – retinopathy of prematurity; GA – gestational age; BWM – birth weight mass

Table 3. Number of days on oxygen therapy and lung diseases

Parameters	Days on oxygen therapy							
	Mean		± SD	Perc. 25	Perc. 75	Min.	Max.	p-values
RDS	no	8.39	6.99	3.5	11.5	1	33	Z = -8.538 p < 0.001
	yes	23.32	15.62	11	32	2	103	
Pneumonia	no	16.09	14.82	5	22	1	103	Z = -4.736 p < 0.001
	yes	23.79	14.64	14	30	2	70	
BPD	no	14.36	10.15	6	19	1	44	Z = -8.312 p < 0.001
	yes	40.46	17.69	29	52	15	103	

ROP – retinopathy of prematurity; BPD – broncho-pulmonary dysplasia

were treated as follows: 99 children (87.6%) with vascular endothelial growth factor (VEGF) inhibitors, 10 children (8.8%) with laser photocoagulation, and seven children (35%) were treated with both treatments.

Table 1 shows clinical data recognized as clinical risk factors for severe ROP development. Statistically significant differences were observed between the ROP group and the control group in mean values of gestational age, BWM at birth, AS, and days of oxygen therapy. Also, frequencies of RDS expression, BPD, intracranial hemorrhage, and requirement for MV were statistically significantly different between two analyzed groups.

Table 2 shows the relationship between GW and BWM of both study groups. From the above table, it can be seen that the largest number of children who required therapy was < 30 weeks of gestation (51; 45.1%), and BWM 1000–1500 g (83; 73.5%). We observed that 14 children (12.4%)with > 32 weeks of gestation required treatment, as well as 12 children (10.6%) above 1500 g of BWM. On the other hand, 19 children (15.1%) of the control group born with < 30 GW did not develop an active form of retinopathy, nor did eight (6.3%) children with BWM < 1000 g.

The average number of days on oxygen for children in the ROP group was 24.28 ± 17.3 days, and for children in the control group 13.4 ± 10.68 days (Z = -5.555; p < 0.001). Children whose ophthalmological findings were normal were on average oxygen therapy for 8.01 ± 5.8 days, while children diagnosed with ROPI and ROPII were on average oxygen therapy for 20.25 ± 11.5 days. Children in the ROP group were on oxygen for an average of 24.28 ± 17.3 days. There is a statistically significant difference between the groups, namely the following: without ROP *vs.* ROP I/II (p < 0.001), without ROP *vs.* ROP (p < 0.001), and ROP I/II *vs.* ROP (p = 1.000).

The statistically significant differences were obtained in the length of oxygen use between children without lung disease and children with lung disease (p < 0.001), which is shown in Table 3. Children with BPD required the longest oxygen support (40.46 ± 17.69 days).

Our study showed that there is a close relationship between lung diseases (RDS, BPD, PA) and GA and BWM. RDS and PA occurs more often in children with lower GA (p < 0.001), while children with a lower BWM at birth were statistically more likely to have perinatal asphyxia (p < 0.001).

DISCUSSION

Retinopathy of premature children occurs because of the incomplete vasculogenesis of the retina at the time of the child's birth and exogenous factors of the external environment, the interaction of which can be a condition for the development of retinopathy. With premature birth, the child reaches conditions that are significantly different from intrauterine. [8]. Retinopathy of prematurity represents the most important field of cooperation between neonatologists and ophthalmologists.

The results of our study showed that low GA and low BWM are risk factors for the development of ROP. Retinal vascularization ends in 42 weeks GA. Premature birth severely disrupts vasculogenesis and changes the conditions

for its further development. Low BWM is a direct consequence of preterm birth [1, 4, 8].

The work of a group of authors shows similar results that prematurity is a dominant risk factor, which indicates that children born before 25 GA are twenty times more likely to develop severe retinopathy compared to children born after 28 GA [13].

In our study, the largest number of children with an active form of the disease was in the group of 1000–1500 g. The number of children with an active form of the disease decreases with increasing BWM (above 1500 g), which is expected. In our sample, 12 children with BWM > 1500 g developed forms of ROP that required therapy. Most guidelines limit the screening to children who were born with BWM ≤ 1500 g and GA ≤ 32 [9]. Our results showed that 14 children with GA > 32 required therapy. Using the recommended screening criteria [9], fourteen children with active disease would be missed, indicating that we still need to stick to broad screening criteria. Scientists from our country, indicating the need for wider regional screening [14], reached the same result. Current screening protocols in high-income nations effectively identify clinically significant diseases with high sensitivity, but cannot be generalized to other regions with different standards of neonatal care [8]. Other authors also draw attention to the risk of missing the active stage of the disease that requires therapy in children born with BWM > 1500 g and GA > 32 weeks [5]. The frequency of the disease that we obtained in groups below 1000 g is usually found in works coming from medium-developed countries [15]. This difference is the result of the application of advanced technology and science of high-income countries, resulting in better neonatal and health care. This results in a high survival rate for children with extremely low BWM. In medium-developed countries, the allocated funds are insufficient and without the possibility of providing a high level of neonatal care. As a result, we have less survival of children under 1000 g.

We monitored the number of days on oxygen and the use of MV in both groups. The average number of days on oxygen in the ROP group was significantly higher compared to the number of days on oxygen in the control group. In addition, MV is significantly more common in the ROP group compared to the control group. It is important to note that the average length of oxygen administration only in the control group of children with normal ophthalmological findings was significantly lower compared to children with forms of ROP that did not require treatment (ROPI and ROPII), while there was no statistically significant difference in the length of oxygen administration between the group of children diagnosed with ROPI/ROPII and ROP group. From this result, we can conclude that other risk factors are also important, because the children of the control group with initial forms of retinopathy (ROPI and ROPII) who regressed and did not require treatment spent a significant number of days on oxygen therapy, which did not statistically differ from the ROP group. Numerous works indicate that the number of days on oxygen therapy and the number of days on MV are considered risk factors for ROP [16, 17]. These colleagues indicate that prematurely born children or children with low BWM often require oxygen supplementation, where hyperoxic exposures at birth can lead to oxidative stress that can affect apoptosis and cell growth. The most difficult task of a neonatologist is to ensure adequate supplementation. The American Academy of Pediatrics suggests maintaining an optimal oxygen pressure of 50–80 mmHg, i.e. 6.7–10.7 kPa [9, 18]. Optimum oxygen pressure is not easy to achieve. Not only hyperoxia and the length of oxygen administration but also episodes of oxygen fluctuations can be serious risk factors for the development of retinopathy. Smaller fluctuations in oxygen saturation and gradual weaning from oxygen therapy are advised [19].

RDS, BPD, pneumonia, lung hemorrhages are conditions accompanied by apnea crises and the need for constant administration of oxygen, often with MV. Respiratory diseases are accompanied by gas exchange disorders and hypoxia. These conditions often require long-term care administration of oxygen, which carries an increased risk of hyperoxia. RDS is closely associated with preterm birth, with surfactant deficiency being the primary cause of RDS. The role of surfactant is to reduce the surface tension in the alveoli and prevent their collapse. In our sample, the frequency of RDS is high in both groups, although statistically significantly higher in the ROP group. Literature review found RDS requiring surfactant therapy to be an independent risk factor for ROP [8]. In our study, the presence of BPD was statistically significantly more frequent in the ROP group compared to the children who were not treated. Pneumonia also proved to be a significant risk factor in our research. Several studies reported a significant association between BPD and ROP [8, 19]. In our study, children with respiratory diseases were significantly longer on oxygen, were born earlier, and had a lower BWM at birth.

Anemia proved to be highly statistically significant as a risk factor in our sample. Some authors agree with our results [20], but in some, anemia did not affect the severity of ROP as an independent risk factor [21]. The role of hyperbilirubinemia as a risk factor is controversial. In our study, we did not determine that it is a risk factor for ROP, while some authors even indicate a protective effect of hyperbilirubinemia, due to its antioxidant effect. [22]. However, some authors have pointed out in their works that hyperbilirubinemia requiring phototherapy represents a surrogate for other risk factors for ROP [23].

ROP and IVH are serious complications in premature infants. The incidence of ROP and IVH has been shown to correlate inversely with GA and BWM. Immature and underdeveloped protection systems explain the vulnerability of the blood network of the CNS and the retina. Most papers show there is a significant difference in the frequency of IVH grade 3 or 4 in different categories depending on birth weight, together with advanced ROP stages compared to the control group [24], which is consistent with the results of our work. However, some authors did not find a significant relationship between IVH and ROP, explaining that with the improvement of neonatal care and the decrease in the frequency of severe IVH, there is a

weakening of the previously observed association between severe IVH and severe ROP [25].

NEC can increase the risk of occurrence of advanced forms of the disease. In our work, NEC occurred as a comorbidity significantly more often in the ROP group than in the control group. Reviewing the literature, the role of NEC in the progression of ROP to more severe stages require further investigation.

CONCLUSION

In conclusion, ROP is a complex disease with many risk factors, not all fully understood. Our work confirmed that low GA and BWM are already accepted risk factors for ROP. The method of delivery and multiple pregnancies did not affect the development of more severe forms of retinopathy. The presence of perinatal asphyxia, the length of oxygen administration, and assisted ventilation are significantly associated with the appearance of active forms of retinopathy, while there was no difference in the appearance of retinopathy between children with intrauterine arrest and children with appropriate BWM at birth. All investigated respiratory risk factors are directly related to the duration of oxygen therapy and the application of MV. Sepsis and anemia were shown to be significantly associated with more severe forms of retinopathy, while hyperbilirubinemia was approximately present in both examined groups. More severe forms of IVH and NEC are significant more common in children with active retinopathy. Our results also indicated the need for a wider screening protocol in our country and that the presence of additional risk factors during the development of the child points to the need for an earlier examination.

ACKNOWLEDGMENT

Presented results are a part of the doctoral dissertation: Pantelic J. Investigation of eNOS gene polymorphisms as a risk factor for the development of retinopathy of prematurity [dissertation]; Faculty of Medicine, University of Belgrade, Belgrade, Serbia, 2016.

Data availability statement: The datasets used and/or analyzed during the current study are available without restriction from the corresponding author. All relevant data are within the paper.

Conflicts of interest: None declared.

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Испитивање фактора ризика за развој ретинопатије код превремено рођене деце

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САЖЕТАК

Увод/Циљ Ретинопатија недоношчади је развојни васкуларни пролиферативни поремећај у непотпуно васкуларизованој мрежњачи превремено рођене деце. Многи фактори успоравају или спречавају нормалан развој васкуларизације мрежњаче код превремено рођених беба.

Циљ истраживања био је да се испитају фактори ризика код недоношчади гестацијске старости 25–36 недеља повезани са појавом тешке ретинопатије недоношчади.

Методе Студија је спроведена као студија пресека. Истраживањем су обухваћени пацијенти праћени скрининг програмом на ретинопатију недоношчади, тј. превремено рођена деца са телесном масом ≤ 2000 *g*, и/или гестационом старошћу ≤ 36 недеља.

Резултати Уочене су статистички значајне разлике између ретинопатије недоношчади и контролне групе у средњим вредностима гестацијске старости, телесне масе при рођењу, Апгар скору и данима терапије кисеоником. Такође, учесталост експресије синдрома респираторног дистреса, бронхопулмоналне дисплазије, интравентрикуларног крварења и потребе за механичком вентилацијом статистички су се значајно разликовале између две анализиране групе.

Закључак Наш рад је потврдио да су ниска гестацијска старост и ниска телесна маса већ прихваћени фактори ризика за ретинопатију недоношчади. Присуство перинаталне асфиксије, дужина примене кисеоника и потпомогнута вентилација значајно су повезани са појавом активних облика ретинопатије. Показало се да су сепса и анемија значајно повезане са тежим облицима ретинопатије, док је хипербилирубинемија била приближно присутна у обе испитиване групе. Тежи облици интравентрикуларног крварења и некротични ентероколитис значајно су чешћи код деце са активном ретинопатијом.

Кључне речи: ретинопатија недоношчади; терапија кисеоником; фактори ризика

DOI: https://doi.org/10.2298/SARH240424080T
UDC: 614.2(497.11); 614.253:331.101.32(497.11)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Examining the impact of managerial support on the performance of healthcare organizations – the mediating role of employee autonomy

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SUMMARY
Introduction/Objective This paper aims to examine the influence of managerial support and employee autonomy on the performance of healthcare organizations. Additionally, it seeks to investigate the mediating influence of employee autonomy on the relationship between managerial support and organizational performance.
Method The study involved 165 employees from four healthcare organizations in the Braničevo District in the Republic of Serbia. Independent variable (managerial support) and mediating variable (employee autonomy) was measured using Corporate Entrepreneurship Assessment Instrument scale. For dependent variable (organizational performance), a scale adapted from previous research was utilized, consisting of financial results, quality of service delivered, productivity, employee satisfaction, patient satisfaction, reputation, and adaptability to change dimensions. Employees of healthcare facilities were surveyed regarding their attitudes on a five-point Likert scale to statements designed to measure the aforementioned variables. The analysis employed descriptive statistics, internal reliability tests, normality distribution tests, correlation, and regression analysis.
Results The scales used for measurement achieved a high level of internal consistency, with Cronbach's α coefficients ranging from 0.870 to 0.937, indicating strong reliability. A high level of Cronbach's α coefficients was defined based on established thresholds, where scores above 0.7 were considered high. The regression analysis reveals a statistically significant and positive influence of managerial support and autonomy on organizational performance ($\beta = 0.539$, $p < 0.000$; $\beta = 0.301$, $p < 0.000$, respectively). Additionally, a mediating effect of autonomy in the relationship between managerial support and organizational performance was identified ($\beta = 0.5579$; $p < 0.0397$).
Conclusion Managerial support significantly impacts the performance of healthcare organizations, with this effect being further enhanced by granting employees autonomy. Therefore, managers in these organizations can enhance organizational performance by improving support and fostering the development of employee autonomy.
Keywords: managerial support; employee autonomy; organizational performance; healthcare organizations

INTRODUCTION

The provision of quality healthcare and the attainment of performance within healthcare organizations are predominantly influenced by the knowledge possessed by healthcare workers [1]. Performance refers to the extent to which the organization has accomplished its predefined objectives. It's essential to recognize that performance encompasses not only financial outcomes but also factors such as innovation, quality, employee behavior, and patient satisfaction [2]. It is a multidimensional concept that reflects the level of efficiency of employees, their knowledge, ability to solve problems and behavior [3, 4]. Improving performance often requires management intervention to increase social support [5].

Managerial support within an organization can manifest in various ways, but its core lies in fostering idea generation among employees, allocating resources, fostering knowledge development, and similar initiatives [6]. Employees perceive managerial support as the extent to which managers care about their needs, value their ideas, and ensure their well-being [7]. Chatterjee et al. [8] point out that management support has three types. Firstly, transitional leadership entails a hierarchical decision-making structure within the organization. Secondly, empowerment leadership involves employee participation and empowerment. Lastly, laissez-faire leadership is a form of leadership where employees take the initiative in action. Consequently, managerial support entails equal treatment of all employees, effective communication, support in problem-solving, ensuring safety and security at work, and sharing of resources, among other aspects [7]. If we consider employee empowerment and laissez-faire leadership, it becomes crucial to emphasize the autonomy of healthcare workers. Autonomy refers to the extent to which employees can independently make decisions during work, aligning with their knowledge, skills, and experience [9]. Healthcare workers possess valuable knowledge that they actively apply in delivering healthcare services. Granting them

Received • Примљено: April 24, 2024
Revised • Ревизија: October 2, 2024
Accepted • Прихваћено: October 2, 2024
Online first: October 9, 2024

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autonomy allows for the utilization of this knowledge, thereby enhancing their human capital. Moreover, autonomy positively impacts their motivational needs and job satisfaction [10]. Managers of healthcare organizations play a crucial role in ensuring autonomy among their staff. They can achieve this by providing support in various forms, such as offering resources and knowledge, communicating clear goals, fostering teamwork, and encouraging collaboration. These efforts contribute to creating an environment where healthcare workers feel empowered to make independent decisions and take ownership of their work [11]. To ground the discussion in established theory, research in the field of human resources (HR) management and motivation is important. For instance, Deci and Ryan's [12] Self-Determination Theory emphasizes the importance of autonomy and intrinsic motivation in enhancing employee engagement and performance. Similarly, Herzberg's Two-Factor Theory highlights how recognition and rewards contribute to job satisfaction and motivation [13]. These theoretical perspectives underscore the significance of managerial support as not just a set of actions but as a fundamental component of effective HR management.

Howell and Avolio [14] state that management support is crucial for innovation within an organization. Besides fostering autonomy, managerial support should be viewed in the broader context of organizational performance. Employees who receive strong support from managers often demonstrate increased levels of discretionary effort, that goes beyond the basic requirements of the job and can significantly contribute to organizational success and effectiveness [15], which in the context of healthcare organizations is of great importance for maximizing the quality of healthcare. Positive attitudes and increased engagement among employees, fostered by managerial support, are conducive to higher productivity levels. This enhanced productivity, in turn, contributes to the overall improvement of organizational performance [7, 16]. Diamantidis and Chatzoglou [17] state that manager support is one of the factors that determines organizational performance and that it is actually one of the most important factors. Also, the literature states that autonomy during work has a positive impact on organizational performance, due to increased efficiency and engagement of employees [10, 11, 18].

Given the lack of research in the mentioned subject area, this paper aims to investigate the influence of managerial support and employee autonomy on the performance of healthcare organizations. Additionally, it seeks to explore the mediating effect of employee autonomy on the relationship between managerial support and organizational performance. This study builds upon previous theoretical positions to address these research aims, and accordingly the following hypothesis can be defined [1, 2, 9, 15, 16]:

Hypothesis$_1$: There is a statistically significant and positive impact of managerial support on the performance of healthcare organizations.

Cho et al. [11] and Imam et al. [9] point out simultaneously the positive influence of employee support and autonomy on organizational performance. Bearing in mind the above, as well as the previous theoretical positions [10, 11, 18], the following hypotheses can be defined:

Hypothesis$_2$: There is a statistically significant and positive influence of the autonomy of healthcare workers on the performance of healthcare organizations.

Hypothesis$_3$: The autonomy of healthcare workers has a statistically significant mediating influence on the relationship between manager support and organizational performance.

METHODS

Study design

To examine the research goals and test the hypotheses, a study was conducted in health centers located in the Republic of Serbia. The research utilized survey methods and questionnaire techniques in four health centers operating within the Braničevo District. The survey was administered using a traditional approach, involving the distribution of written surveys. For the purposes of research in the health center, a form for the informed consent of the respondents was used instead of The Approval of the Committee on ethics. This form confirmed that the respondents had read the research notification document and received information about the type, method, and purpose of the research, as well as their obligations. The respondents agreed to participate in the research and to cooperate with the researchers. The cooperation requested from respondents involved the thorough and honest questionnaire completion, but no further interaction or identification was required. Also, they agreed that the research results could be made available to professional bodies and published in scientific journals or presented at scientific meetings. The respondents confirmed that they had received all the necessary information about the research and that they agreed to participate by filling out the questionnaire. Besides that, they also understood that participation was voluntary and that they could withdraw at any time without consequences. Research standards are aligned with the Helsinki Declaration on Human Rights and legal norms of the Republic of Serbia, especially the Law on personal data protection ("Official Gazette of the Republic of Serbia" No. 87/2018), as well as the General Data Protection Regulation of the European Union. The research was anonymous, so the consent did not contain the respondent's signature.

Instruments

The independent variable in the model is managerial support, measured using statements from the Corporate Entrepreneurship Assessment Instrument (CEAI) scale. Additionally, the CEAI scale was employed to measure the autonomy, serving as the moderator variable in the model. The scale encompasses dimensions beyond managerial support, including autonomy, reward, time availability, and organizational obstacles [6]. The selection of this scale is

justified by its ability to capture the essence of the findings, particularly regarding managerial support and autonomy, which are intrinsic factors in rewarding and motivating health workers. This scale provides a comprehensive framework for assessing these crucial aspects, enabling a thorough examination of their impact on organizational outcomes in healthcare settings [19].

The dependent variable was observed through organizational performance. As previously pointed out, organizational performance is often a multidimensional construct [2, 3, 4]. Therefore, the dependent variable was constructed to encompass not only financial results and costs but also the quality of service delivered, productivity, employee satisfaction, patient satisfaction, reputation, and adaptability to change. As a result, it was designed based on the research model applied by Savović [20] in her work, which comprehensively addresses these various aspects of organizational performance. The absence of a universal model for measurement and the multidimensional nature of organizational performance justifies the application of this research method. The Quality of Services dimension examines improvements in the quality of services provided by the organization compared to the previous period, using one item (*The organization enhances the quality of services provided compared to the previous period*). The Cost Reduction dimension measures the organization's ability to reduce operational costs over time, also assessed with one item (*The organization reduces costs compared to the previous period*). For Employee Productivity, the focus is on changes in productivity levels among employees, evaluated with one item (*Employee productivity has risen compared to the previous period*). The Employee Satisfaction dimension gauges the overall job satisfaction of employees, using one item (*Employee satisfaction has been enhanced compared to the previous period*). The Patient Satisfaction dimension measures the level of satisfaction among service users (patients) with the organization's services, also assessed with one item (*The satisfaction of service users (patients) has improved compared to the previous period*). Finally, the Organizational Reputation and Responsiveness dimension includes two aspects: the organization's reputation (*The organization's reputation has seen improvement compared to the previous period*) and its ability to adapt quickly to changes, evaluated with two items (*The organization demonstrates the ability to promptly respond to changes in the environment* and *The organization quickly adapts to changes in technology*). Respondents also expressed their views on the above-mentioned statements on a five-point scale.

Study sample

Respondents expressed their views on the aforementioned statements using a five-point Likert scale, where Grade 1 indicated complete disagreement and Grade 5 indicated complete agreement with the stated position. Additionally, the questionnaire included a section to collect demographic information about the respondents. The study involved healthcare professionals, including general practitioners, specialists, nurses, and medical technicians. It encompassed employees of various genders, ages, educational backgrounds, and lengths of service, as well as those in managerial roles. The research was conducted across four healthcare organizations in the Braničevo district, all operating at the primary level of care: the health centers in Golubac, Veliko Gradište, Malo Crniće, and Žabare. To collect data, a convenience sampling was employed. Convenience sampling offers the benefits of reduced effort in participant selection, low cost, minimal time investment due to easy accessibility of the target population, the absence of a need to list all population elements, and the ability to generate a satisfactory and qualitative sample in various situations [21]. The convenience of the sampling in this case lies in the selection of health organizations within the same region, allowing the researcher easy access to the participants.

Respondents were approached through organizational HR departments. HR managers distributed the questionnaires to employees. To maintain anonymity, respondents were not asked for any personal information or identifiers. Each questionnaire was placed in a separate envelope, which respondents used to return their completed forms. Additionally, a secure, closed box was provided for respondents to submit their questionnaires, with access restricted to the researcher via a special unlocking code. Out of 250 distributed questionnaires, 165 were completed, resulting in a response rate of 66%. According to Holtom et al. [22], academic research response rates have been steadily increasing, averaging 68% over the past five years making the response rate in this study quite comparable to the recent average.

The collected data were processed in the IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Among statistical techniques, descriptive statistics [mean and standard deviation (SD)], internal reliability test, distribution normality test, correlation and regression were applied.

RESULTS

In the total sample of 165 respondents, 28.5% were male and 71.5% were female. Regarding age distribution, 44.2% were aged 41–50 years, 26.7% were aged 31–40 years, 17% were aged 51–60 years, followed by respondents over 60 years old with 6.7%, while the smallest proportion was aged 20–30 years (5.5%). In terms of education, 64.2% had completed secondary school, 23.6% had a university degree, and 12.1% had postgraduate education. Regarding length of service, 37.6% of respondents had worked in the existing organization for 21–30 years, 24.2% had worked for 11–20 years, 17% had more than 30 years of service, 12.7% had worked for 6–10 years, and 8.5% had 1–5 years of service. Furthermore, 80.6% of respondents worked in medical positions, while 19.4% worked in non-medical positions. Finally, 9.7% of respondents held managerial positions, while 90.3% held non-managerial positions.

The initial stage of the analysis involved applying descriptive statistics, starting with the independent variable. The results are presented in the following Table 1.

Table 1. Results of descriptive statistics: managerial support

Items	Mean	SD
1. My organization is quick to use improved work methods.	3.8182	1.0947
2. My organization is quick to use improved work methods that are developed by workers.	3.6242	1.1600
3. In my organization, developing one's own ideas is encouraged for the improvement of the corporation.	3.7879	1.1934
4. Upper management is aware and very receptive to my ideas and suggestions.	3.8061	1.1092
5. Promotion usually follows the development of new and innovative ideas.	3.1576	1.1993
6. Those employees who come up with innovative ideas on their own often receive management encouragement for their activities.	3.5152	1.1402
7. The "doers" are allowed to make decisions on projects without going through elaborate justification and approval procedures.	3.1697	1.1022
8. Senior managers encourage innovators to bend rules and rigid procedures in order to keep promising ideas on track.	2.8121	1.2424
9. Many top managers have been known for their experience with the innovation process.	3.5636	1.0435
10. Money is often available to get new project ideas off the ground.	3.2182	1.2050
11. Individuals with successful innovative projects receive additional reward and compensation for their ideas and efforts beyond the standard reward system.	2.8061	1.1364
12. There are several options within the organization for individuals to get financial support for their innovative projects and ideas.	3.3212	1.1841
13. Individual risk takers are often recognized for their willingness to champion new projects, whether eventually successful or not.	3.0182	1.0328
14. People are often encouraged to take calculated risks with new ideas around here.	3.1030	0.9280
15. The term "risk taker" is considered a positive attribute for people in my work area.	2.9573	1.0529
16. This organization supports many small and experimental projects realizing that some will undoubtedly fail.	3.0667	1.1105
17. A worker with a good idea is often given free time to develop that idea.	3.1273	1.1695
18. There is considerable desire among people in the organization for generating new ideas without regard to crossing departmental or functional boundaries	3.2909	1.1316
19. People are encouraged to talk to workers in other departments of this organization about ideas for new projects	3.4121	1.2590

Table 2. Results of descriptive statistics: organizational performance

Items	Mean	SD
1. The organization enhances the quality of services provided compared to the previous period.	3.9030	1.0944
2. The organization reduces costs compared to the previous period.	3.5091	0.9666
3. Employee productivity has risen compared to the previous period.	3.7091	1.0122
4. Employee satisfaction has been enhanced compared to the previous period.	3.5273	1.1559
5. The satisfaction of service users (patients) has improved compared to the previous period.	3.7212	1.0156
6. The organization's reputation has seen improvement compared to the previous period.	3.7455	1.0339
7. The organization demonstrates the ability to promptly respond to changes in the environment.	3.7818	1.0304
8. The organization quickly adapts to changes in technology.	3.9212	1.0417

The highest mean is achieved by the statement "My organization is quick to use improved work methods" (3.8182), indicating strong managerial support for implementing changes and adopting new work methods. Conversely, the item "Individuals with successful innovative projects receive additional reward and compensation for their ideas and efforts beyond the standard reward system" has the lowest mean (2.8061), suggesting that management does not consistently reward employees for their innovative contributions. However, the standard deviation of 1.1364 indicates some variability in attitudes from the mean. The highest homogeneity (SD = 0.9280) is observed with the item "People are often encouraged to take calculated risks with new ideas around here," indicating consistent encouragement from management for employees to be creative and innovative, even when it involves taking risks. Table 2 presents the descriptive statistics for the dependent variable – organizational performance.

According to the results in Table 2, the item "The organization quickly adapts to changes in technology" (3.9212) has the highest mean, indicating that the organization effectively embraces technological advancements. This aligns with earlier findings suggesting that management supports changes, including the adoption of new technologies, in the workplace. All other items also achieve relatively high results, with values greater than three on a five-point scale, indicating favorable perceptions of organizational performance. The highest homogeneity is observed with the item "The organization reduces costs compared to the previous period" (SD = 0.9666), suggesting a consensus among respondents regarding the organization's ability to achieve cost efficiency over time. The results of descriptive statistics for the mediator variable, employee autonomy, are shown in the Table 3.

Table 3. Results of descriptive statistics: employee autonomy

Items	Mean	SD
1. I feel that I am my own boss and do not have to double check all of my decisions.	2.8000	1.3122
2. Harsh criticism and punishment result from mistakes made on the job.	3.1455	1.2747
3. This organization provides the chance to be creative and try my own methods of doing the job.	3.1091	1.2098
4. This organization provides freedom to use my own judgment.	3.5939	1.1523
5. This organization provides the chance to do something that makes use of my abilities.	3.7879	1.1883
6. I have the freedom to decide what I do on my job.	3.1697	1.3598
7. It is basically my own responsibility to decide how my job gets done.	4.1576	1.0118
8. I almost always get to decide what I do on my job.	3.2788	1.2126
9. I have much autonomy on my job and am left on my own to do my own work.	3.5758	1.1694
10. I seldom have to follow the same work methods or steps for doing my major tasks from day to day.	3.8000	1.0998

According to the results in Table 3, statement 7, "It is basically my own responsibility to decide how my job gets

done" (4.1576), indicates that healthcare workers perceive their tasks and the quality of healthcare within their own sphere of responsibility, allowing them to decide how to carry out their duties. This statement also achieved the highest level of homogeneity of attitudes (SD = 1.0118), suggesting a strong consensus among respondents regarding this aspect of autonomy. On the other hand, the least favorable statement is statement 1, "I feel that I am my own boss and do not have to double check all of my decisions" (2.8). This statement reflects a sense of autonomy among healthcare workers, as they perceive themselves as having the authority to make decisions without needing validation from managers.

The Cronbach α test was used to assess internal reliability. The value of this coefficient should be at least 0.7 for the variable to be considered reliable [23]. As the results in Table 4 show, all variables achieve a very high reliability level, which indicates a high internal consistency of the used variables, which justifies the further process of analysis.

Table 4. Results of the Cronbach α test

Variable	Cronbach α
Managerial support	0.937
Organizational performance	0.933
Employee autonomy	0.870

Before applying correlation analysis, it is necessary to analyze the distribution of the data, in order to assess whether they follow a normal distribution. For these purposes, the Kolmogorov–Smirnov and Shapiro–Wilk tests were used (Table 5).

The results of the Kolmogorov–Smirnov and Shapiro–Wilk tests show that the variables managerial support and organizational performance follow a normal distribution, as well as the Shapiro–Wilk test for autonomy ($p < 0.05$). Kolmogorov–Smirnov for the specified variable is statistically significant at the 0.1 level. Accordingly, it is necessary to apply the Pearson correlation coefficient, the results of which are shown in Table 6.

Table 5. Normality distribution test

Variable	Kolmogorov–Smirnov			Shapiro–Wilk		
	Statistics	df	Sig.	Statistics	df	Sig.
Managerial support	0.086	165	0.005	0.981	165	0.026
Organizational performance	0.070	165	0.046	0.959	165	0.000
Employee autonomy	0.064	165	0.093	0.982	165	0.031

Table 6. Results of correlation analysis

Variables	Managerial support	Organizational performance	Employee autonomy
Managerial support	1	0.734**	0.659**
Organizational performance	0.734**	1	0.549**
Employee autonomy	0.659**	0.549**	1

**- Correlation is significant at the 0.01 level (2-tailed)

Cohen [24] states that the correlation coefficient at the level of -/+ 0.5–1 can be considered high. Accordingly, it can be stated that there is a high direct correlation between managerial support and organizational performance, as well as autonomy and organizational performance. An identical correlation coefficient is also present in the relationship between managerial support and autonomy.

The results of the regression analysis in Table 7 show a statistically significant and positive influence of managerial support on organizational performance ($\beta = 0.734$, $p < 0.001$). The coefficient of determination (R^2) is 0.539, as a result of which it can be stated that 53.9% of the variability of the dependent variable is explained by the independent one. When it comes to the second regression model, autonomy achieves a statistically significant and positive impact on organizational performance ($\beta = 0.549$, $p < 0.001$). The coefficient of determination (R^2) in this case is 0.301, which means that 30.1% of the variability of the dependent variable is explained by the independent one. The value of the variance inflation factor is less than five, i.e., 1000 in both models and as such shows the absence of multicollinearity problems [25]. In order to examine the moderator effect, a moderator analysis was applied, using the Hayes process approach in SPSS [26]. Mediator analysis starts from the position that the influence of the independent variable on the dependent variable is modified by the influence of the third, i.e. mediator variable [27, 28], where in this research, the starting point is that this influence is strengthened. Figure 1 shows the research model. The results of the mediator analysis are shown in Table 8.

Table 7. Results of regression analysis

Regression model	R2	β	F	Sig.
1. Managerial support → Organizational performance	0.539	0.734	190.251	0.000
2. Employee autonomy → Organizational performance	0.301	0.549	70.190	0.000

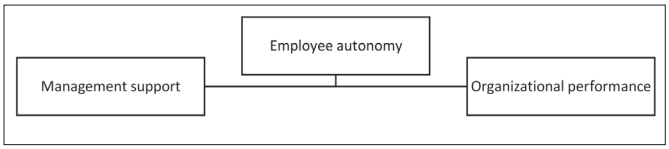

Figure 1. Mediator model

Table 8. Mediator analysis results

Model	R2	t	Sig.
X: Managerial support Y: Organizational performance W: Job autonomy	0.5579	74.6072	0.000
		9.1958	0.000
		1.4278	0.1553
Int-1		-2.0739	0.0397

Int-1 – mediator model

If mediator analysis is included in the regression model, the results are statistically significant at the $p < 0.001$ level. The coefficient of determination is (R^2) 0.5579, which means that the independent and mediator variables explain 55.79% of the dependent variable. Int-1 in Table 8 represents the mediator model (Figure 1). As can be seen, the result is statistically significant at the $p < 0.05$ level, and

the coefficient of determination (R^2) has increased from the previous 0.539 to 0.5579, as a result of which it can be said that the increased effect of managerial support on organizational performance has been achieved. In other words, there is a statistically significant mediating effect of autonomy on the relationship between managerial support and organizational performance.

DISCUSSION

In healthcare organizations, the analysis revealed that managerial support peaks when implementing new work methods, aiming to enhance clarity and efficiency in healthcare delivery. Managers actively encourage and welcome innovative ideas from employees, fostering a culture of open communication and knowledge exchange. Leveraging their expertise, managers facilitate multi-sector collaboration, enhancing organizational flexibility and responsiveness to change. Employees are empowered to make independent decisions on project tasks, promoting innovation without rigid processes. While financial incentives are common, there's room for managers to further motivate employees with promotions, knowledge development, and recognition, which have proven impactful in healthcare settings [17, 19].

The performance of healthcare organizations reflects a positive response to change, particularly in adopting new technologies, supported by managerial encouragement. This commitment to innovation translates into high-quality healthcare services, fostering patient satisfaction and employee morale. As a result, healthcare workers exhibit heightened productivity, contributing to the organization's stellar reputation and financial success. Within healthcare organizations, autonomy empowers employees to take ownership of their work, promoting efficiency and quality in healthcare delivery. Employees are afforded flexibility to devise optimal solutions, underpinned by managerial support for their knowledge and skills. However, amidst the emphasis on autonomy, the importance of adherence to established protocols cannot be overlooked. To mitigate potential shortcomings, ongoing managerial guidance and support are essential, ensuring optimal outcomes in healthcare provision.

Examining the set hypotheses, the results of the analysis showed that there is a statistically significant and positive influence of managerial support on organizational performance, as a result of which $Hypothesis_1$ can be accepted. In accordance with the previous views, managers who provide support to employees in terms of encouragement to generate new ideas, share knowledge and information, as well as adequate rewards for such efforts, leads to positive attitudes and individual productivity. At the organizational level, such employee behavior improves overall organizational performance. Such results have been confirmed in similar studies conducted around the world [1, 3, 7]. The analysis has shown a statistically significant and positive influence of employee autonomy on the achieved performance of healthcare organizations, which is the expected result confirmed in other studies as well [9, 10, 11, 18]. Adequate managerial support leads to job satisfaction of healthcare workers, where job satisfaction is often a determinant of achieved performance [29, 30]. Accordingly, $Hypothesis_2$ can also be confirmed. Finally, the results of the mediation analysis showed a statistically significant mediating influence of employee autonomy in the relationship of managerial support to organizational performance, thus confirming $Hypothesis_3$. When autonomy is included in the relationship between managerial support and organizational performance, a stronger effect is achieved.

Research of this nature is notably scarce within academic circles in the Republic of Serbia, underscoring the significance of this study in laying the groundwork for further inquiry. Moreover, healthcare organization managers stand to gain practical insights into enhancing organizational performance through the provision of managerial support and autonomy. However, the study is not without limitations, which warrant consideration in future research endeavors. Important among these limitations is the size and composition of the sample. Future studies would benefit from an expanded sample size encompassing a broader array of healthcare organizations, both within Serbia and internationally. Employing representative sampling methods will be essential to ensure the sample's optimal composition. While the utilization of scales in this study is justified, future research could benefit from incorporating measurement scales designed to assess managerial support, autonomy, and organizational performance in healthcare. Additionally, employing robust statistical techniques such as factor analysis or structural equation modeling can yield more objective insights into the influence of latent variables, further enhancing the research's rigor and validity. It is useful to apply tests for comparing means, in order to determine whether some of the socio-demographic factors, such as gender, age, education, etc., affect the perception of managerial support, autonomy, organizational performance, etc.

CONCLUSION

Managerial support and autonomy play pivotal roles in driving organizational performance within healthcare organizations, as evidenced by their statistically significant and positive impact. Moreover, autonomy serves as a significant mediating factor in the relationship between managerial support and organizational performance. Effective management within healthcare entails fostering an environment where employees are encouraged to innovate, take risks, share knowledge, and are provided with resources and rewards. By doing so, healthcare organizations can enhance their performance across financial and non-financial metrics, ultimately fostering success in their operational endeavors.

Conflict of interest: None declared.

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Испитивање утицаја подршке руководилаца на учинак здравствених организација – медијаторска улога аутономије запослених

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САЖЕТАК

Увод/Циљ Циљ рада је испитати утицај подршке руководилаца и аутономије запослених на учинак здравствених организација. Додатно, циљ рада био је испитати медијаторски утицај аутономије запослених на однос између подршке руководилаца и учинка здравствених организација.

Методе У истраживању је учествовало 165 запослених из четири здравствене организације Браничевског округа у Републици Србији. Независна варијабла (подршка руководилаца) и медијаторска варијабла (аутономија запослених) мерене су помоћу Инструмента за процену корпоративног предузетништва. За зависну варијаблу (организациони учинак) коришћена је скала прилагођена претходним истраживањима, која се састоји од димензија финансијских резултата, квалитета пружене услуге, продуктивности, задовољства запослених, задовољства пацијената, репутације и прилагодљивости променама. Запослени у здравственим установама анкетирани су у погледу својих ставова на петостепеној Ликертовој скали према тврдњама које су дизајниране за мерење поменутих варијабли. Анализа је подразумевала коришћење дескриптивне статистике, тест интерне конзистентности поузданости, тестове дистрибуције нормалности, корелацију и регресиону анализу.

Резултати Скале коришћене за мерење варијабли остварile су висок ниво интерне конзистентности, са Кронбаховим *α* коефицијентима у распону од 0,870 до 0,937, што указује на високу поузданост. Висок ниво Кронбахових *α* коефицијента дефинисан је на основу утврђених прагова, при чему се резултати изнад 0,7 сматрају високим. Регресиона анализа показује статистички значајан и позитиван утицај подршке руководилаца и аутономије на организациони учинак ($\beta = 0{,}539$, $p < 0{,}000$; $\beta = 0{,}301$, $p < 0{,}000$, респективно). Поред тога, идентификован је медијаторски ефекат аутономије у односу између подршке руководилаца и организационог учинка.

Закључак Подршка руководилаца утиче на учинак здравствених организација, а тај ефекат је појачан давањем аутономије запосленима. Руководиоци ових организација могу унапређењем подршке, кроз развој аутономије запослених, унапредити организациони учинак.

Кључне речи: подршка руководилаца; аутономија запослених; организациони учинак; здравствене организације

DOI: https://doi.org/10.2298/SARH240629082M
UDC: 343.6:618-051(497.11); 614.253(497.11)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Modalities and legal treatment of obstetrical violence in the Republic of Serbia

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SUMMARY
Introduction/Objective The problem of obstetric violence is a relatively new topic both in the field of medicine and in the field of law. The aim of the work is to analyze the problem and propose a solution in order to encourage the adequate application of the normative framework, improve the treatment of pregnant women and women in labor in gynecological-obstetrical institutions, protect women's reproductive health, restore trust, respect and understanding in the mutual communication between health workers and pregnant women/birth mothers.
Methods Several scientific methods were used in the work – desk research, descriptive method and analysis, and synthesis of available literature as well as relevant announcements, normative method, and logical research. In the research part of the paper, the primary method is the case study and analysis of obstetric violence in practice. Finally, a functional analysis was performed.
Results Through the analysis of case studies and modalities of obstetric violence in gynecological-obstetrical institutions in Serbia, as well as the analysis of research carried out so far, as many as 16 forms of obstetric violence were identified.
Conclusion Adequate implementation of legal and by-laws governing this area should be systematically encouraged, the treatment of pregnant women and women in labor in gynecological-obstetrical institutions should be improved, women's reproductive health should be protected with dedication, proper application of medical treatments, be treated with respect and understanding, exclude acts of discrimination, torture, inhumane and humiliating treatment, and ensure adequate and functional conditions for the stay of pregnant women and mothers in labor in a gynecological-obstetrical institution.
Keywords: obstetric violence; women's reproductive health; family; Family Law; Criminal Code

INTRODUCTION

The Constitution of the Republic of Serbia [1] stipulates that everyone has the right to protect their physical and mental health, as well as that human life is inviolable. The Law on Health Care [2] regulates, among others, the principle of respect for human rights and values and the rights of the child in health care, which implies ensuring the highest possible standard of human rights and values in the provision of health care, as well as guiding the best interests of the child in all activities health care provider. The Law on Patients' Rights [3] stipulates that the patient is guaranteed an equal right to quality and continuous health care in accordance with his health condition, generally accepted professional standards and ethical principles, in the best interest of the patient and with respect for his personal views. This law provides for a whole set of rights that patients enjoy. The Law on Prohibition of Discrimination [4] prescribes a general prohibition of discrimination and stipulates that everyone is equal and enjoys equal status and equal legal protection, regardless of personal characteristics.

The Constitution of the Republic of Serbia [1] stipulates that everyone has the right to freely decide on the birth of children, as well as that the mother is provided with special support and protection before and after childbirth. The Family Law of the Republic of Serbia [5] stipulates that a woman can freely decide on giving birth, and that mother and child enjoy special protection from the state. The provisions of the Criminal Code [6] in the chapters that prescribe criminal offenses against human health, against sexual freedom, freedoms and rights of man and citizen and against life and body protect, in terms of the object of criminal protection, precisely the right to mental and physical health within rights to health care, sexual freedoms, freedoms and rights of man and citizen, and human life and body, as values that are very often the object of injury or endangerment by various actions, which not infrequently happen precisely in the sphere of exercising the right to health care for children, pregnant women and maternity.

The aforementioned provisions certainly speak of the values that we unequivocally protect with the modern legal order, which are the embodiment of the democratic framework of living and acting. Why is it important to point out the whole set of constitutional and legal provisions that protect the right to health care of all citizens, especially children, pregnant women and mothers in labor, and the right to protect the physical and mental health of every citizen? It is important because the violation, among

Received • Примљено: June 29, 2024
Revised • Ревизија: October 20, 2024
Accepted • Прихваћено: October 29, 2024
Online first: November 1, 2024

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others, of these provisions is directly related to the problem of violence against women during pregnancy, before and after childbirth. It should be said that the problem of violence against women before childbirth, during and after childbirth was not recognized for a long time in the wider social context, nor was it analyzed from either a medical or a legal point of view. Until the middle of the 20th century, obstetric violence, nor actions directly or indirectly related to obstetric violence, were the subject of critical review by neither the scientific or professional public. The problem of violence against women during childbirth therefore and according to the opinion of other authors „represents a relatively new topic both in medical studies and in sociological-feminist research on violence against women in general, and until the end of the last century it was sporadically thematized in wider feminist literature, becoming more visible only in the last two decades" [7].

At this point, before elaborating in more detail the concept and forms of obstetric violence, the importance and consequences it leaves on society and the individual, it is necessary to point out certain standards regarding the ethics and professional behavior of health workers, highlight the principle of *Primum non nocere*, and the postulates of the Hippocratic Oath which represents the foundation of the ethics of healthcare workers since the fourth century BC, when Hippocrates gave the first codification of ethical principles.

Namely, the principle *Primum non nocere* is one of the oldest ethical principles of ancient medical practice, which was also established by Hippocrates, with the basic meaning "to help or at least to do no harm." This principle is based on three very important postulates, namely morality, honesty, and fairness in dealing. Having said that, the determination of morality, which in principle consists of two components of moral reasoning and moral behavior as a psychological function, implies "man's ability to dictate to himself the norms that he will adhere to during his life, as well as to punish himself if he does not adhere to the norms that he gave himself." Each person possesses morality, and morality is, in addition, "the right and obligation of the individual to live and behave according to the principles of honesty and integrity" [8].

There is no doubt that the changes in the health system of the states have been changing for centuries in accordance with "social and technological requirements," [9] whereby the problem of overtime work of health workers "as a situation that is very common in practice but which should be avoid" [10] but the fact that "today in all countries there is a code of ethics for health workers" [11], the basis of which is certainly Hippocrates' point of view on medical ethics, whose premises were contained even in Hammurabi's code (2100 BC).

The basic values that healthcare professionals should stand for are: "human and nation health, the life of patients, and the physical and psychological integrity of individuals and certain vulnerable groups" [11]. In Geneva in 1948, the World Medical Association adapted the Hippocratic Oath to current times. The Declaration of Geneva "emphasizes all four fundamental principles of medical ethics from the Hippocratic Oath. A doctor is ordered to perform his duties conscientiously and with dignity, to respect and be grateful to his teachers and to his colleagues as to brothers and sisters" [12].

Consequently, "observing the existence of violence during childbirth is related to the protection of women's basic human rights to physical and personal integrity, self-determination and privacy" [7]. Namely, the application of certain procedures, interventions and ways of dealing with health care workers, which include "coercion, denial of information, disrespect and obstetric violence and inciting fear in the person giving birth are completely inconsistent with the goals of organizing healthy, safe and civilized ways of childbirth, which are globally changed the conditions of obstetrics during the 20th century" [7].

Building on what has been said, and before proceeding to the analysis of the case study, it is necessary to define the concept, meaning, scope and appearance of forms, i.e., the modalities of behavior which in modern literature is denoted by the term obstetric violence, and which actually refers to the actions of health workers which contains elements of violence against women during pregnancy, before childbirth, during childbirth and immediately after childbirth.

Based on past experience in practice, obstetric violence is considered to be any type of negligent treatment of women in gynecological-obstetrical institutions, and any type of physical, psychological or emotional abuse during pregnancy, before and during childbirth, as well as after childbirth. Obstetric violence represents "a specific form of violence against women that violates the regulations governing human rights" [13], rights guaranteed by family law, rights in the field of health care and patients' rights. Obstetric violence is a modern term that in practice can include a series of specifically committed acts that contain the elements of a criminal offense, for which the Criminal Code foresees criminal liability. Obstetric violence can include a series of actions by health workers that can produce different consequences both for the pregnant woman and the woman giving birth, as well as for the entire family – degrading and inhumane births, health complications for both the mother and the child, psychological disorders, postpartum trauma, mistrust in the health care system, and often the death of the mother and/or baby.

Obstetric violence very often implies an inhumane approach, unscrupulous attitude of health workers towards pregnant women and mothers who use "their authority and an obvious disproportion in their position in relation to pregnant women and mothers" [14], "abuse of interventionist measures, medicalization and returning the process from natural to pathological , which results in the loss of a woman's right to decide about her own body and negative impacts on the quality of life of herself and the child" [15]. Therefore, different modalities of obstetric violence can be recognized in the world, regardless of the level of development of the country, political system, social status of women, level of education and any other parameter, and these modalities are most often related to verbal violence, physical violence, sexual violence, social discrimination,

neglect and inadequate use of medical procedures and skills by health workers, despite the fact that such an approach is unacceptable for the profession they perform, and for society itself [16].

In 2019, the International Organization for Human Rights during Childbirth published a report entitled "Abuse and violence against women during the provision of health care during the reproductive period," with an emphasis on childbirth, in which it presented the position of women during pregnancy, childbirth, and after childbirth. The report points out that "abuse and violence against women in terms of reproductive health protection is present all over the world and occurs most in situations when women ask for medical treatment to reduce their pain and alleviate suffering, or when they ask to explain to them the medical treatment that will be carried out, the consequences of the treatment and her current state of health" [17].

According to research carried out in Serbia on a sample of 30 women from Belgrade selected by combined purposive and snowball sampling, evenly distributed on the basis of age (from 18 to 55 years) and education (primary, secondary, and higher education), according to the set criteria of rudeness and disrespect the intimacy of a woman giving birth, connected with the indicators related to the testimonies of rude treatment, excessive infliction of pain, and exposure of the woman's body to examination and the view of an excessive number of people, the following conclusion was reached, among other things: "the rudeness of health workers during the delivery of a woman consisted in ugly and incorrect treatment, with disrespect for the intimacy of the person giving birth, in some cases in not maintaining hygienic conditions, in insults, sexist remarks, but also in direct violence, which, all together, bearing in mind the number of such responses (since appears in almost every interview), cannot be treated as an anomaly in relation to the usual way of dealing in maternity wards, but as a custom that is widely represented" [7].

METHODS

Several scientific methods were used in the work – desk research (bibliographic and hemerographic research that enables the creation of an acceptable previous theoretical framework, because it is based on the analysis of available modern bibliographic documents), descriptive method and analysis and synthesis of available professional and scientific contemporary literature from the country and abroad, as well as relevant announcements with respect to the chronological approach, the normative method in the analysis of current national legislation, and logical research. In the research part of the paper, the primary method is the case study and analysis of obstetric violence in practice. Finally, a functional analysis was performed.

RESULTS

In mid-January 2024, Serbia was shaken by the news from Sremska Mitrovica regarding alleged violence against a woman during childbirth. It is a case of childbirth in a hospital in Sremska Mitrovica, a city about 75 kilometers away from Belgrade.

For one woman, Marica Mihajlović, the world stopped on January 12, 2024 when she did not hear her baby's cry after giving birth. According to her statement sent to the public from her account on a social media network six days after the unfortunate event, she suffered violence that affected both her health and the life of the child, who died during childbirth. Her statement read: "The doctor hit and insulted me, squeezed my jaw, threatened to hit me... to crush my head, he insulted me on ethnic grounds" [18].

The autopsy of the baby of Marica Mihajlović indicated that death occurred due to a violent birth. According to the conclusion of the forensic pathologists: "Based on the clinical course and the autopsy findings, we are of the opinion that the unfavorable outcome occurred due to severe perinatal asphyxia of the fetus and massive aspiration of meconium, and the consequent occurrence of bilateral pneumothorax and bilateral suprarenal hemorrhage. The presence of a subgaleal hematoma was also verified." [19, 20].

This case alarmed Serbia and encouraged other women to tell similar, bitter experiences. It turned out that obstetric violence in Serbia is not a new topic. For years, women in Serbia have been faced with certain modalities of obstetric violence during pregnancy, during childbirth, and after childbirth – emotional threats and blackmail, conditions for the provision of services, failure to provide pregnant women with enough information to make their own decisions, disrespect for the privacy and preferences of the mother-in-law, denial of food or water, vaginal examination without consent, neglect of complaints and pain of the woman in labor, verbal and emotional insults and humiliation, inability to move and forced to lie down, sexual comments or sexual abuse, physical violence, medical procedures without the consent of the pregnant woman, non-presentation and domineering behavior etc.

In 2015, the "Center for Mothers" association conducted a survey on the experiences of women in maternity wards, which produced worrying results. From then until today, almost nothing has changed. The research was part of a regional campaign called "Freedom to Give Birth", whose aim was to draw public attention to the treatment of women and their rights during childbirth, as well as the importance of good communication between staff and birth attendants during childbirth [21]. The research showed that "maternity wards in Serbia are places where pregnant women come with anxiety and give birth in an unpleasant atmosphere, where unknown people do not explain what is happening to them, nor support them during childbirth, but follow their birth plan and make decisions for themselves." The father is almost completely excluded from the birth, and even when he attends the birth, he is present primarily as an "assurance that there will be no

verbal abuse of the woman in labor, and not as support and help during the birth" [22].

Even before the case of Marica Mihajlović from Sremska Mitrovica, numerous experiences of obstetric violence in gynecological-obstetrical institutions were publicly reported, which showed that medical treatments for the protection of women's reproductive health were not applied in accordance with regulations, and that national regulations (in the first in line with the Constitution and the laws whose key provisions are listed at the beginning of the work) are very often completely ignored or inadequately applied in the practice of the actions of health-care workers.

Research conducted by three female lawyers in Serbia during 2022 included the analysis of over two hundred cases and experiences of women who experienced obstetric violence in gynecological and obstetric institutions. The respondents confirmed with their experiences that obstetric violence is not an individual problem, but a serious systemic problem. A total of 110 respondents gave their consent for quoting the statements they gave as part of the research. The results of the research showed that 16 forms of violence and abuse, i.e., inhumane treatment of the examined patients, were identified [17]. Research shows that "various forms of obstetric violence are present, and that their form ranges from verbal insults, through abuse with serious physical injuries, to the death of the woman or the baby." In each form of obstetric violence, different intensities of violence with different degrees of consequences were observed [17]. Figure 1 shows the types of violence in gynecological-obstetrical institutions, which were found through the aforementioned research.

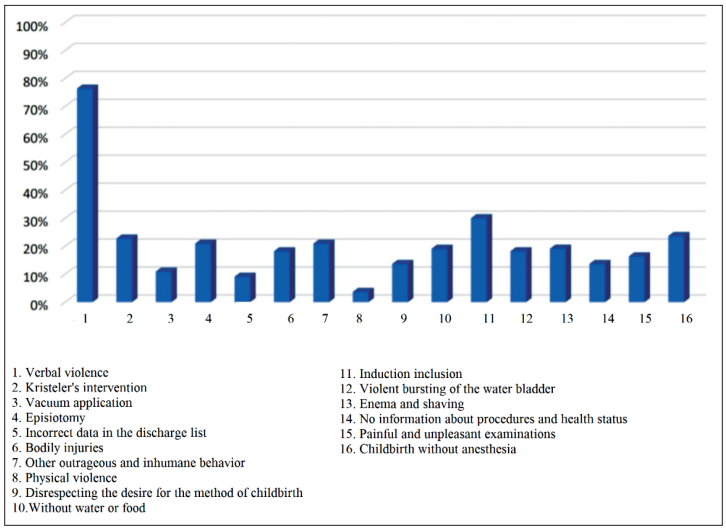

Figure 1. Types of violence in gynecological and obstetric institutions

Source: Mijatović M, Stanković J, Soković-Krsmanović I. Treatment of women in gynecological and obstetric institutions, Belgrade, 2022, 42.

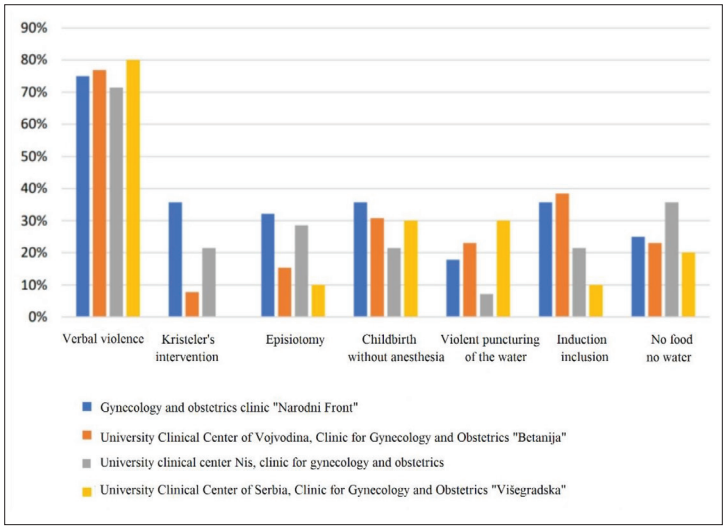

Figure 2. The most common forms of violence in four gynecological and obstetric institutions with the most reports

Source: Mijatović M, Stanković J, Soković-Krsmanović I. Treatment of women in gynecological and obstetric institutions, Belgrade, 2022, 43.

The research yielded data that the most reports of obstetric violence were for four health institutions (Narodni Front Gynecology and Obstetrics Clinic; University Clinical Center of Vojvodina, Betanija Clinic for Gynecology and Obstetrics; University Clinical Center of Niš, Clinic for Gynecology and Obstetrics; University Clinical Center of Serbia, Višegradska Clinic for Gynecology and Obstetrics) [17]. Figure 2 shows the most common forms of violence in the four gynecological and obstetric institutions with the most reports.

DISCUSSION

From the presented case from Sremska Mitrovica and the analysis of the modality of obstetric violence in gynecological-obstetric institutions in Serbia, it can be concluded that the main problem with obstetric violence until now was that any form of violence by health workers in gynecological-obstetric institutions was understood for years as an individual problem, and not a systemic problem that society has been facing for a long time.

Obstetrical violence violates not only the provisions of the Constitution as the highest legal act of the state, but also the entire legal framework that provides certain guarantees and security to citizens, protecting concretely defined values whose protection and security is a feature of the modern state and society. At the beginning of the work, the laws are listed, each of which in its domain provides valid guarantees to all citizens in the field of health care, health insurance, rights and duties of patients and general prohibition of discrimination, and in accordance with these provisions, and support, among other things, to women in the field of application of medical treatments in order to protect women's reproductive health.

The provisions of the Family Law of the Republic of Serbia, which stipulates that a woman can freely decide on giving birth, and that mother and child enjoy special state protection, are also key. The Family Law also stipulates that everyone is obliged to be guided by the best interest of the child in all activities concerning the child. The state has the obligation to take all necessary measures to protect the child from neglect. The state has an obligation to respect, protect and promote the rights of the child [5]. The provisions of the Family Law and Family Law, formulated in this way, are the basis of the provisions of the Criminal Code of the Republic of Serbia, which prescribes criminal offenses against human health, criminal offenses against sexual freedom, criminal offenses against the freedoms and rights of man and citizen, and criminal offenses against life and body, which protect, in in terms of the object of criminal law protection, the right to mental and physical health within the right to health care, sexual freedom, freedom and rights of man and citizen, and the life and body of man, as values that are very often the object of injury or endangerment by various actions, which are not they rarely happen precisely in the sphere of exercising the right to health care for children, pregnant women and mothers in labor. It should be said that "every type of violence manifests itself by injuring and jeopardizing first and foremost safety and trusting relationships, and is characterized by power and control over the victim" [22]. However, even though the provisions of the criminal legislation in the domain of criminal liability of persons responsible for the commission of an offense which in a specific case may have features of a criminal offense (which in each specific case is assessed by the prosecution through the preliminary investigation procedure and investigation) cannot be bypassed, it should be investigated that the protection of the family, makes mother and child "primarily family law, so here the criminal law protection is actually subsidiary, i.e., it is resorted to only in those cases of attacks on the stated values, when they cannot be adequately protected by the norms of another branch of law" [23].

In accordance with what has been said, it should be said that the laws properly, in accordance with the constitutional norms, regulate the areas concerning the protection of women's reproductive health, the life and health of children and the rights of the family. It is essential to draw conclusions from past experiences regarding the need for proper enforcement of existing regulations, improved communication and collaboration within gynecological-obstetrical institutions, and more effective judicial actions. Specifically, authorities should address the criminal liability of individuals whose actions—or lack thereof—endanger the health and lives of mothers and children, whether in abstract terms or in concrete situations during pregnancy, childbirth, and postpartum.

CONCLUSION

Considering the various forms of violence and abuse, including inhumane treatment of women before, during, and after childbirth, it is important to emphasize several critical points. Research from 2022 identified 16 distinct forms of obstetric violence, with medical procedures often performed in ways that cause unnecessary suffering and pain. It is not uncommon for doctors to leave a patient in labor for other, seemingly more pressing obligations, raising concerns about how well the next doctor is informed about the patient's condition. Obstetric violence is not an isolated issue. Poor treatment by healthcare workers in gynecological-obstetrical institutions extends beyond the experiences of individual women who share their stories. Public awareness must be raised to address this systemic problem, as silence and tacit approval of inhumane treatment, especially towards women in their most vulnerable moments, will not lead to meaningful change. Let us be reminded that the Law on Patients' Rights [3] stipulates that the exercise of patient rights is based on the partnership of the patient as a recipient of health services and a health worker, that is, a health associate as a provider of health services. The partnership implies mutual trust and respect between the patient and the healthcare worker, i.e., the healthcare associate at all levels of healthcare, as well as the rights and duties of partners in that relationship. This law foresees a whole set of rights that patients enjoy, among which are: the right to access to health care, the right to information, the right to the quality of health service provision, the right to patient safety, the right to information, the right to free choice, the right to other professional opinion, right to consent, and other rights.

It is necessary to systematically encourage the adequate application of legal and by-laws governing this area, to improve the treatment of pregnant women and mothers in obstetrics and gynecological institutions, to protect women's reproductive health with dedication and proper application of medical treatments, to treat women with respect and understanding, to exclude acts of discrimination, torture, inhumane and humiliating treatment, and provide adequate and functional conditions for the stay of pregnant women and mothers in labor in a gynecological-obstetrical institution. In other words, it is necessary to systematically approach the prevention of any form of obstetric violence, with an adequate and legally prescribed approach to the criminal liability of responsible persons in situations where any form of violence from this sphere occurs.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

Conflict of interest: None declared.

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Модалитети и законски третман акушерског насиља у Републици Србији

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САЖЕТАК

Увод/Циљ Проблем акушерског насиља представља релативно нову тему и у области медицине и у области права. Циљ рада је анализа проблема и предлог решења како би се подстакла адекватна примена нормативног оквира, побољшао третман трудница и породиље у гинеколошко-акушерским установама, заштитило репродуктивно здравље жене, повратило поверење, поштовање и разумевање у међусобној комуникацији здравствених радника и трудница/породиље.

Методе У раду је коришћено више научних метода – деск истраживање, дескриптивни метод и анализа и синтеза доступне литературе као и релевантних саопштења, нормативни метод, те логичко истраживање. У истраживачком делу рада примаран је метод студије случаја и анализе акушерског насиља у пракси. На крају је извршена функционална анализа.

Резултати Анализом студије случаја и модалитета акушерског насиља у гинеколошко-акушерским установама у Србији, као и анализом до сада спроведених истраживања, идентификовано је чак 16 облика акушерског насиља.

Закључак Треба системски подстаћи адекватну примену законских и подзаконских прописа који уређују ову област, побољшати третман трудница и породиља у гинеколошко-акушерским установама, заштити репродуктивно здравље жена посвећеношћу, правилном применом медицинских третмана, односити се према њима са поштовањем и разумевањем, искључити акте дискриминације, мучења, нехуманог и понижавајућег поступања, и обезбедити адекватне и функционалне услове боравка трудницама и породиљама у гинеколошко-акушерским установама.

Кључне речи: акушерско насиље; репродуктивно здравље жене; породица; Породични закон; Кривични законик

DOI: https://doi.org/10.2298/SARH240606093B
UDC: 616.341-006-089

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Gastrointestinal stromal tumor of the ileum – case report of life-threatening bleeding

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SUMMARY

Introduction Gastrointestinal stromal tumor (GIST) is relatively rare neoplasm and according to data in the literature, makes up less than 1% of all tumors of the gastrointestinal tract with the most frequent incidence in the sixth decade of life. The development and discovery of new molecular, biochemical and immunohistochemical methods contributed significantly to the successful identification and better understanding of this type of neoplasm. The most common localization of GIST is stomach, causing merely discomfort and occasional pain in the abdomen as the only complaint.

Case Outline Our patient, a 71-year-old male, came for an outpatient surgical examination due to gastrointestinal bleeding and low hemoglobin values in laboratory findings. We conducted the endoscopic examination of the upper parts of the digestive tract; there were neither active nor old signs of gastrointestinal bleeding. The patient underwent an ultrasound examination and then a computed tomography (CT) of the abdomen. CT scan showed tumor mass in the lower parts of abdominal cavity, highly suspicious for GIST of small intestine (ileum). The patient underwent emergency surgery, with the resection of bleeding tumor and creation of primary anastomosis. The patient recovered well from the surgery and was discharged home in good general condition.

Conclusion The goal of surgery is to achieve an optimal resection line R0 with an intact pseudocapsule of the tumor. Postoperative adjuvant therapy with imatinib is indicated in certain cases, in order to ensure the most favorable clinical and oncological outcome.

Keywords: emergency surgery; GIST; ileum; bleeding; imatinib

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a relatively rare neoplasm. According to the data in literature, it makes up less than 1% of all tumors of the gastrointestinal tract, with the most frequent incidence in the sixth decade of life [1, 2]. The development and discovery of new molecular, biochemical, and immunohistochemical methods contributed significantly to the successful identification and better understanding of this type of neoplasms [2, 3]. The paradigm shift related to this type of tumor has occurred in the last two decades, meaning that GISTs are now considered as mesenchymal tumors with predictable behavior and outcome in treatment. The change of name occurred as well, replacing old one such as leiomyoma, schwannoma, and leiomyosarcoma in pathological nomenclature [4]. The name was first coined in 1983 for a special set of mesenchymal tumors of the gastrointestinal tract that do not have ultrastructural and immunohistochemical characteristics of smooth muscle differentiation. In 1998, it was proven that the true precursor of these tumors is a pluripotent mesenchymal stem cell predefined to differentiate into an interstitial Cajal "pacemaker" cell, responsible for initiating and coordinating the motility of the digestive tract. The turning point in the identification of GIST as a unique clinical entity is certainly represented by the discovery of the role of c-kit proto-oncogene mutation in these tumors. Following that discovery, targeted molecular adjuvant and neoadjuvant therapy with thyroxine kinase inhibitors such as imatinib was established in standard treatment protocols and daily clinical practice [5]. GISTs may occur along the entire digestive tract, from the esophagus to the rectum, but generally remain undiagnosed, causing discomfort and occasional abdominal pain as the only complaint reported by the patients [6, 7]. The stomach represents the most common localization of GIST described in the literature. The other parts of digestive tube are recorded less, often as sporadic cases and therefore represent a curiosity in clinical practice [7, 8]. According to the previous data in literature, the crucial moment occurs when the tumor exceeds 4 cm in diameter which could be manifested as an urgent condition in abdominal surgery. That implies abundant gastrointestinal bleeding (due to necrosis of the wall of the hollow organ), intestinal obstruction or perforation (usually in the small intestine as the primary site of tumor localization) [4, 5]. Due to its localization, especially in the case of the small intestine, as well as the possibility of extraluminal growth, this type of neoplasm may be difficult to detect with

Received • Примљено: June 6, 2024
Revised • Ревизија: November 27, 2024
Accepted • Прихваћено: December 11, 2024
Online first: December 13, 2024

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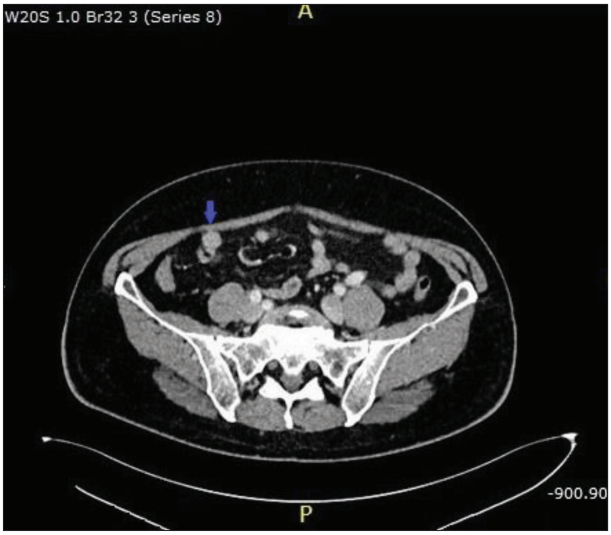

Figure 1. The blue arrow indicates hyperdense neoplasm close to the abdominal wall

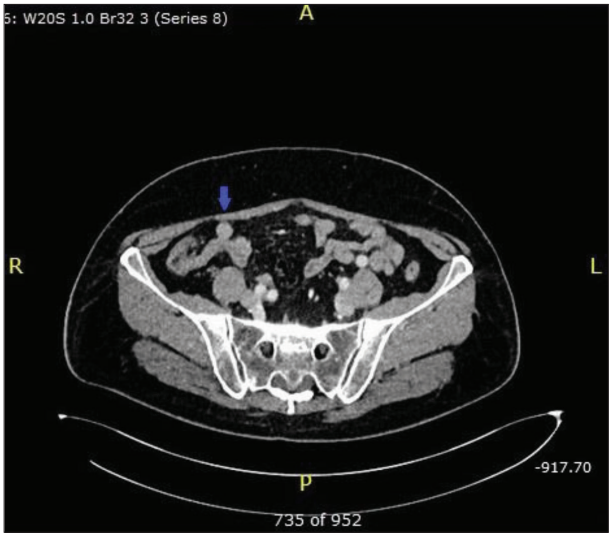

Figure 2. The blue arrow indicates tumor mass in the distal ileum in close relation to the caecum and the right external iliac artery, without radiological signs of infiltration

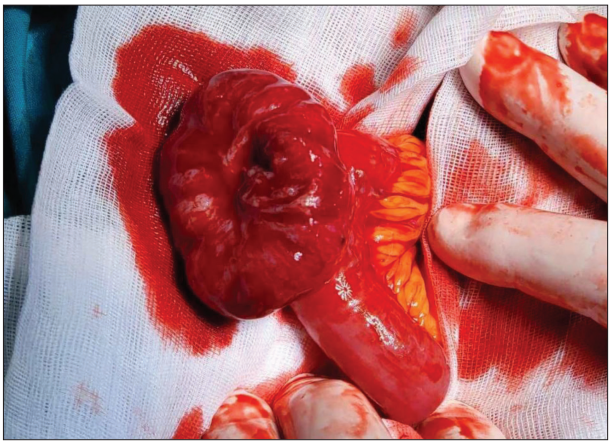

Figure 3. Specimen obtained after the resection showing the signs of bleeding

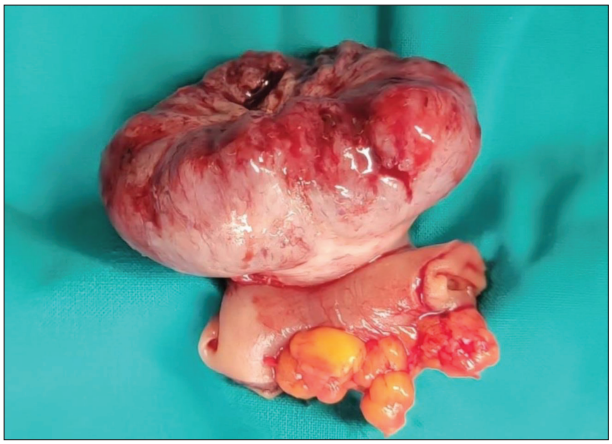

Figure 4. Extraluminal tumor mass of small intestine (ileum)

routine endoscopic examination of the digestive tract [9]. This could be the main reason why it is one of the most difficult causes of gastrointestinal bleeding to detect in emergency setting. Therefore, computed tomography (CT) scan of the abdomen and angiography are sometimes needed in order to verify the tumor and exact site of bleeding [7].

In our case report, we will refer to a GIST of the ileum, which manifested as severe and life-threatening gastrointestinal bleeding.

CASE REPORT

Our patient, a 71-year-old male, came for an outpatient surgical examination, for the first time due to black colored stools and a hemoglobin value of 120 g/L (ref. value 138–175 g/L) in laboratory findings. The patient was examined by the surgeon and referred to a gastroenterologist. There were neither active nor old signs of gastrointestinal bleeding detected on endoscopy of the upper digestive tract. The patient reported that he sporadically took iron supplementation, but did not consume food that would cause pseudomelaena. There was no previous excessive intake of non-steroidal anti-inflammatory drugs, anticoagulant nor antiplatelet therapy. After the examination, he was discharged home with the prescription of proton pump blockers and advice to undergo an elective colonoscopy.

The patient came back later to the Clinic for Emergency Surgery for another outpatient examination due to the persistence of black stools, now with admixtures of fresh blood and with hemoglobin values of 98 g/L in laboratory analyses. We decided to repeat the ultrasound examination of the abdomen. Radiology reported the exophytic mass of the distal ileum with a diameter of 46 × 32 mm, highly suspicious of a GIST.

The patient was admitted to the hospital and CT scan of the abdomen was performed. Radiology reported an exophytic, hyperdense tumor mass in the distal ileum, measuring about 43 × 49 × 52 mm in diameter, which could correspond to GIST (Figure 1). The mass was described as being in close relation to the caecum and the right external iliac artery, without radiological signs of infiltration. A smaller amount of free fluid (up to 25 mm thick) was also verified in the rectovesical pouch (Figure 2).

The patient underwent emergency surgery, due to the bleeding exophytic tumor mass of the distal ileum (with hemoglobin value of 63 g/L on admission) (Figure 3). We performed medial laparotomy with the exploration of abdominal cavity. In the further course of the operation, we made resection of small bowel with the tumor in the length of 10 cm. The procedure was followed by creation of hand-sewn end-to-end ileo-ileal anastomosis, in conventional two layers. The part of resected ileum with the tumor was sent to further histopathological analysis (Figure 4).

The patient recovered well from the surgery and was discharged in good general condition, five days after the surgery. The histopathological findings showed mesenchymal tumor of the ileum. Additional immunohistochemical analysis revealed that it was a "low risk" GIST of the ileum, with moderate metastatic potential and a 24% risk of progression. According to the TNM classification, the tumor was classified as pTNM 8: G-1; T3 Nx Mx.

Further clinical follow-up of the patient was conducted. The patient was referred to the Oncology Council, whose decision was to continue with regular checkups. The reason for that kind of decision was the absence of rest/recurrence of the disease or signs of secondary dissemination on postoperative CT scan. Laboratory findings (including conventional tumor markers for the of digestive tract) were also within the reference values.

We obtained verbal and signed consent of the patients to publish the case report. All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments.

DISCUSSION

In the case of GIST which clinically presents as acute and massive gastrointestinal bleeding, emergency surgery represents the most adequate form of treatment. The goal of surgery is to achieve the R0 line of resection with an intact pseudocapsule of the tumor. This scenario, if implemented on time, ensures the best oncological outcome for the patient. [8]. According to available data from the literature, these tumors do not show a potential to give metastases to regional lymph nodes and therefore do not make lymphadenectomy necessary [7].

Data available from the literature show that tumors of the small intestine make up only 5% of all tumors of the gastrointestinal tract [10]. The small intestine and ileum in this particular case, stands for the rarest location of GIST [11]. GISTs occur in a slightly higher percentage in males, usually in their sixth decade of life. Those patients could be referred to emergency department due to hematochezia with melena, accompanied by extremely low hemoglobin values in laboratory analyses. Therefore, the above mentioned classifies GIST of the small intestine as extremely rare cause of gastrointestinal bleeding [12].

Discussion goes in the direction of whether the greater benefit for the patient is creation of primary anastomosis or performing a stoma. If the surgeon decides for primary anastomosis, there is always a risk of dehiscence in the presence of peritonitis and the poor vitality of intestine. On the other hand, there are metabolic disorders if it is a high or proximal jejunostomy/ileostomy [13, 14]. In our case, in absence of peritonitis and due to potential losses from the ileostomy in initially hemodynamically unstable patient, we decided for creation of primary anastomosis. Anastomotic leak after the surgery still remains the major concern among surgeons despite surgical progress and technological advances. The awareness of risk factors should influence treatment and procedure-related decisions [15, 16].

Further discussion is being conducted in the terms of intraoperative abdominal lavage, i.e., whether, what type and amount of solution should be used [14]. Lavage with physiological solution can have a physical/mechanical effect in terms of dilution of tumor cells and bacteria. Utilization of antibacterial and antiseptic agents may act in terms of lysis of the bacterial or cell wall [17, 18]. In the literature, there is still not enough evidence regarding the optimal margin of resection of a tumor mass towards macroscopically healthy tissue. In any case, a negative line resection is necessary to prevent local recurrence [19, 20].

When it comes to a gastrointestinal tumor that exceeds 10 mm in diameter, the previously mentioned imatinib is recommended as adjuvant postoperative therapy. Furthermore, it is mandatory in pathologically classified "high risk" cases. Previous studies have shown that imatinib provides an absolute reduction in the recurrence rate of 14%, achieving a 97% recurrence-free survival [20, 21].

The Republic Fund for Health Insurance of Serbia has registered imatinib as an adjuvant therapy for pathohistologically confirmed GIST. Taking into account that we achieved R0 resection line, with the GIST being marked as "low risk", in the absence of rest/recurrence and secondary dissemination of the disease on follow-up examinations, the decision of the Oncology Council was to continue with clinical, laboratory and radiological follow-up of the patient every six months, up to two years after surgery, then every year regularly.

Conflict of interest: None declared.

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Гастроинтестинални стромални тумор илеума – приказ случаја животно угрожавајућег крварења

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САЖЕТАК

Увод Гастроинтестинални стромални тумори (ГИСТ) релативно су ретки и према подацима из литературе чине мање од 1% свих тумора гастроинтестиналног тракта, са најчешћом инциденцијом у шестој деценији живота. Развој и откривање нових молекуларних, биохемијских и имунохистохемијских метода значајно су допринели успешној идентификацији и бољем разумевању ове врсте неоплазми. Најчешћа локализација ГИСТ-а је желудац, док су нелагодност и повремени болови у трбуху често једине тегобе које болесници наводе.

Приказ случаја Наш пацијент, мушкарац стар 71 годину, дошао је на преглед са ниским вредностима хемоглобина у лабораторијским анализама и због сумње на гастроинтестинално крварење. Урадили смо ендоскопски преглед горњих партија дигестивног тракта; није било знакова активног нити старог гастроинтестиналног крварења. Пацијенту су индиковани ултразвучни преглед и потом компјутеризована томографија абдомена, која је показала туморску масу у доњим деловима трбушне дупље, са високим степеном сумње на ГИСТ танког црева (илеума). Пацијент је хитно оперисан, када је урађена ресекција крварећег тумора са примарном анастомозом. Оптимално се опоравио од операције и отпуштен је кући у добром општем стању.

Закључак Циљ хирургије је постизање оптималне ресекционе линије – *R*0 са интактном псеудокапсулом тумора. У одређеним случајевима потребна је постоперативна адјувантна терапија иматинибом, како би се обезбедио што повољнији клинички и онколошки исход.

Кључне речи: ургентна хирургија; ГИСТ; илеум; крварење; иматиниб

DOI: DOI: https://doi.org/10.2298/SARH240403084L
UDC: 616.68-007.1

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Torsion of the undescended testis in a healthy adult male

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SUMMARY

Introduction Torsion of undescended testis (UDT) in adults is rare, with only several published cases so far, and represents a urological emergency.

Case outlines We present a case of UDT torsion in 31-year-old, otherwise healthy, man who had right-side inguinal pain for six hours before he was admitted to hospital. Swelling was palpable in the area of the right groin region. The diagnosis was established based on Doppler ultrasound and exploratory surgery findings. A right-sided orchiectomy was performed. According to the available data, there are no published cases on this topic in the region.

Conclusion Although torsion of the UDT is a rare condition, it must be considered when symptoms of abdominal pain or swelling and pain in the groin region occur. Orchiectomy is suggested.

Keywords: UDT; torsion; orchiectomy

INTRODUCTION

Testicular torsion represents a urological emergency. Torsion of an undescended testis (UDT) is unlikely after the first year of life, with only several reports in adults. Orchiectomy is suggested, especially in adult cases. In this article, we present a case of undescended testis torsion in a 31-year-old, otherwise healthy adult.

CASE REPORT

A 31-year-old patient was presented to the Emergency Center due to a sudden onset of pain in the right groin region that had lasted six hours before the patient's arrival at the hospital. He did not suffer from any acute or chronic diseases. The family history was negative for congenital deformities and defects. The patient reported having two healthy children.

A clinical examination revealed a tender palpable mass in the right groin. The skin above mass was without signs of redness and elevated temperature (Figure 1). The right testicle was not palpable in the scrotum. Doppler ultrasonography of the scrotum, testicles, and abdomen revealed a hypoechoic ovoid mass in the right groin, measuring 2.7 × 1 cm, with no visible color Doppler signal. One enlarged lymph node measuring 1 cm was identified in the immediate vicinity of the hypoechoic mass.

Laboratory findings were normal, except slightly elevated white blood cells count (12.2×10^9/L) and blood glucose 6.6 mmol/L (NV 4–5.9 mmol/L). Tumor markers serum levels were within range limits.

Based on the clinical examination and additional diagnostics mentioned above, immediate surgical exploration was indicated. The right groin was exposed through inguinal incision (Figure 2). The hypotrophic right side cryptorchid testicle was livid due to a 180° torsion of the seminal cord. A right-sided orchiectomy was performed. Cefuroxime 2 g / 24 hours i.v., nadroparin calcium 0.3 ml / 24 hours s.c., pantoprazole 40 mg / 24 h p.o., as well as symptomatic analgesic therapy, were administered during the postoperative course. The patient was discharged on postoperative day 2. The pathohistological examination confirmed hemorrhagic infarction of the testicle, suggesting testicular torsion.

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

Testicular torsion is one of the most common urological emergencies, which is misdiagnosed in 20% of cases among adults [1, 2]. The incidence of UDT torsion is unknown [3]. UDT torsion can mimic acute abdomen, strangulated inguinal hernia, and inguinal lymphadenitis [2, 4]. Generally, 70% of UDT are palpable. Non-palpable testicles can be found in the inguinal-scrotal area in 30% and 55% of cases, respectively. Vanishing or absent

Received • Примљено: April 3, 2024
Revised • Ревизија: October 25, 2024
Accepted • Прихваћено: November 14, 2024
Online first: November 15, 2024

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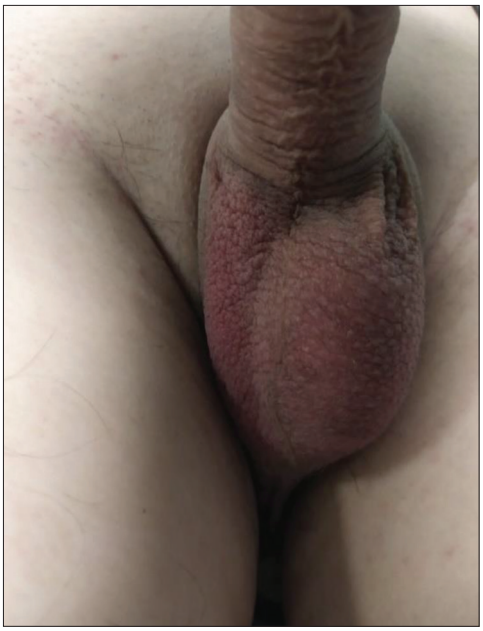

Figure 1. A clinical inspection – swell of the right groin region

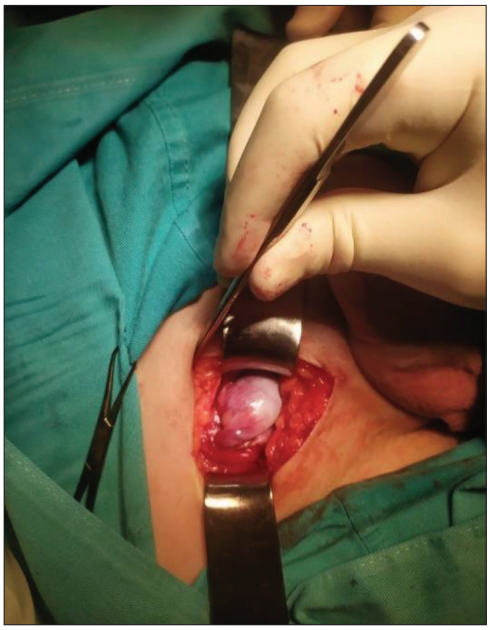

Figure 2. Surgical exploration of the right inguinal region – inguinal approach

testicle is found in 15% of patients [5, 6]. Both testicles are absent in 3–5% of cases [7]. Mechanism of UDT torsion is unclear, with two possible theories proposed. The first theory proposes that abnormal contractions or spasms of the cremasteric mucles cause spermatic cord torsion, as in patients with spastic neuromuscular diseases [4, 8, 9]. The second theory proposes that the size of the undescended testis is associated with the risk of UDT torsion, as in association with testicular tumors [4, 10, 11].

The clinical symptoms of UDT torsion are nonspecific, including abdominal and groin pain, sometimes vomiting and poor oral intake [4].

Ultrasound with color Doppler is the most common imaging modality [12]. CT, MRI, and scintigraphy are not widely used [12, 7]. One of three cases treated with exploration-detortion resulted in testicular ischemia [13]. Orchiectomy is suggested, especially in adult cases, since salvage rates in UDT are less than 10% [4].

In adults, even as a rare occasion, UDT torsion could be the cause of sudden abdominal pain, swelling, nausea, and vomiting. Proper history, physical examination of scrotum following ultrasound examination is to be performed in every case of UDT. Surgical exploration is obligatory. Orchiectomy is suggested, especially in adult cases having normal contralateral testicle.

Conflict of interest: None declared.

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Торзија неспуштеног тестиса код здравог одраслог мушкарца

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САЖЕТАК

Увод Торзија неспуштеног тестиса код одраслих је ретка, са само неколико објављених случајева до сада, и представља ургентно стање у урологији.

Приказ болесника Приказујемо случај торзије неспуштеног тестиса код здравог мушкарца старог 31 годину, који је примљен у болницу због десностраног ингвиналног бола који је трајао шест сати пред пријем. Била је присутна палпабилна тумефакција у пределу десне препонске регије. Дијагноза је постављена уз помоћ доплер ултразвука и експлоративне хирургије. Начињена је десностранa орхиектомија. Према доступним подацима, до сада није било објављених случајева на ову тему у региону.

Закључак Иако је торзија неспуштеног тестиса изузетно ретко стање код одраслих, мора се имати у виду када се јаве симптоми абдоминалног бола или отицање и бол препонске регије. Орхиектомија је метода избора.

Кључне речи: неспуштени тестис; торзија; орхиектомија

DOI: https://doi.org/10.2298/SARH240921083K
UDC: 616.74-002.4; 616.98:579.862

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Effective local treatment of necrotizing fasciitis using a chlorine solution obtained by electrolysis

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SUMMARY

Introduction Severe surgical wound infection as necrotizing fasciitis is one of the leading causes of death in the postoperative period. Large wounds affecting the skin and soft tissues are a particular problem, as such wounds are difficult to heal, especially in immunocompromised patients. Local treatment is important, and different antiseptics are in clinical use.

Case outline A 45-year-old woman with terminal kidney failure, with hypothyroidism and iodine allergy was admitted to the hospital with multiple abscess formation in the abdominal wall. After the first surgery, necrotic fasciitis and sepsis were diagnosed. Complete parenteral therapy, including antibiotics, other supportive therapy, and hemodialysis was performed. Successive debridement and local treatment with chlorine solution obtained by electrolysis as irrigation solution and wet wound dressing used daily lead to complete healing. Delayed wound closure was performed. She was discharged in good general condition, and the wound was healed completely.

Conclusion The application of a chlorine solution obtained by electrolysis (Aqualor H 200, SIGMA DOO, Kula, Serbia) in a concentration of 0.2 mg/l is effective for local treatment of wounds by washing and applying wet dressing in the wound on skin and soft tissue, especially necrotizing fasciitis as wound with mixed bacterial infection.

Keywords: antiseptics; electrolysis; chlorine-based antiseptic; wound infection; necrotizing fasciitis

INTRODUCTION

Surgical wound infection is one of the leading causes of death in the postoperative period. In developed countries, surgical site infection occurs in 16% of patients receiving hospital treatment and 38% of all surgical patients [1]. The bacterial burden in the wound can lead to infection, subclinical, or clinically evident and this continuous process of the inflammation in the wound is divided into five stages:

1. Contamination
2. Colonization
3. Local infection
4. Spread of infection beyond 2 cm from the edge of the wound or to regional lymph nodes.
5. Systemic infection – sepsis [1–4].

The treatment of each wound must be individual (holistic), adequate, and continuous in order to ensure the goal of healing, in a clinical and economic point of view [5]. Hemodialysis patients belong to the group of immunocompromised patients. Infections in those patients could have a fatal course. Large wounds with necrotizing fasciitis are difficult to heal. Targeted antibiotic therapy is mandatory according to the findings of the wound swab, and local treatment of the wound has key importance. Various antiseptic solutions are used for wound washing as iodine solution or solution of boric acid 3%. Sodium hypochlorite solution has been used for wound treatment known as Dakin's solution used in the First World War [6].

An electrolytic solution of sodium chloride contains hypochlorite, which is formed when an aqueous solution of sodium chloride is subjected to the action of current. The concentration of chlorine oxidants in that solution is sufficient as an antiseptic and acts on a large number of microorganisms. Hypochlorite is identified as an endogenous substance in the human cells. It is produced by leukocytes in open wound on the skin [7]. There are a number of advantages of antiseptics based on chlorine oxidants:

1. Hypochlorous acid (HOCl) can be applied to the skin.
2. HOCl produced by leukocytes is the first line of defense against microorganisms in oxidative stress that converts O_2 into H_2O_2. and it reacts with the chlorine ion Cl^- from the cells to form HOCl.
3. 0.05% HOCl is used to treat atopic dermatitis.
4. HOCl is bactericidal for most microorganisms [8].

Active chlorine released by electrolysis from sodium chloride is molecular chlorine Cl_2. Molecular chlorine is rapidly hydrolyzed into a number of different chlorine compounds: hypochlorous acid (HOCl), chloride ions Cl^- and hypochlorite ion (OCl^-) (Figure 1) [8].

By contacting the electrolytic solution with the wound, the pH of the solution is lowered,

Received • Примљено: September 21, 2024
Revised • Ревизија: November 3, 2024
Accepted • Прихваћено: November 4, 2024
Online first: November 6, 2024

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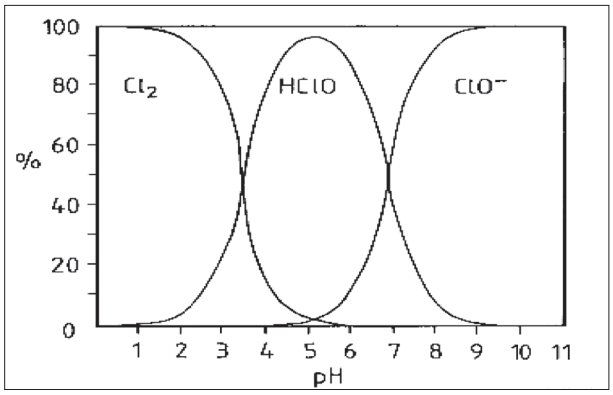

Figure 1. The ratio of hypochlorous acid and hypochlorous ion depending on the pH of the electrolytic sodium hypochlorite solution

releasing hypochlorous acid, NaClO, OCl- ion, which all have a bactericidal effect [9]. That highlight the special advantage of applying chlorine solution due to its low price [10]. Wound healing is a complex morphological and pathophysiological process that is influenced by a number of factors, such as the degree of tissue damage, the strains of bacteria present in the wound, the intensity of the inflammatory process, the capacity for tissue regeneration, the general state of health and the presence of accompanying diseases [3].

Chlorine solutions obtained by electrolysis have a high necrolytic activity, antimicrobial, and local immunomodulatory effect. It has an effect on gram-positive and gram-negative microorganisms, including muti-resistant microorganisms, and also exhibits fungicidal effects [11, 12]. For difficult-to-heal wounds with biofilm formation, hypochlorous acid is recommended [11, 13]. Hypochlorous acid solution has low cytotoxicity [13]. In the study conducted by Serena et al. [14], 82% of wounds that are difficult to heal were found to be contaminated with different microorganisms. Despite a series of proven facts about the effect of various antiseptics *in vitro* and in experiments, a more extensive clinical examination of the effectiveness of antiseptic solutions in clinical studies is necessary, especially for wounds that are difficult to heal [14]. One of such infections is necrotic fasciitis, which is presented in this paper. The aim of the work is to demonstrate the effectiveness of the chlorine solution obtained with electrolysis (Aqualor H200, SIGMA, DOO, Kula, Serbia) for the treatment of deep infected wounds.

This research was approved by the Ethical Committee of the University Clinic Center of Niš, Serbia, no. 39906/3 dated on December 22, 2023, and written consent form was obtained from the patient.

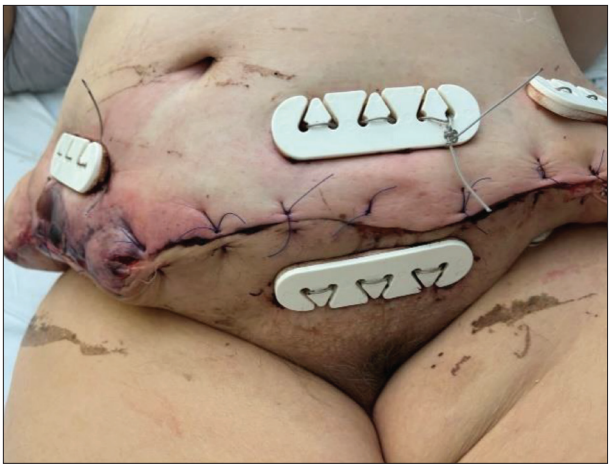

Figure 2. Wound condition after initial excision; the wound was opened and successive necrotomies were performed

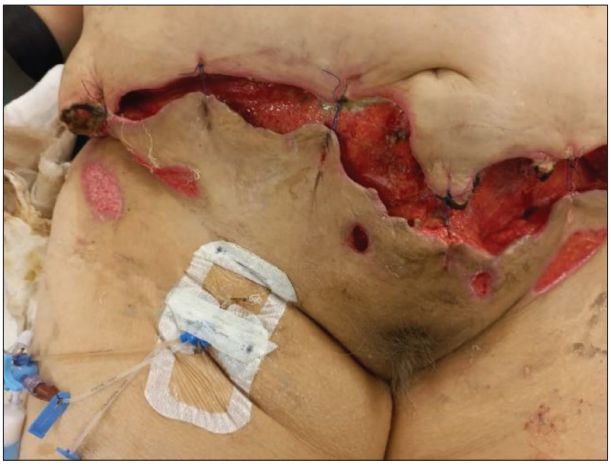

Figure 3. Necrotizing fasciitis of the anterior abdominal wall after multiple necrectomies and placement of sutures

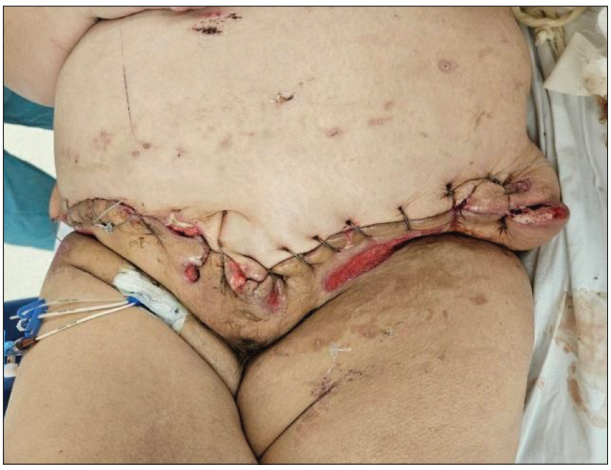

Figure 4. The wound is completely closed

CASE REPORT

A 45-year-old female patient has been on a hemodialysis program for five years due to end-stage renal failure. She suffers from hypothyroidism and is allergic to iodine.

She was admitted due to multiple subcutaneous abscesses of the abdominal wall. In the first surgery, excision of the skin and subcutaneous tissue was performed, and the wound was closed (Figure 2).

In the postoperative course, antibiotics were administered according to biogram. In the first swab, *Staphylococcus aureus* was isolated. Biochemical parameters were corrected in accordance with the laboratory results. Wound dehiscence occurs and necrotic fasciitis

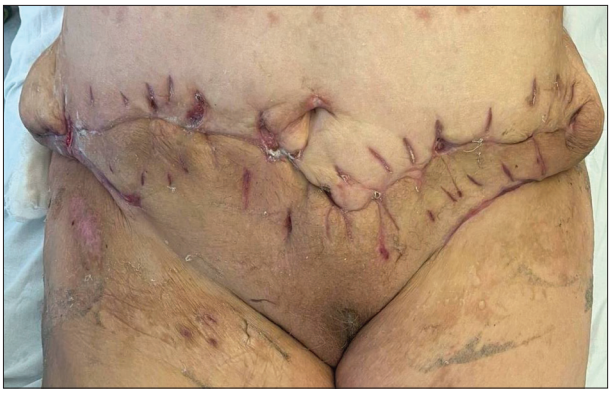

Figure 5. Definitive result after removal of suture material

is noted on the anterior abdominal wall. *Staphylococcus aureus*, *Proteus mirabiliss*, *Pseudomonas aeruginosa* and *Enterococcus faecalis* were isolated in wound swabs. The patient was transferred to the intensive care unit with developed sepsis.

The wound extends transversely across the entire hypogastrium. Infection *with Proteus mirabilis*, *Pseudomonas aeruginosa* and *Enterococcus faecium* was recorded. Clinically, there is a biofilm and pyogenic membrane on the wound without signs of granulation tissue formation. Further, *Proteus mirabiliss*, *Corynebacterium* and *Pseudomonas aeruginosa* are proven in wound. The parameters of sepsis were elevated, reaching very high values (white blood cells 30×10^9/L, C-reactive protein 248.1 mg/L and procalcitonin 99 ng/L). The wound is treated daily, successive necrectomies are performed and generous washing with a chlorine solution obtained by electrolysis. Strips soaked in chlorine solution remain in the wound (moist dressing). The wound shows abundant purulent discharge and has an unpleasant odor. Signs of wound secretion are progressively reduced. After two weeks, granulations appeared on the walls of the wound. Additional necrectomy of devitalized tissue was performed. Temporary sutures were placed (Figure 3 and 4).

Wound was gradually sutured. The general condition has stabilized. Throughout the hospital stay, caloric intake was corrected after each dialysis, which significantly improved wound healing capacity.

On discharge, the wound was completely healed and the patient was discharged (Figure 5).

DISCUSSION

Treatment of severe infections of the skin and subcutaneous tissue is a great challenge even in the modern era. Necrotic fasciitis with mixed bacterial colonization was particularly notable [15]. The most common causative agents are *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* [16]. Colonization of *Staphylococcus aureus*, *Proteus mirabiliss*, *Pseudomonas aeruginosa* and *Enterococcus faecalis* was found in this patient. Adequate local treatment of that wound is particularly important. Although most antiseptics were introduced a long time ago, their importance is relevant nowadays, as iodine solution, hydrogen peroxide, boric-acid solution and chlorine antiseptics. The treatment of immunocompromised patients receiving hemodialysis, patients receiving chronic corticosteroid therapy, or diabetic patients is particularly specific. Wound healing is a very complex process. The phases of healing are hemostasis, inflammation, proliferation and the remodeling phase. Wound healing is also influenced by the systemic factors as the state of nutrition, hypoxia, infection, immunosuppression, chronic diseases, the age of the patient, and genetic factors [16]. The patient presented in this paper suffers from hypothyroidism and terminal renal failure and has a proven allergy to iodine. In the wound, active chlorine solution containing chlorine, hypochlorite ion and hypochlorous acid, disrupt cellular homeostasis by acting on the dissolution of the biofilm formed by *Pseudomonas*. Although some authors state that the effect of chlorine preparations on breaking biofilms in *in vivo* and clinical studies has not yet been clarified [16], in our patient, biofilm was present, without signs of granulation tissue formation and *Pseudomonas aeruginosa* infection present. During treatment with restricted debridement, washing the wound and applying wet bandages with chlorine, the biofilm was effectively removed.

The effectiveness of chlorine preparations for local wound treatment has been shown to be significant in reducing bacterial burden of the wound and accelerating the healing [16]. Chlorine produced by electrolysis has beneficial effects on the healing of infected wounds. The pH of the wound environment is of great importance in the control of wound healing by increasing antimicrobial activity, modulating the activities of proteases, of which matrix metalloproteases and tissue inhibitors of metalloproteases are significant, reducing the toxicity of bacterial products and accelerating epithelialization and angiogenesis [17]. Acidified electrolytic water is a synonym for chlorine solution obtained by electrolysis. It is effective in inactivating microorganisms, and Dunnill et al. [18] proved its effectiveness on *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The immune response and the response to oxidative stress in wound healing, which is shortened by the effect of acidified water, were also investigated. During wound healing, a certain amount of reactive oxygen species (ROS) is produced, which plays a significant role in normal wound healing by affecting phagocytosis processes or are secondary messengers in immune cells and regulate angiogenesis. [18]. Free radicals oxidize chemical groups containing nitrogen and sulfur on the surface of the bacterial cell and thus block membrane functions [19, 20, 21]. The chlorine solution obtained by electrolysis can be used as an antiseptic solution both for washing wounds and as a wet wound dressing. The price is very low, and its effectiveness is proven, so the price-efficiency ratio is extremely favorable. In several clinical studies, it has been proven that 0.05% sodium hypochlorite electrolytic solution shows safe effects in the treatment of infected skin wounds and can be recommended as the agent of first choice for wound treatment [12]. The application of a chlorine solution obtained

by electrolysis (Aqualor H 200, SIGMA DOO) in a concentration of 0.02 mg/dl is effective for local treatment of wounds (washing and wet dressing), especially for wound with mixed bacterial infection. Treatment with chlorine solution led to the complete healing of the wound, despite of severe sepsis and necrotizing fasciitis.

Conflict of interest: None declared.

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Ефикасан локални третман некротизирајућег фасциитиса раствором хлора добијеног електролизом

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САЖЕТАК

Увод Тешка инфекција хируршке ране, као што је некротизирајући фасциитис, један је од водећих узрока смртних исхода у постоперативном периоду. Опсежне ране које захватају кожу и мека ткива су значајан проблем, посебно ране које тешко зарастају код имунокомпромитованих болесника. Посебно је важан локални третман применом различитих антисептичних раствора у клиничкој пракси.

Приказ случаја Болесница стара 45 година која има терминалну бубрежну слабост, хипотироидизам и алергију на јод примљена је у болницу због мултиплих апсцеса у трбушном зиду. После прве операције дијагностиковани су некротизирајући фасциитис и сепса. Примењена је комплетна парентерална терапија укључујући антибиотике и другу супортивну терапију и рађене су хемодијализе. Свакодневно су рађени серија дебридмана и локални третман ране испирањем раствором хлора добијеним електролизом и применом влажног завоја са газама натопљеним овим антисептиком, све до потпуног зарастања ране. Рана је секундарно сутурирана. Болесница је отпуштена кући у добром општем стању, а рана је потпуно зарасла.

Закључак Примена раствора хлора добијеног електролизом (*Aqualor H* 200, СИГМА ДОО, Кула, Србија) у концентрацији 0,2 *mg/l* ефикасна је за локални третман рана испирањем и применом влажног завоја на рани на кожи и поткожном ткиву, посебно за некротизирајући фасциитис, као ране са мешовитом бактеријском инфекцијом.

Кључне речи: електролиза; хлорни антисептици; инфекција ране; некротични фасциитис

DOI: https://doi.org/10.2298/SARH240915085J
UDC: 616.74-007.23; 616.155.392-053.2

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Spinal muscular atrophy and acute lymphoblastic leukemia – is it just a coincidence?

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SUMMARY

Introduction Spinal muscular atrophy (SMA) and acute lymphoblastic leukemia (ALL) are rare diseases, with usual onset in childhood. To date, no cases have been reported where these conditions co-exist in one patient. Nusinersen has not been used concurrently with chemotherapy for ALL in children. The aim of the paper is to present two patients with two rare diseases and the results of their therapy.

Outlines of cases We describe two patients diagnosed with SMA and ALL. The first patient received nusinersen, while the second did not receive SMA treatment. ALL in both patients was successfully cured by the appropriate treatment protocol. In the first patient, nusinersen was temporarily discontinued but restarted during the maintenance phase of chemotherapy. The chemotherapy regimen in the first patient was modified during the maintenance of ALL treatment.

Conclusion The concomitant use of nusinersen and chemotherapy for ALL in our first case was safe, demonstrating good efficacy and tolerance without significant interactions or adverse events. We consider the occurrence of ALL and SMA in our both patients to be just coincidental; however, further research is needed to clarify many dilemmas about potential connections between these two rare diseases.

Keywords: rare disease; nusinersen; chemotherapy; concomitant

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare neurodegenerative disorder characterized by progressive muscular weakness and hypotonia. It is caused by the homozygous deletion of the survival motor neuron 1 gene (SMN1), leading to the degeneration of alpha motor neurons in the spinal cord. The incidence of SMA is approximately 1 in 6000 to11,000, but the carrier frequency is much higher [1, 2].

Until recently, SMA had a devastating prognosis. A new therapeutic era began when the first SMA treatment, nusinersen, was approved. [3]. Administered intrathecally, nusinersen targets the *SMN2* gene, resulting in increased production of SMN proteins. It has shown efficacy, improving global motor function and quality of life [4].

Acute lymphoblastic leukemia (ALL) is the most prevalent malignant disease in childhood [5]. The incidence of ALL ranged from 1–2 per 100,000 [6]. Despite being the most common malignancy in childhood, ALL remains a rare condition.

This paper presents two patients diagnosed with two rare diseases – SMA and ALL – as an unusual comorbidity, as well as the results of their therapy. In our cases, neither disease significantly influenced the clinical course of the other.

REPORTS OF CASES

Case 1

Our first patient was a four-year-old girl who was diagnosed with SMA type 2 at three months of age, with three copies of the *SMN2* gene. The diagnosis had been suspected prenatally due to a positive chorionic villus test. At the time of diagnosis, she was asymptomatic, and neurological examinations were normal.

The first clinical symptoms became observable at seven months of age, presenting as moderate hypotonia, weakness, and areflexia. She achieved independent sitting at nine months of age, but there was no further improvement. The initial CHOP-INTEND score was 44/64. The HINE score was 4/26. Other pediatric examinations and blood tests were normal, with no respiratory complications. Over time, moderate disease progression was observed consistent with the natural course of the disease.

Nusinersen was started at the age of two years and two months according to a standard protocol. After the fourth dose, a mild motor improvement was observed. All laboratory tests had been normal over time. However, 1.5 months after the fourth dose of nusinersen, she began to feel sick, with poor appetite, pallor, and anorexia. The blood samples revealed anemia (hemoglobin 3.1 g/dL) and thrombocytopenia (17,000/mm^3). The bone marrow aspiration showed 95% L1-type lymphoblasts,

Received • Примљено: September 15, 2024
Accepted • Прихваћено: November 16, 2024
Online first: November 20, 2024

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and B-cell ALL was diagnosed, with no central nervous system involvement (CNS stage 1) [6]. All genetic tests were normal without any common genetic mutations (e.g., Bcr/Abl, MLL/AF4, PBX1/E2A gene fusions etc.) [7].

ALL therapy was immediately started according to IC-BFM 2009 protocol [six-month induction phase of chemotherapy, followed by a maintenance phase including four intrathecal methotrexate (MTX) doses] [8], while nusinersen was discontinued. Complete remission established on the 33rd day, classified into the intermediate-risk group [9]. Consequently, ALL treatment continued with the IC-BFM 2002 protocol for the next 23 months.

Four months after the beginning of the maintenance phase of ALL therapy and 13 months after the last dose of nusinersen, the SMA therapy was continued. Regarding to ALL therapy, slight modifications were made to the MTX regimen in the maintenance phase, with the reduction of two intrathecal MTX doses (administered on the fourth and 20th weeks instead of the fourth, eighth, 12th and 16th weeks of the maintenance phase).

Despite the successive administration of two different drugs through the same route and the modification to the MTX regimen, our patient did not experience significant adverse effects and drug interactions. No significant SMA progression was observed during ALL therapy, and the results of the follow-up motor tests were almost identical to the previous ones (12/26 *vs*. 13/26 in the HINE test).

Case 2

Our second case is a 20-year-old woman diagnosed with SMA type 3 at 20 months of age with three copies of the *SMN2* gene. The first clinical symptoms appeared at 18 months of age, after she had started walking. She did not receive any causal SMA therapy due to the unavailability of treatment at that time. Clinical progression followed the natural course of the disease, and she lost the ability to walk by six years of age.

At the age of four years, she began to feel unwell, tired, apathetic, and pale. The complete blood count revealed anemia (hemoglobin 8.7 g/dL) and thrombocytopenia (60,000/mm^3), raising suspicion of malignant blood disease. The results of bone marrow aspiration showed 97% L1-type lymphoblasts, leading to a diagnosis of pre-B type ALL with no central nervous system involvement (CNS 1) [6]. The standard ALL treatment according to the ALL IC-BFM 2002 protocol was initiated, and complete remission was achieved on the 33rd day of treatment. Classified as an intermediate-risk group [9], she continued treatment according to the same ALL protocol for the remaining 23 months.

Despite the concurrent SMA, our patient showed a favorable clinical response to ALL therapy and did not experience any unexpected adverse effects related to SMA. The course of SMA followed its natural progression without any unexpected deterioration due to ALL.

All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

We present two patients diagnosed with two rare diseases – SMA and ALL. SMA in the first patient treated with nusinersen, while the second did not receive any SMA treatment due to the unavailability of specific therapy at the time. ALL in both patients was successfully treated according to the appropriate treatment protocol [10]. In the first patient, simultaneous therapy with nusinersen and chemotherapy demonstrated good efficacy and tolerance, with no interactions or significant adverse events. This paper may serve as an example of a clinical approach for managing ALL in children with SMA treated with nusinersen.

The question arises: is there a relationship between the two diseases – genetic, geographical, or environmental – or are they merely coincidental? To the best of our knowledge, we did not find any observable direct or indirect association in the occurrence, development, and course of these two rare diseases. SMA is a rare autosomal recessive monogenic disease caused by biallelic mutations – deletion in the *SMN1* gene located on the 5q13 chromosome in 95% of cases. In less than 5% of cases, it may be caused by a heterozygous mutation of the *SMN1* gene associated with a point mutation on the other *SMN1* allele [2]. ALL is an acute sporadic malignant disease of the blood characterized by abnormal proliferation of the malignant immature B- or T-cells of the blood. Its etiology is unknown and involves multifactorial influences, including environmental and genetic factors such as translocations (e.g., t(1;19) [TCF3-PBX1], t(12;21) [ETV6-RUNX1], t(9;22) [BCR-ABL1]), MLL rearrangements, hypo/hyperdiploidy, intrachromosomal amplification of chromosome 21, mutations of the *JAK2* gene [11, 12, 13].

According to the literature, there is limited information regarding chromosome 5 abnormalities in the context of B-cell ALL. Trisomy of chromosome 5 has been reported in some cases B- or T-cell ALL and now presents one of the cytogenetic subgroups of ALL in the pediatric population with a poor prognosis [14]. Deletion of the long arm of chromosome 5 (5q) has been observed in myelodysplastic syndromes (10–15%) and acute myeloid leukemia, and rarely in T-cell ALL in both adults and children, but not in B-cell leukemia [15]. Among the rare cases reporting chromosome 5 abnormalities in ALL patients, none have 5q13 abnormalities, which is a significant gene locus for SMA occurrence [16].

According to our best knowledge, this paper is the first presentation of two patients with both SMA and ALL. Although there have been a few reported cases of SMA co-occurring with other malignancies, none of these patients were treated with nusinersen [17–21]. Yaris et al. [17] reported a case of a child with SMA and disseminated alveolar rhabdomyosarcoma. Three years later, Rudnik-Schöneborn et al. [18] described two cases of SMA type

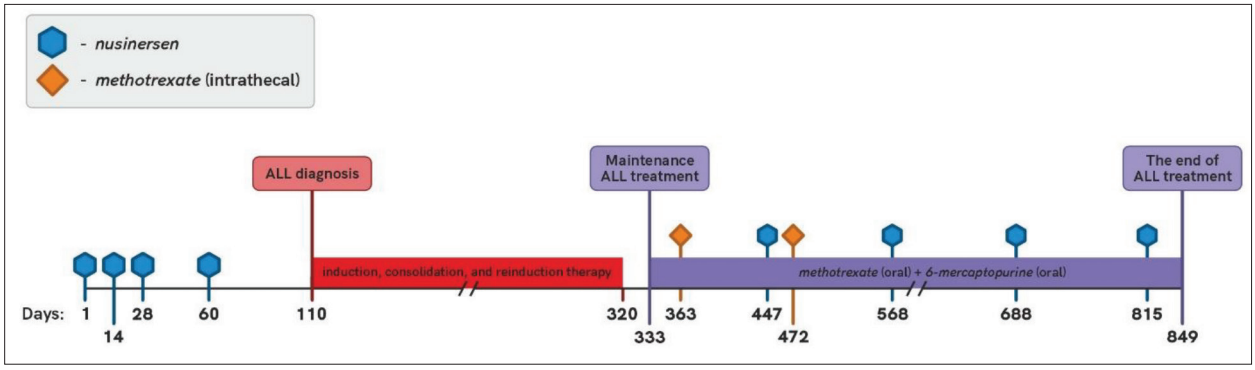

Figure 1. Schedule of spinal muscular and acute lymphoblastic leukemia (ALL) treatment in case presentation 1

II and IIIa associated with alveolar rhabdomyosarcoma, diagnosed at the age of 15 and 19 years, respectively. In 2015, Sag et al. [19] documented a four-month-old infant with SMA type 1 and neuroblastoma, while Blatt and Gold [20] reported a three-year-old diagnosed with stage-4 neuroblastoma, whose sister had SMA type 1. Additionally, there is one documented case of ependymoma in an adult female with SMA type 4 [21].

The revolution in SMA treatment and the availability of specific therapy for SMA raise several questions: Are there any connections between SMA therapy and the occurrence of ALL? How might SMA therapy influence ALL treatment, and vice versa? What are the implications of administering different medications through the same route? According to previous clinical studies, nusinersen, the first approved specific therapy for SMA for patients of all age groups, has proven to be effective, especially in presymptomatic patients, and is considered to be safe treatment as well. The adverse effects of nusinersen are generally mild and temporary [3, 4, 22]. Myotoxicity, a common adverse effect of chemotherapy, has not been reported as a side effect of nusinersen, although it can lead to mild thrombocytopenia. Besides mild changes in urine protein levels, nusinersen does not significantly change other laboratory parameters [23, 24].

Considering the well-known adverse effects of chemotherapy, we had several concerns about the simultaneous use of nusinersen and ALL therapy in our first patient, especially considering the same route of administration for nusinersen and MTX [25]. According to literature on the pharmacokinetics, nusinersen has demonstrated minimal drug-to-drug interactions. Intrathecal administration of nusinersen results in low plasma concentration, with minimal impact on peripheral tissues, blood, and the CYP450 system in the liver [26]. Given this consideration, we anticipated no significant interactions between nusinersen and chemotherapy in our patient. However, due to limited knowledge regarding the concurrent use of these medications, we temporarily discontinue nusinersen during the induction phase of ALL treatment and restart it during the maintenance phase, when the ALL treatment regimen is less intense. We resumed nusinersen four months after the initiation of the maintenance phase of ALL therapy. Despite the significant interval between nusinersen doses (almost 13 months between the fourth and fifth dose), we opted to continue nusinersen according to the standard maintenance protocol every four months. In addition, we modified the intrathecal MTX schedule during the maintenance phase of ALL therapy to mitigate potential interactions between nusinersen and intrathecal MTX, and to reduce the frequency of lumbar punctures. Throughout the maintenance phase, our patient received four doses of nusinersen and two doses of MTX intrathecally, with at least one-month interval between nusinersen and MTX (Figure 1). Our patient did not experience adverse effects or interactions from either therapy [3, 4, 26].

Finally, we question whether nusinersen has had any impact on carcinogenesis in our first patient. Preclinical studies have suggested that subcutaneous nusinersen administration in mouse models could increase the risk of vascular tumors [26]. However, according to current references, there is no evidence suggesting that nusinersen influences the development of other malignancies. To the best of our knowledge, we do not believe nusinersen affected malignancy in our patient; nevertheless, further research is needed to resolves these concerns.

ACKNOWLEDGMENT

We thank all who contributed to the diagnosis and treatment of our patients: Prof. Dr. Dimitrije Nikolić, University Children's Hospital, Belgrade; Dr. Vesna Branković, Clinic for Neurology and Psychiatry for Children and Youth, Belgrade; Dr. Dragan Mićić, Institute of Serbia for Mother and Child, Belgrade; and Prof. Dr. Dušanka Savić-Pavićević, Faculty of Biology, University of Belgrade.

Conflict of interest: None declared.

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Спинална мишићна атрофија и акутна лимфобластна леукемија – да ли је само случајност?

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САЖЕТАК

Увод Спинална мишићна атрофија (СМА) и акутна лимфобластна леукемија (АЛЛ) ретке су болести које се обично јављају у детињству. До сада није забележено да ове две болести коегзистирају код једног болесника. Нусинерсен још увек није примењен у комбинацији са хемиотерапијом код деце.

Циљ овог рада је да представи два болесника са две ретке болести, као и резултате њиховог лечења.

Приказ болесникâ Приказујемо два болесника код којих је дијагностикована СМА и АЛЛ. Први болесник је примао нусинерсен, док други болесник није добио ниједну СМА модификујућу терапију. АЛЛ је код оба болесника успешно излечена помоћу одговарајућих терапијских протокола. Код првог болесника нусинерсен је привремено обустављен, али је поново уведен током фазе одржавања. Протокол лечења АЛЛ је модификован током фазе одржавања.

Закључак Код првог болесника истовремена примена нусинерсена и хемиотерапије била је сигурна, ефикасна и добро толерисана, без значајних интерреакција и нежељених ефеката. Сматрамо да је појава АЛЛ и СМА код наших болесника случајна; међутим, потребна су даља истраживања како би се разјасниле дилеме о могућим везама између ове две ретке болести.

Кључне речи: ретке болести; нусинерсен; хемиотерапија; истовремено

DOI: https://doi.org/10.2298/SARH241014086S
UDC: 616.12-008.331.1-053.2:616.61

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Severe renovascular hypertension in an asymptomatic child – 11 years of follow up

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SUMMARY

Introduction Renovascular hypertension is a rare cause of arterial hypertension in the pediatric population. The aim of this report was to present the treatment outcome in a girl with severe stenosis of the renal artery on a solitary kidney.

Case outline A 6.5-year-old girl, otherwise healthy, was found to be highly hypertensive (up to 200/140 mmHg) during a systematic examination for school enrollment. The imaging evaluation revealed that she had a single kidney with critical renal artery stenosis. Medication with three antihypertensive drugs was unsuccessful. The angioplasty attempt was complicated by artery wall dissection and the pseudoaneurysm development. This complication was treated surgically with an autologous saphenous vein graft by-pass. Postoperatively, acute kidney injury developed, which required continuous renal replacement therapy for two days, followed by hemorrhagic shock and the need for reintervention with retroperitoneal hematoma evacuation. After three years, aneurismal dilated vein graft was replaced by a synthetic one (PTFE) in London. Angioplasty of the synthetic graft was performed twice due to the development of proximal stenosis and restenosis. After 11 years of follow-up, the girl has well controlled blood pressure under two antihypertensives, with normal renal function without proteinuria.

Conclusion This case illustrates that angioplasty for single artery stenosis in children is a high-risk procedure, which may result in an aneurism formation or bleeding and a need for several kidney revascularization procedures. In order to preserve kidney function, it requires a serious multidisciplinary approach by nephrologists, interventional radiologists/cardiologists, and vascular surgeons.

Keywords: renal artery stenosis; single kidney; hypertension; renal angioplasty; aorto-renal graft; children

INTRODUCTION

Renovascular hypertension (RVH) is a term that refers to an increased blood pressure (BP) due to renal artery stenosis (RAS) and consequent renal hypoperfusion that leads to the activation of the renin-angiotensin-aldosterone system [1]. In children and adolescents, RAS accounts for about 10% of all causes of secondary hypertension. In Europe and North America, the most common cause of RAS is fibromuscular dysplasia, while it is "Takayasu" arteritis in Asia and South Africa [2]. RAS can be classified into the following categories: genetic syndromes, acquired/inflammatory such as polyarteritis nodosa, idiopathic RAS, mid aortic syndrome ("Mid aortic sy"), external compression of the renal artery and other causes. The most common genetic syndromes that lead to RVH are: neurofibromatosis type 1 "Alagille sy," "Williams sy," tuberous sclerosis, Marfan syndrome [3]. A number of radiological tests are used to diagnose RVH ranging from the screening method – Doppler echosonography of renal blood vessels to contrast angiography, which is the gold standard for diagnosing RAS. Various pharmacological agents can be used in RVH therapy, but very often this hypertension is pharmacoresistant with the requirement to perform different kidney revascularization techniques [4]. The primary option is revascularization by percutaneous transluminal angioplasty (PTA), and in case of its failure, the options are surgical procedures aimed at establishing the best perfusion of the kidney and preserving its function. The association of congenital anomalies of the urinary tract such as a solitary kidney and severe renovascular disease is rarely described in the literature [5]. Here we report our experience in diagnostics, treatment, complications, and long-term outcome in a girl with severe single-kidney RAS.

CASE REPORT

A 6.5-year-old previously healthy girl was noted to be hypertensive with BP 200/140 mmHg during investigations done for school application. On admission to our clinic, the girl was without symptoms, well grown with normal physical findings. BP on the leg was also elevated 200/120 mmHg with palpable femoral pulses. There was no personal and family history of significance. Laboratory investigations revealed normal glomerular filtration rate (GFR – 112 ml/min / 1.73 m^2) and electrolytes. Left ventricular hypertrophy was seen

Received • Примљено: October 14, 2024
Accepted • Прихваћено: November 16, 2024
Online first: November 21, 2024

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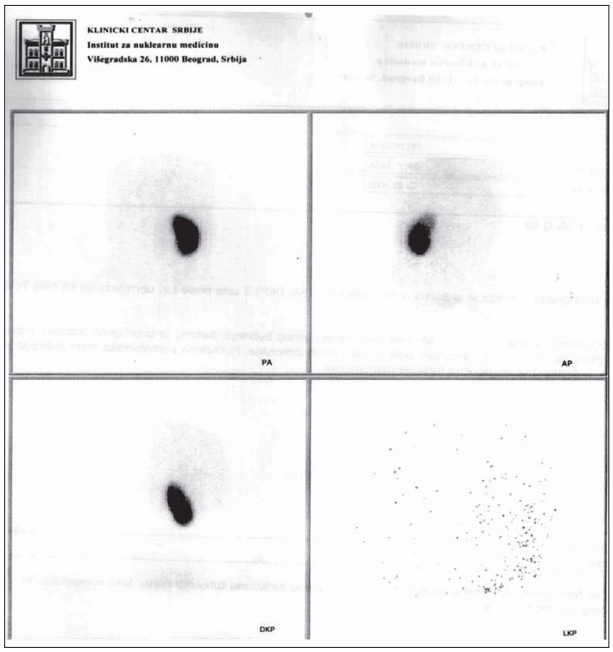

Figure 1. Dimercaptosuccinic acid scan confirmed left kidney agenesis

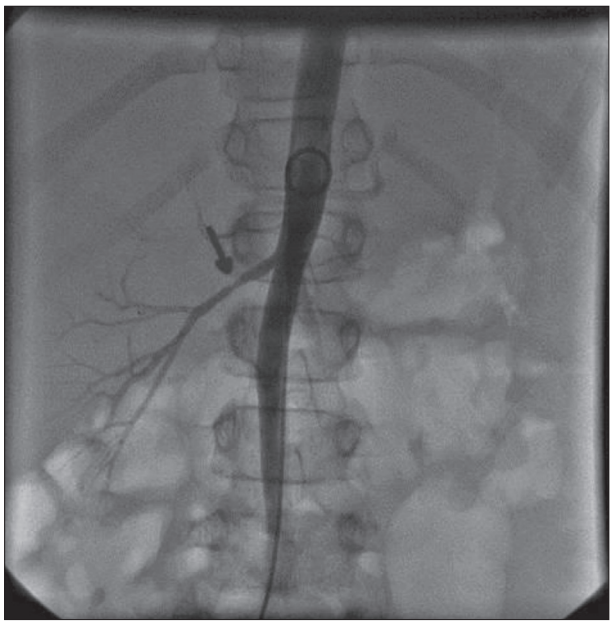

Figure 2. Angiography demonstrated critical stenosis in the middle part of main renal artery with minimal lumen ~ 1 mm (arrow shows the narrowest segment)

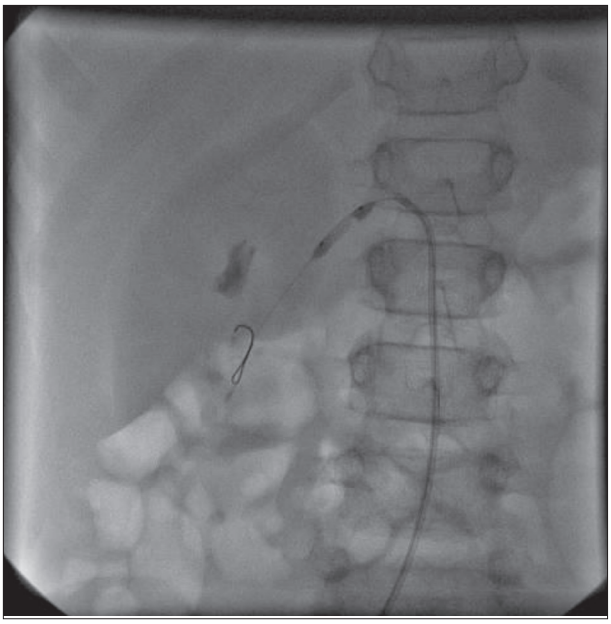

Figure 3. Balloon angioplasty attempt

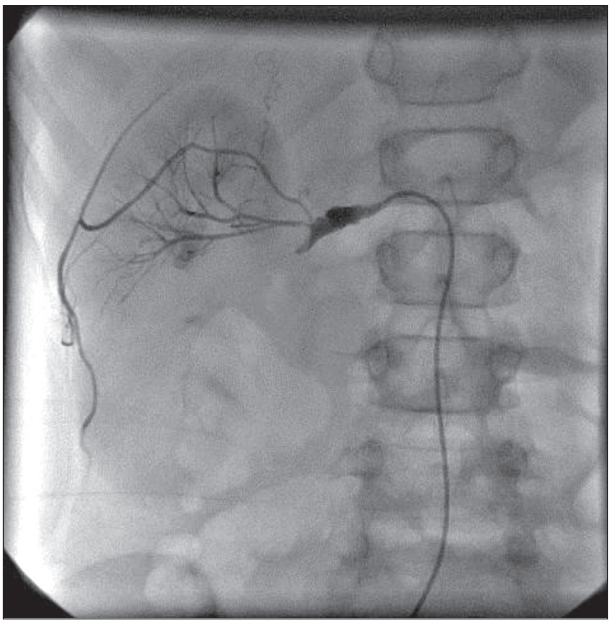

Figure 4. Distal right renal artery lesion with compromised circulation in the lower part of the single kidney

on echocardiography. Abdominal ultrasound showed the right solitary kidney with normal echo structure, 9.4 cm in length (50th centile for age and height and single functioning kidney). Renal artery duplex ultrasound showed an increase in the peak systolic velocity > 300 cm/s at the origin of the right renal artery with post stenotic turbulence indicating a right renal stenosis. Dimercaptosuccinic acid scan confirmed the absence of the left kidney (Figure 1). Three medications failed to control BP: nifedipine, carvedilol, and minoxidil. Due to suspected RVH, the patient underwent angiography, which demonstrated critical stenosis in the middle part of main renal artery (Figure 2). This stenosis was crossed with guidewire and the first attempt of 3.5 mm balloon dilatation failed (Figure 3). A larger balloon of 4 mm was ruptured and induced a lesion of the distal part of the renal artery (Figure 4). The patient was hemodynamically stabile, but kidney function worsening with creatinine increase after 48 hours (55–127 umol/L) and transitory polyuria developed. After two weeks, control angiography revealed pseudoaneurysm formation on the upper-pole segmental branch (Figure 5), with invasive BP in the aorta of 192/96 mmHg. Ten days later, the patient underwent surgery with aneurysm resection and creation of saphenous vein patch. Due to postoperative anuria, continuous veno-venous hemodiafiltration (CVVHDF) was done during 48 hours. Activated clotting time during CVVHDF was at the recommended levels ~165 s. Despite

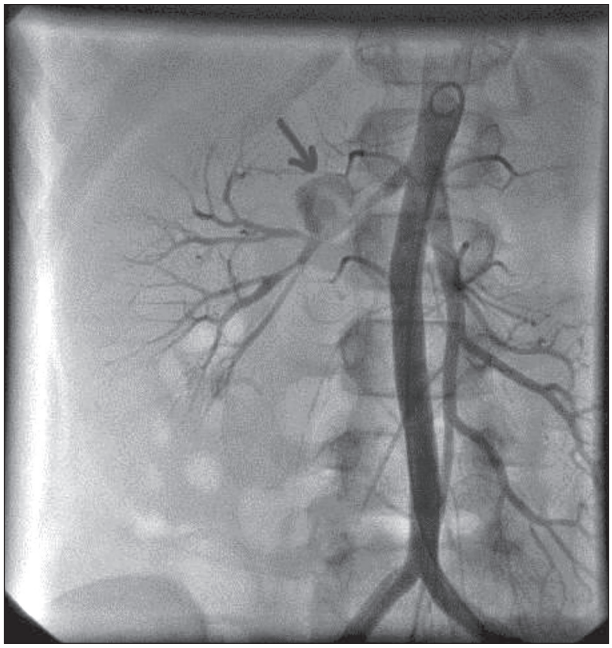

Figure 5. Control angiography revealed a pseudoaneurysm 18 × 15 mm in size on the upper pole segmental branch (arrow shows circular pseudoaneurysm)

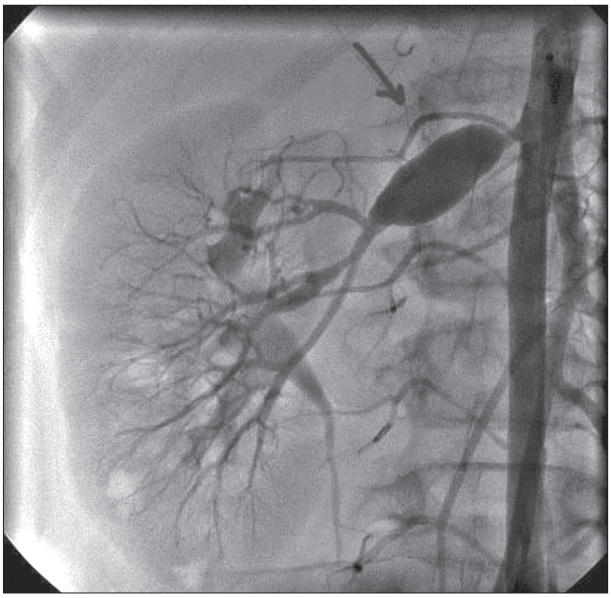

Figure 6. Saphenous patch dilatation on angiography (arrows shows enormous vein patch dilatation)

this, the patient developed massive abdominal bleeding which resulted in hemorrhagic shock (BP: 89/43 mmHg; Hgb 52 g/L). Relaparotomy resulted in evacuation of large number of intraabdominal hematomas with suture of small perivertebral vessels. Immediately after reoperation, diuresis appeared and CVVHDF was stopped. In the following three years, there was satisfactory control of BP (office measurement of 125/80 mmHg) with two antihypertensives (carvedilol and nifedipine), normal renal function (GFR 98 ml/min / 1.73 m^2) and with regression of the left ventricular mass. However, three years after the surgery, the girl became hypertensive, and an aneurysmal dilatation of the vein patch was verified (Figure 6). The next operation with resection of the vein graft and implantation of synthetic polytetrafluoroethylene (PTFE) was performed in London, Great Ormond Street Hospital. Systolic BP target was kept at 120 mmHg with carvedilol. Nifedipine was stopped. After two years, hypertension worsened and Doppler showed a high degree of stenosis at the proximal site of the implanted graft, resulting in angioplasty of PTFE in London. On that occasion, significant intrarenal narrowing was seen on angiography. Four years after the PTFE angioplasty and 11 years after the first operation, a duplex ultrasound revealed a significant narrowing > 70% of the graft lumen. PTFE redilatation was performed in London. At the most recent follow-up, 11 years after the first operation, and three months after the last intervention, the patient's BP is satisfactory, 130/85 mmHg under double medications (carvedilol and doxazosin). Kidney function remained normal (GFR 99 ml/min / 1.73 m^2), without proteinuria.

This case report was approved by the Clinical Ethics Committee and written consent was obtained for the publication of this case report from the patient and her parent.

DISCUSSION

Idiopathic stenosis of the renal artery, or fibromuscular dysplasia, is a heterogeneous group of systemic, non-inflammatory and non-atherosclerotic diseases of the blood vessel wall that led to the development of RVH [1]. It is interesting that RVH is discovered accidentally in as many as 26–70% of asymptomatic children, to which group our patient belongs [1, 6]. The younger population of children may exhibit neurological symptoms (convulsions) or cardiac symptoms such as congestive heart failure. An example of cardiac dysfunction and hypertension due to renovascular stenosis in a single functioning kidney in an infant was presented by Hall et al. [7]. The association of congenital anomalies of the urinary tract such as a solitary kidney and severe renovascular disease as we present here is rarely described in the literature [5, 7]. The diagnosis of RVH in children is often made with a long delay, which significantly affects the course of the disease and the prognosis. The reason for this is that the symptoms are often non-specific or absent, and children older than three years often do not have their BP measured, despite clear recommendations [2]. In children with suspected RVH, duplex ultrasound is a widely accepted method as a screening test [8]. RVH is suggested, like the findings in our patient, by peak systolic velocity > 2 m/s and the finding of the "parvus-tardus" type blood flow waves distal to the stenosis [9]. Contrast angiography, in addition to being the gold standard in diagnostics, also provides the best view of intrarenal blood vessels, and can also be a therapeutic procedure. [3]. As a rule, this type of hypertension is resistant to medication, as in the case of our patient, but one should always try, so there are data that in as much as 65.8% of cases of RAS in the pediatric population conservative treatment was successful after long-term follow-up [10]. Renal revascularization by PTA or surgical procedures are important therapeutic options

aimed at establishing the best perfusion of the kidney and preserving its function. In a large retrospective study by Agrawal et al. [12], 27 years of experience using PTA in the treatment of children with RVH are presented. PTA is a safe, less invasive procedure that can be performed with balloon dilatation, the so-called balloon angioplasty or with stent placement (considered in older children who have finished growing). This method is effective in over 50% of patients (normalization of BP without drugs or reduction of the number of drugs), with restenosis occurring in about 25–30% of treated children [11, 12]. In the case of resistant stenoses, cutting balloons can significantly improve the results even in a single functioning kidney [7, 13]. Possible complications of this method are: contrast nephropathy [14], artery spasm, dissection or even perforation which ultimately can lead to hemorrhagic shock [1]. In our patient, the non-invasive method (PTA) failed due to the dissection of the artery wall and a pseudoaneurysm formation. Pseudoaneurysm as a complication of PTA was described in one of 13 pediatric patients with RAS [14]. Kari et al. [15] showed complications after PTA in 11.4% of procedures (13 out of 114), one of which was fatal and led to death. Namely, in an eight-year-old patient, repeated angioplasty of a single kidney synthetic graft led to dissection of the blood vessel wall, resulting in fatal bleeding. Surgical revascularization has a higher success rate than PTA (70–80%), however, it is generally an option if PTA fails. There are several surgical procedures: resection of the narrowed segment and primary reanastomosis, aorto-renal bypass, autotransplantation or nephrectomy (if there is significant atrophy of the renal parenchyma). In order to prevent potential complications of PTA, Doshi et al. [16] reported a surgical correction as the first revascularization option in a young girl with one functioning kidney. In this case, the cutting of the narrowed segment, which made significant kinking during expirations, after six months of follow-up showed a normal finding on ultrasound Doppler without the use of antihypertensive drugs. In a meta-analysis by Trinquart et al. [17], which included two pediatric studies with a total of 60 patients treated for RAS, aortorenal bypass was most often from the saphenous vein, in 62% of cases, and nephrectomy was performed in 22% of patients. In the first included study, 59.2% of children had BP < 150/90 mmHg after six months without therapy, and in the second study, 87.9% of patients had BP lower than 140/90 mmHg during at least 12 months of follow-up [17]. The saphenous patch in our patient achieved satisfactory BP control (office measurement of 125/80 mmHg) under two antihypertensives for three years, but then it became insufficient due to the development of graft dilatation. Aneurysmal dilatation of the autologous graft from the saphenous vein was described in a study by Sandmann et al. [18] in 9% of cases (42 pediatric and two adult patients) with RAS who required reconstructive surgery. Due to saphenous patch dilatation and worsening of hypertension in our patient, reintervention and Dacron graft replacement had to be performed. An artificial graft was placed in London, but with subsequent *de novo* stenoses that required repeated redilatation. In the aforementioned paper, restenoses in patients with PTFE grafts were treated with stenting in one case or reconstruction with a suitable patch in the other [18]. Despite the development of intrarenal stenoses in our patient and the described numerous complications, renal function was preserved without residual proteinuria with satisfactory BP control. Clinically, RVH should be suspected when high BP refractory to multiple antihypertensive drugs is present, especially in a younger child.

This case illustrates that angioplasty for single-artery stenosis in children is a procedure of high risk, which may results in aneurism formation or bleeding and the need for several kidney revascularization procedures.

ACKNOWLEDGMENT

The authors would like to thank the patient and her family, our chief of the nephrology Mirjana Kostić, consultant pediatric nephrologist Jelena Stojanović at Great Ormond Street Hospital in London (London, England), our surgical team lead by Zoran Krstić and Lazar Davidović from the University Clinical Centre of Serbia for surgical support.

Conflict of interest: None declared.

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Тешка реноваскуларна хипертензија код детета без симптома – једанаест година праћења

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САЖЕТАК

Увод Реноваскуларна хипертензија је редак узрок артеријске хипертензије у педијатријској популацији. Циљ овог рада је био да прикажемо исход лечења код девојчице са тешком стенозом реналне артерије на солитарном бубрегу.

Приказ болесника На систематском прегледу за упис у школу шестоипогодишњој девојчици без здравствених тегоба измерен је крвни притисак од максималних 200/140 *mmHg*. Учињеним испитивањима је откривено да има један функционални бубрег са критичном стенозом на реналној артерији. Медикаментозна терапија са три антихипертензивна лека је била безуспешна, а покушај ангиопластике је био компликован дисекцијом зида артерије и развојем псеудоанеуризме. Компликација је збринута хируршком интервенцијом и креирањем бајпаса аутологним графтом вене сафене. Постоперативно се развило акутно оштећење бубрега, које је током два дана захтевало хемодијафилтрацију и хеморагијски шок праћен реинтервенцијом и евакуацијом ретроперитонеалног хематома. После три године венски графт је због развоја анеуризматског проширења замењен синтетичким (ПТФЕ) у центру у Лондону. Потом је у два наврата рађена ангиопластика синтетичког графта због развоја проксималне стенозе и рестенозе. После 11 година праћења, девојка има добру контролу крвног притиска са два антихипертензива, нормалну бубрежну функцију без протеинурије.

Закључак Овај случај показује да је ангиопластика код стенозе реналне артерије једног функционалног бубрега процедура високог ризика, која може довести до формирања псеудоанеуризме или искрварења и потребе за спровођењем више процедура реваскуларизације. У циљу очувања функције бубрега, захтева постојање озбиљног мултидисциплинарног тима који обухвата нефролога, интервентног радиолога/кардиолога и васкуларног хирурга.

Кључне речи: стеноза реналне артерије; један бубрег; хипертензија; ренална ангиопластика; аорто-ренални графт; деца

DOI: https://doi.org/10.2298/SARH240703090M
UDC: 616.5-002.828

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Tinea incognita misdiagnosed as rosacea and eczema of the face

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SUMMARY

Introduction Tinea incognita is a dermatophyte skin infection with atypical clinical presentation modified using previous topical immunosuppressive therapy.

Case outline We present a 59-year-old female patient with a pruritic rash on her face. Over three months, she was misdiagnosed with rosacea, contact dermatitis, and atopic dermatitis, and treated with various topical steroids, metronidazole cream, oral antihistamines, dexamethasone, and methylprednisolone. At the first examination in our clinic, she had a pruritic widespread erythema, papules, and plaques on the face, eyelids, and neck, and a few plaques on the chest and extremities (covered with a thick layer of corticosteroid ointment), resembling various skin conditions. Two days after the exclusion of topical treatment, sharply demarcated erythematous lesions with raised scaly edges and numerous pustules appeared. Fungal culture was positive for *Trichophyton mentagrophytes var. granulosum*. A skin biopsy confirmed dermatophyte fungal infection, and the lesions resolved after systemic and topical antifungal therapy.

Conclusion We present the case of an unrecognized fungal infection of the skin to highlight the importance of a simple laboratory examination of fungal smears and culture before prescribing topical steroids and other immunosuppressive agents in order to avoid misdiagnosis and inappropriate treatment of patients in the future.

Keywords: tinea incognita; tinea atypica; *Trichophyton mentagrophytes*; topical immunosuppressive therapy

INTRODUCTION

Tinea incognita (TI) is a dermatophyte infection modified by inappropriate and prolonged use of topical or systemic steroids and topical immunomodulating agents [1–5]. It may resemble various skin disorders and the diagnosis is frequently missed or delayed. [4, 6–10]. Immunosuppressive effects of topical corticosteroids allow unhindered fungal growth, and their anti-inflammatory activity alters clinical features of the skin lesions, which could explain such a variety of clinical manifestations [9].

CASE REPORT

A 59-year-old female was referred to the dermatologist with a pruritic rash on her face that appeared three months earlier when she was moving to a new house and was exposed to dust. She was misdiagnosed with rosacea, contact, and atopic dermatitis by several doctors, including dermatologists, and treated unsuccessfully with various topical steroids, metronidazole cream, oral antihistamines, dexamethasone, and methylprednisolone.

During the first examination in our clinic, she had a burning sensation on her skin, and could not sleep for days. Physical examination revealed widespread pruritic erythema, papules, and plaques on the face, eyelids, and neck, and a few on the chest and the extremities. The scaling was not found. Two days after the suspension of topical treatment, sharply demarcated erythematous lesions with raised scaly edges and numerous pustules appeared (Figure 1). Due to the long-lasting use of corticosteroids, the cushingoid aspect of her face was noticed. Direct microscopy was positive for fungal hyphae; *Trichophyton mentagrophytes var. granulosum* grew in the fungal culture on *Sabouraud* agar. Histopathological findings suggested dermatophyte fungal infection and fungal hyphae were detected in the corneal layer with periodic acid-Schiff (PAS) staining. The lesions resolved after five weeks of systemic treatment with terbinafine (250 mg daily) and topical antifungal therapy (Figure 1).

This report does not contain any studies with human participants or animals performed by any of the authors. Formal informed written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

The disease was first described by Ive and Marks [11] in 1968 as a dermatophyte skin infection incorrectly treated with topical and

Received • Примљено: July 3, 2024
Accepted • Прихваћено: December 1, 2024
Online first: December 2, 2024

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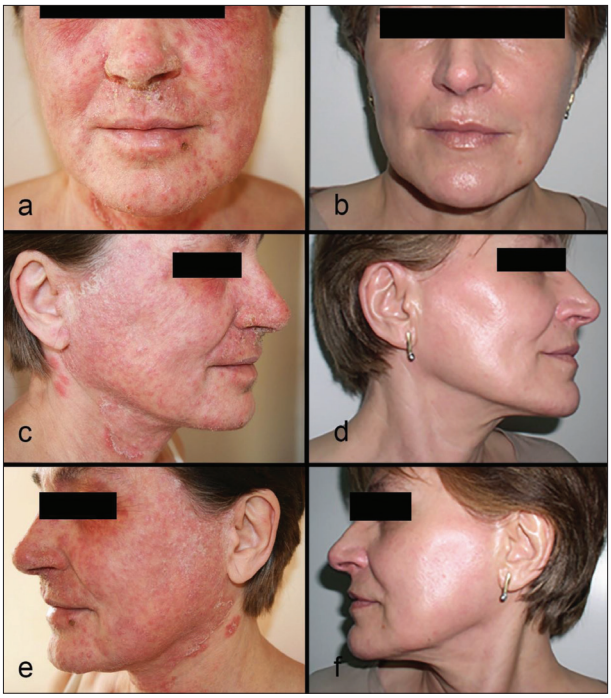

Figure 1. Photographs before (a, c, e) and after (b, d, f) the treatment; lesions covered the face (a), extending to submandibular and upper neck regions (c, e); note prominent scaling (e), and pustules (a); complete resolution after treatment (b, d, f)

systemic corticosteroids. Due to the wide use of calcineurin inhibitors, numerous authors reported an increased number of patients with modified tinea. They proposed that TI should be redefined as dermatophytosis with unusual clinical presentation after prolonged use of systemic or topical corticosteroids or topical calcineurin inhibitors [1, 4, 12].

Lesions in patients with TI have a less scaly look, less raised margins, pustules, and are often highly irritated. Atzori et al. [13] proposed a new term – *tinea atypica* – instead of *tinea incognito.* Hematoxylin and eosin staining has a rather typical finding, but bearing in mind the sensitivity of this staining, it is advised to also perform PAS staining [14]. The most frequently identified anthropophilic dermatophyte was *Trichophyton rubrum* [1, 4, 15], followed by two zoophilic dermatophytes, *Trichophyton mentagrophytes* and *Microsporum canis* [1]. Studies suggest that the most affected site was the trunk, followed by the face [1, 4]. In a Korean study, one-third of patients also had fungal disease involving distant body areas, such as feet and nails [4]. This coexistence of fungal infection could be important for clinicians because *tinea pedis* or *tinea unguium* could cause autoinoculation for any other body part, especially if a patient has been previously treated with immunosuppressants [4]. Our patient developed lesions predominantly on her face, a rarely involved site. The infection was caused by *Trichophyton mentagrophytes*, which is a less common culprit.

The incidence of TI has increased worldwide. In multiple articles, a vast number of TI patients were misdiagnosed by dermatologists. TI can mimic various skin diseases, and this should be the prime reason for properly conducting mycological evaluation before starting topical treatment with corticosteroids or calcineurin inhibitors [16, 17].

We presented a case of TI to highlight the importance of a simple laboratory examination of fungal smear and culture before prescribing topical steroids or calcineurin inhibitors to avoid misdiagnosis and inappropriate treatment of patients in the future.

ACKNOWLEDGEMENT

Funding: This work was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Grant No. 451-03-66/2024-03/200110).

Conflict of interest: None declared.

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Tinea incognita на лицу погрешно дијагностикована као розацеа и екцем

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САЖЕТАК

Увод *Tinea incognita* представља дерматофитну инфекцију коже са атипичном клиничком презентацијом, која је последица претходне локалне примене имуносупресивне терапије.

Приказ болесника Приказујемо болесницу старости 59 година са пруригинозним променама на лицу које има уназад три месеца. Иницијално је лечена под дијагнозом розацее, контактног дерматитиса, а потом и атопијског дерматитиса, различитим топикалним кортикостероидним препаратима, метронидазолом, оралним антихистаминицима, декстаметазоном и метилпреднизолоном. Приликом првог прегледа на нашој клиници болесница је имала на читавом лицу, укључујући и капке, и на врату еритематозне плакове и папуле, као и неколико сличних промена на предњој страни грудног коша и на горњим екстремитетима (промене прекривене дебелим слојем кортикостероидне масти). Два дана након обуставе локалне кортикостероидне терапије, диференцирале су се јасно ограничене еритематозне лезије са издигнутим ивицама, прекривене беличастом сквамом. Уз то, биле су присутне и бројне пустуле. Миколошком културом изолован је *Trichophyton mentagrophytes var. granulosum*. Учињена је биопсија коже, чији је налаз одговарао гљивичној инфекцији. После примене системске и локалне антимикотичне терапије дошло је до комплетне регресије промена.

Закључак Приказујемо случај иницијално непрепознате гљивичне инфекције коже са циљем да истакнемо значај спровођења једноставног лабораторијског теста – преглед скарификата коже на присуство гљивичних елемената и његово култивисање пре прописивања топикалне кортикостероидне и имуносупресивне терапије, како би се избегло постављање погрешне дијагнозе и неадекватно лечење таквих болесника.

Кључне речи: *tinea incognita*; *tinea atypica*; *Trichophyton mentagrophytes*; топикална имуносупресивна терапија

DOI: https://doi.org/10.2298/SARH240925092B
UDC: 615.277.3.065

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Ribociclib-induced phototoxicity – the era of new drugs and new toxicities

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SUMMARY

Introduction Ribociclib belongs to the family of cyclin-dependent kinases 4/6 inhibitors and it has been approved in 2017 for the treatment of patients with hormone receptor-positive (ER^+) and human epidermal growth factor receptor 2-negative ($HER2^-$) advanced breast cancer. As a drug that has been used for treatment of breast cancer for only few years its rare side effects are described through different case reports. Skin photosensitivity represents a range of dermatological conditions that are caused or exacerbated by sunlight exposure. Drug-induced photosensitivity can be seen in patients treated with all kinds of oncology treatments, including chemotherapeutic agents, targeted anticancer therapies, and immune checkpoint inhibitors.

Case outline We present a case of a patient with metastatic hormone receptor positive and $HER2^-$ metastatic breast cancer who developed phototoxic skin changes during the treatment with ribociclib/letrozole. During the treatment, the patient developed mild redness of the skin in a strict photosensitive distribution and rash changed to erythematous confluent plaques on the neck and upper part of the chest, face, and forearms. After treatment cessation the skin changes did not reappear.

Conclusion As the observed cutaneous adverse effect subsided after the treatment cessation and did not reappear after the initiation of palbociclib/letrozole treatment, it can be concluded that the adverse effects were the consequence of ribociclib action. Management of cutaneous adverse effects is different depending mostly of grade of cutaneous adverse effect and its severity.

Keywords: ribociclib; breast cancer; phototoxicity

INTRODUCTION

Ribociclib belongs to the family of cyclin-dependent kinases 4/6 inhibitors (along with palbociclib and abemaciclib). It is administered orally and it operates by preventing oncogene retinoblastoma phosphorylation, thus blocking cell division [1]. Ribociclib has been approved in 2017 for the treatment of patients with hormone receptor-positive (ER^+) and human epidermal growth factor receptor 2-negative ($HER2^-$) advanced breast cancer. The approval of ribociclib was supported by Phase III of the Mammary Oncology Assessment of LEE011's Efficacy and Safety – NCT01958021 (MONALEESA-2) study, where its benefits both in progression-free survival and in overall survival were demonstrated [2]. More specifically, when administered together with the aromatase inhibitor letrozole, ribociclib achieved a 30% or greater reduction in tumor size in more than 53% of patients with measurable disease in comparison to letrozole monotherapy [2].

The most common adverse reactions of ribociclib, observed in 20% or more of patients, are neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain. Also, hypersensitivity of the patient to the active substance or to peanuts and soy is a contraindication for the drug use [2]. Ribociclib may provoke several cutaneous adverse effects including rashes, vitiligo, and bullous dermatitis [3]. Also, one case erythema dyschromicum perstans was reported after the use of ribociclib [4].

As an adverse effect, skin photosensitivity can be observed in patients treated with all kinds of oncology treatments, including chemotherapeutic agents, targeted anticancer therapies and immune checkpoint inhibitors [5]. Recently, one case of ribociclib-induced phototoxicity was documented in a woman that received ribociclib (600 mg) for seven months. It initially manifested as dyschromia over sun-exposed forearms and neck and subsequently as bullae formation [6]. Since the varieties of ribociclib-provoked skin photosensitivity have been rarely documented, we present this case report to add to the list of possible strong adverse effects that include development of rash and erythematous confluent plaques on sun-exposed body parts.

CASE REPORT

The initial treatment of the left breast cancer started in February 2022, when partial resection of the left breast was done and the diagnosis of infiltrating ductal cancer (hormone receptor

Received • Примљено: September 25, 2024
Revised • Ревизија: December 8, 2024
Accepted • Прихваћено: December 9, 2024
Online first: December 10, 2024

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positive, HER2 negative) was confirmed. Postoperative radiotherapy was next performed and patient was on adjuvant hormonal therapy, oral tamoxifen, from April 2022 until January 2023. At this point, computed tomography scan revealed multiple liver metastases. The treatment with letrozole and ribociclib has started from March of 2023. Laboratory findings were all in normal ranges. Ribociclib was introduced in a dose of 600 mg orally once a day, and letrozole of 2.5 mg, once a day.

The patient exhibited an atopic constitution and because of the already established allergy to one or several types of pollen she received antihistaminic treatment during the first cycle of ribociclib-letrozole (21 days). However, the patient stopped antihistaminic treatment around day 15. During the break from ribociclib (that lasts for seven days, from days 21–28), she developed mild redness of the skin in a strict photosensitive distribution (face, neck and upper part of the chest) on day 26. She started with second cycle of ribociclib/letrozole from day 28 and on day 2 (during second cycle) rash changed to erythematous confluent plaques on the neck and upper part of the chest (Figure 1), face (Figure 2) and rash on the forearms (Figure 3). The treatment with ribociclib/letrozole was discontinued.

After all skin changes subsided and completely disappeared, in May of 2023 (around day 30 from the last treatment), the treatment continued with a different cyclin-dependent kinases 4 and 6 (CDK4/6) drug – palbociclib, along with letrozol, and the further treatment was without complications.

The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal.

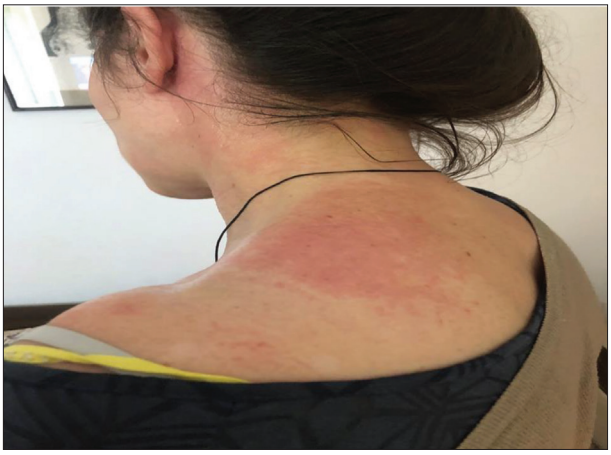

Figure 1. Erythematous confluent plaques on the neck and upper part of the chest

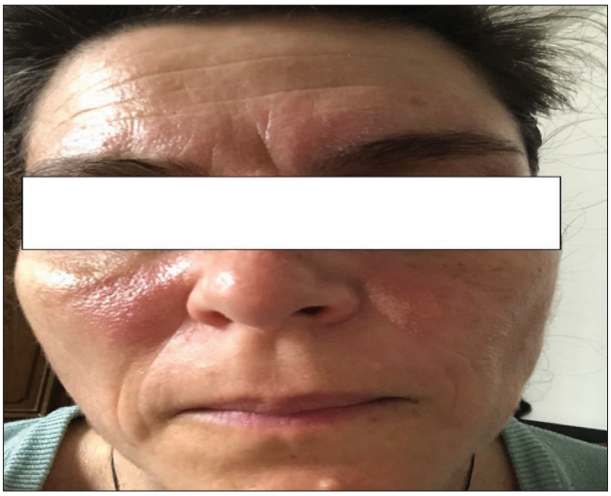

Figure 2. Erythematous confluent plaques on the face

DISCUSSION

Drug-induced photosensitivity can be classified as either phototoxic or photoallergic reactions based on the underlying pathophysiological mechanism [5, 7]. Phototoxicity is a nonimmune-mediated response to cytotoxic damage caused by UV-induced generation of reactive oxygen species [5]. It is typically manifested as an exaggerated sunburn response with clearly demarcated erythema and edema occurring on sun-exposed skin. The main feature of phototoxicity as that it starts rapid, within hours of exposure to the agent and UV radiation, and progressively develops to localized or more diffuse hyperpigmentation [5, 7]. The personalization of therapies in breast cancer has favored the introduction of new molecular-targeted therapies into clinical practice. Among them, CDK4/6 inhibitors have acquired increasing importance, with the approval in recent years of palbociclib, ribociclib, and abemaciclib in combination with endocrine therapy (ET) [8]. MONALEESA-2 is a phase III randomized, double-blind, placebo-controlled study of ribociclib combined with letrozole for the treatment of postmenopausal women with $HR^+/HER2^-$ advanced breast cancer who received no prior therapy for advanced disease [9]. In this study, adverse event of any grade that occurred in at least 35% of the patients in either group were neutropenia, nausea, infections, fatigue, and diarrhea [10]. MONALEESA-3 is a phase III randomized, double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for treating postmenopausal women and men with $HR^+/HER2^-$ advanced breast cancer who have received no or only one line of ET for advanced breast cancer [11], and in this study neutropenia, nausea, and tiredness were the most prevalent of all-grade adverse events observed in 30% of patients [12].

Ribociclib-induced phototoxicity was already documented as dyschromia over sun-exposed forearms and neck and subsequent bullae formation [6]. On the other hand, the cutaneous manifestations observed in this case study (rash and erythematous confluent plaques) are likely photoallergic as the rash occurred after a few days of starting the drug and was gradually progressive. This is in line with the literature evidence as the most common clinical presentation of photoallergy, eczematous eruption, appears usually 24–72 hours after sunlight exposure and treatment

Figure 3. The rash on the forearm

with causative agent. Symptoms tend to worsen and peak 48–72 hours after onset and mostly resolves after removal of the causative agent and sun avoidance [5, 7].

Photoallergic drug reactions are mediated by a T cell-mediated immune mechanism, resulting in a delayed type IV hypersensitivity response, so they manifest only in presensitized individuals and are much more rare than phototoxic drug reactions [5, 7]. Having in mind the atopic constitution of the patient, it is reasonable to assume that the observed cutaneous changes can be driven by the exaggerated immune reaction.

In general, CDK4/6 inhibitors can provoke rash as a side effect (data obtained from meta-analysis evaluating toxicity end points), but further details on the type of rash were not available [13]. Specifically, for ribociclib, conclusions drawn from the phase I trial performed to determine dose-limiting toxicity and maximum-tolerated dose of ribociclib (performed on 21 patients), suggest that the rash is a common side effect as it presented in 52% of patients along with oral mucositis. Again, further details on rash type were not available [14].

In 2024, a retrospective cohort study of all patients with $HR^+/HER2^-$ advanced breast cancer treated with ribociclib at Humanitas Cancer Center between June 2017 and December 2022 was conducted and 14.3% of all patients experienced treatment-related cutaneous adverse events. The most frequent cutaneous adverse events were eczematous dermatitis (53.8%) and maculo-papular reaction (15.4%) [15]. Another study compared adverse events associated with CDK4/6 inhibitors based on FDA's adverse event reporting system and reported that different skin toxicities were observed in all three CDK4/6 inhibitors used [16].

The patient presented in this case report received a combination therapy (ribociclib/letrozole), and therefore, the possibility that photoallergy was initiated by letrozole action has to be taken into consideration. Letrozole is an aromatase inhibitor and is known to have cutaneous side effects. In phase 2 of a randomized study in postmenopausal women with breast cancer, receiving letrozole, skin rash was noted as a side effect in 23 out of 125 (18.4%) patients. The type of skin lesions was described as exfoliative, nodular, follicular, generalized, maculo-papular, and others [17]. However, no such cutaneous effects were observed after the treatment of the same patient with palbociclib/letrozole suggesting that the observed side effects were provoked by the action of ribociclib.

Establishing a diagnosis of photosensitive reactions induced by anticancer agents can be challenging and requires close evaluation of the clinical presentation and medication history of the patient. Also, these patients are often treated in combination with a range of other therapies that may be potentially involved in the occurrence of photosensitive reactions, and it can be very challenging to identify the most likely causative agent [7].

The involvement of ribociclib in the observed cutaneous adverse effect is straight-forward as the symptoms subsided after the treatment cessation, and they did not appear again when the treatment option was changed. Letrozole was a part of both treatment options, and therefore the impact of this drug on the cutaneous adverse effects can be excluded. Although photoallergic dermatitis is a rare side effect of ribociclib, strict photoprotection should be advised to these patients while prescribing this medication. As different dermatologic adverse events can lead to dose modifications and interruption or discontinuation of anticancer treatments in severe cases, the prophylactic behavior of the patient is strongly encouraged. In cases where preventative measures fail and photosensitivity occurs, symptomatic treatment with topical or systemic corticosteroids may help to reduce the impact of the photosensitive eruptions on patient quality of life and allow potentially life-saving cancer therapies to be continued without dose modification.

Recently, Abemaciclib [18] and Ribociclib [19] demonstrated to significantly improve the invasive disease free survival in intermediate and high risk populations of early $HR^+/HER2^-$ breast cancer patients so the treatment with CDK4/6 inhibitors is being implemented in treatment of breast cancer patients with early breast cancer, as well as metastatic breast cancer, so the understanding and management of all side effects is crucial.

Conflict of interest: None declared.

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Рибоциклибом индукована фототоксичност – ера нових лекова и нових токсичности

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САЖЕТАК

Увод Рибоциклиб припада породици инхибитора киназа зависних од циклина 4/6 и одобрен је 2017. године за лечење болесница са узнапредовалим карциномом дојке позитивним на хормонски рецептор ($ЕР^+$) и негативним на рецептор за хумани епидермални фактор раста 2 ($ХЕР2^-$). Пошто се рибоциклиб за лечење рака дојке користи само последњих неколико година, његови ретки нежељени ефекти описани су кроз различите приказе случајева. Кожна фотосензитивност обухвата широк спектар дерматолошких стања узрокованих или погоршаних током излагања сунцу. Фотосензитивност изазвана лековима може да се испољи код онколошких болесника који се лече свим модалитетима системске терапије: хемиотерапеутицима, циљаном терапијом и имунолошком терапијом.

Приказ болесника Приказујемо случај болеснице са метастатским карциномом дојке позитивним на хормонски рецептор и негативним на рецептор за хумани епидермални фактор раста, код које се јавила кожна фототоксичност током примене терапије рибоциклибом/летрозолом. Током третмана појавило се благо црвенило коже у строго фотосензитивној дистрибуцији и осип се променио у еритематозне спојене плакове на врату и горњем делу грудног коша, лица и подлактица. После прекида примене лека промене на кожи се нису поново појавиле.

Закључак Пошто се испољено кожно нежељено дејство повукло после прекида терапије и није се поново јављало после примене терапије палбоциклибом/летрозолом, може се закључити да је нежељено дејство последица примене рибоциклиба. Лечење кожних нежељених ефеката је различито, углавном у зависности од степена кожних нежељених ефеката и његове тежине.

Кључне речи: рибоциклиб; карцином дојке; фототоксичност

DOI: https://doi.org/10.2298/SARH241008091K
UDC: 612.111.08:577.17

REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

How hormones acting on their receptors influence mature erythrocytes

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SUMMARY
Anemia is the most common disorder globally and one of the conditions that general practitioners most frequently encounter. Human erythrocytes, also known as red blood cells, or RBC, are exposed to constant stress while they circulate in the blood (e.g. shear stress, osmotic stress, oxidative stress). The scope of this review was to analyze the literature data on what the hormonal receptors do on mature erythrocytes and how they relate to the risk of anemia.
We investigated the literature data in the most recent five-year period (*PubMed*, *Google Schoolar*) and analyzed the effects of hormonal receptors on four specific characteristics of mature erythrocytes: osmotic resistance, deformability/rheology, erythrocyte hemoglobin affinity to oxygen and eryptosis.
We found that the hormones have a strong impact in regulating erythrocyte survival and functionality. These receptors increase the physiological plasticity of mature erythrocytes and serve as the effective tool for deeper effects of integral regulatory mechanisms that promote their survival and whole-body homeostasis. Additionally, these hormonal receptors are closely associated with the risk of anemia: when the supportive function of hormones and their receptors is not effective, eryptosis increases and, consequently, the number of mature erythrocytes in the circulation decreases.
Keywords: physiological phenomena; blood cells; chemicals and drugs – hormones; osmotic fragility; diseases, hematologic – anemia

INTRODUCTION

Erythrocytes are the most numerous blood and body cells

Human erythrocytes, also known as red blood cells, RBC, are organelle-free cells packaged with hemoglobin that are specialized for oxygen transport. With an estimated total number of 25 trillion cells per person, erythrocyte is the most numerous cell type not only in blood but in the entire organism [1, 2].

Anemia is a condition in which the number of erythrocytes or their oxygen-carrying capacity is insufficient to meet physiological needs [1, 3]. It is one of the most widespread disorders worldwide and among the conditions most commonly encountered by general practitioners. According to World Health Organization global database, anemia affected approximately 1.76 billion individuals worldwide in 2019 [3].

Additional overlooked erythrocyte functions

Our understanding of erythrocytes as a simple "bag" that contains hemoglobin and performs its essential task as an oxygen shuttle has dramatically evolved. Over the past several decades, the efforts of cell and molecular biologists, physiologists, biochemists, and hematologists have contributed to our better understanding of the complexity of the erythrocyte structure and revealed that erythrocytes can also perform the following: serve as sink for exogenous RNA [4]; play a significant role in the immunometabolic interactions that control immunity [5]; contain an important pool of the bioactive gas – nitric oxide [6]; play a role in water- [7] and reverse cholesterol-transport [8]; and can be used as a drug carrier (pharmaceutical uses) [9].

Additionally, it is postulated that in regions of low pO_2, the mobile erythrocytes also serve as oxygen sensors and modulators of vascular tone, since they have the ability to match microvascular oxygen supply with tissue oxygen demand, by releasing ATP [10]. It is amazing how many essential complex physiological functions are provided by erythrocytes. An impressive number!

Received • Примљено: October 8, 2024
Revised • Ревизија: November 27, 2024
Accepted • Прихваћено: December 2, 2024
Online first: December 4, 2024

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Erythrocytes are constantly subjected to multiple stresses while circulating in the bloodstream

While travelling through rapid, dynamic, and quickly changeable circulatory system, erythrocytes face many challenging conditions and locations [1, 11]. Firstly, with each passage through the renal medulla, erythrocytes are exposed to the osmotic stress/shock, since they undergo significant changes in their hyperosmotic environment, reaching levels as high as 1200 mOsmol/L [12]. Secondly, mature erythrocytes endure the shear stress (mechanical deformation of the membrane) while passing through tight capillaries and sinusoids [13]. Thirdly, when in the lungs, they also face oxidative stress due to the elevated oxygen pressure [11]. Furthermore, during inflammation, whether it is systemic or chronic, erythrocytes are constantly exposed to circulating inflammatory mediators [14].

Consequently, all of these multiple stresses can result in molecular and structural damage of erythrocytes, ultimately leading to their degradation and quick removal from circulation. A rapid and severe reduction in erythrocyte levels results in the development of hemolytic anemia [1].

Even though erythrocytes are constantly subjected to multiple stresses, they lack the ability to replenish proteins that have lost their function, since they have lost all of their organelles by the time they mature [1, 15].

Altogether, due to all of these difficulties, erythrocytes are highly vulnerable and sensitive cells that require various defense mechanisms to support their viability and avert their premature clearance [15, 16].

The intimate relationship between erythrocytes and the endocrine system

Numerous clinical and experimental observations have confirmed that there is a close connection between the rate of hematopoiesis and endocrine hormones, as evidenced by changes in bone marrow and peripheral blood components [17, 18, 19]. For instance, hypothyroidism is related to anemia and an underactive marrow, while hyperthyroidism is linked to an excessively cellular marrow, lymphocytosis, and lymphoid hyperplasia [20].

This intimate relationship exists especially between immature erythrocytes and the endocrine system. It is well known that human erythropoietin (Epo), a glycoprotein hormone composed of 165 amino acids, is a crucial factor for the survival, viability and proliferation of erythrocyte progenitor cells [1, 17]. In bone marrow, Epo binds to the homodimeric Epo receptor, and through JAK-2/STAT-5 signaling pathways induces the expression of anti-apoptotic proteins (e.g. Bcl-xL) and promotes the survival of erythrocytic progenitors, particularly the colony-forming unit-erythroid (CFU-E) [21]. Apart from this, Epo activates genes promoting proliferation, differentiation, and maturation of immature forms of erythrocytes. Approximately four days after an increase in Epo levels, there is a rise in the number of reticulocytes and mature erythrocytes that enter the bloodstream [1, 2, 18].

In addition to Epo, the male hormone testosterone strongly stimulates erythropoiesis [1, 18]. The mechanisms by which testosterone promotes erythropoiesis are not well understood. It is hypothesized that testosterone induces erythrocytosis by stimulating the production of Epo [15]. Testosterone also acts directly on the bone marrow, increasing the number of Epo-responsive cells [1, 22, 23].

Surprisingly, comprehensive research on erythrocyte biochemical pathways, metabolism, and structure-activity relationship with a substantial number of publications has revealed that a relatively large number of endocrine hormone receptors are expressed not only on humane immature but also on mature erythrocytes [24, 25, 26]. This discovery rises the questions whether these hormonal receptors represent only the remnants of receptors from young (immature) forms of erythrocytes, or do they have their own physiological function and pathophysiological significance. Are they functional in mature erythrocytes? The literature lacks data explaining how erythrocytes have a relatively long lifespan, of 120 days, despite their low complexity and their inability to transcriptionally upregulate antioxidant (and all other stress-related) defense mechanisms. The goal of this literature review is to summarize the protective and supportive impacts of hormones on four mature erythrocyte vital characteristics: volume homeostasis (osmotic resistance and fragility), deformability/rheology, affinity of erythrocyte hemoglobin to oxygen, and eryptosis.

We investigated the literature data (*PubMed, Google Schoolar*) from the latest five years with the following keywords employed: hormonal receptors, mature erythrocytes. The number of articles found was not systematically quantified, as the focus was not on providing an exhaustive coverage of all relevant studies but rather on identifying representative and key sources that support the narrative analysis.

ERYTHROCYTE VOLUME HOMEOSTASIS

Preserving of cellular volume homeostasis is essential for the survival of erythrocytes [1]. Disturbance of this homeostasis, a feature of several inherited anemias, leads to abnormal erythrocytes. Several pathways mediate water and solute homeostasis in normal erythrocytes, where cellular volume is primarily controlled via the sodium–potassium ATPase pump (Na^+/K^+ATPase), that maintains the intracellular low sodium, high potassium composition by actively transporting sodium out of and potassium into the erythrocytes [1].

Hormones that affect the function of Na^+/K^+-ATPase and RBC osmotic fragility

Thyroid-stimulating hormone (TSH) is a glycoprotein synthesized by the thyrotrophs of the anterior pituitary gland and its main role is to stimulate the thyroid gland to secrete thyroxine (T_4) and triiodothyronine (T_3). TSH

acts through TSH receptors (TSHr), which are G-protein coupled receptors [1].

Balzan et al. [27] identified the TSHr on human erythrocyte membranes in 2007. Subsequently, in 2009, they demonstrated that TSH binds to TSHr, affecting Na^+/K^+-ATPase [28]. Additionally, Mendonça-Reis [29] in 2024 found that TSH enhanced erythrocyte resistance to hemolysis by inhibiting the AMPK-dependent pathway and activating the PI3K/Akt signaling pathway.

Further, research indicates that individuals with subclinical hypothyroidism exhibit decreased Na^+/K^+-ATPase function in erythrocytes, suggesting its potential role as an early indicator of hypothyroidism [17]. Moreover, elevated TSH levels in sickle cell anemia patients correlate with disease severity and duration, implying a potential influence of TSH on disease progression [20]. The identification of a functional TSHr in erythrocytes and the elucidation of associated pathways suggest that TSH can influence erythrocyte behavior and fate.

From a physiological point of view, it seems reasonable to assume that TSH enhances the osmotic resistance of erythrocytes to hemolysis in a state of elevated metabolism, since all the end-products of metabolism are osmotically active, and because of that they inevitably induce osmotic stress to erythrocytes.

Angiotensin II (Ang II) can enhance erythrocyte osmotic resistance and decrease hemolysis, particularly beneficial for individuals with sickle cell anemia [12]. Although the precise mechanisms by which Ang II influences erythrocytes are not entirely clear, it is understood that the ATR_2 receptor can impact multiple signaling pathways related to cell survival and osmotic control.

Cortisol binds to the erythrocyte membrane, impairing epinephrine binding and resulting in an increase in the microviscosity of the membranes and a rise in Na^+/K^+-ATPase activity [30, 31].

Endothelin-1 (ET-1), a peptide hormone composed of 21 amino acids, is a potent vasoconstrictor in humans. Within erythrocytes, ET-1 enhances the activity of protein disulfide isomerase, an enzyme involved in regulating ion channels that promote potassium and water loss from cells, resulting in erythrocyte dehydration and heightened susceptibility to hemolysis [32]. In sickle cell anemia, elevated ET-1 activity can induce dehydration of sickle erythrocytes, increasing their stiffness and propensity to aggregate. Investigations into ET-A receptor antagonists as potential therapies aim to mitigate these adverse effects, potentially enhancing the well-being of individuals with sickle cell anemia.

See Table 1 for hormones influencing erythrocyte osmotic resistance/fragility.

Table 1. Hormones influencing red blood cells' osmotic resistance/fragility

Increases osmotic resistance	Decreases osmotic resistance
TSH	Endothelin-1
Angiotensin II	
Cortisol	

RBC FLEXIBILITY AND RHEOLOGY

The hemorheologic responses involved in the body's reactions to stress, energy regulation, and growth are not fully understood [18, 33]. Erythrocyte flexibility refers to the cells' capacity to adjust their shape in response to dynamically changing flow conditions. The indicators that expressed the erythrocyte membrane flexibility are RBC deformation index (RDI: 0.47–0.55) and erythrocyte rigidity index (Male: 7.16, Female: 7.14) [33]. The hormones can either enhance or reduce red cell deformability, thereby aiding in adjusting microcirculatory blood flow accordingly [30]. The stiffening of erythrocytes may either be reversible or part of the sequence of events culminating in programmed red cell death (eryptosis).

Hormones that improve the RBC flexibility/rheology

Catecholamines, during stress, regulate erythrocyte rheology via α- and β-adrenergic receptors [25, 33]. This is consistent with the other classical effects of catecholamines mediated by β-adrenergic receptors (vasodilation, increased cardiac output, etc.) that all lead to an increased blood flow. The effect of these hormones on erythrocyte deformability is mostly under the control of intracellular Ca^{2+}-regulating pathways [25]. In contrast to this beneficial effect of catecholamines on erythrocyte deformability in physiological conditions, a decreased erythrocyte deformability was observed in untreated pheochromocytoma [34].

Erythropoietin improves red cell deformability [16, 17, 30]. Chronic kidney disease-associated hemorheological disturbances (reduced erythrocyte deformability) were corrected with treatment using recombinant human Epo (rhEPO) [35]. In cancer patients, rhEPO increases red cell deformability and decreases red cell aggregation [30].

TSH. The results indicate that the TSHr decreases hemoglobin S polymerization and enhances the deformability and adhesion of sickle erythrocytes [29].

Leptin, a hormone released by adipocytes, has been shown to improve erythrocyte deformability via a NO- and cGMP-dependent mechanism [30]. Aditionally, the specific binding of leptin to erythrocytes delivers pancreatic hormones and stimulates ATP release [36]. Leptin is involved in regulatory loops that link energy stores and circulation [16].

Hormones that impair the RBC flexibility/rheology

On the other hand, several hormones have been identified to decrease erythrocyte membrane flexibility.

Thyroid hormones. Erythrocytes also exhibit receptors for the thyroid hormone [20]. Whether thyroid hormones are regulators of blood rheology remains unclear, but a decrease in erythrocyte deformability has been reported to exist in hyperthyroidism [20, 37, 38] and to be reversible after the successful treatment of the disease [20, 37].

Prostaglandins. PGE_2 decreases the deformability of erythrocytes and increases their aggregability [15, 39].

Female sex hormones. The effects of sex hormones on erythrocyte rheology may contribute to the very complex mechanisms of ovulation and, consequently, play a role in the regulation of fertility [16, 26].

Insulin-like growth factor 1 (IGF-1). Clinical report from an exercise-test in 39 male elite athletes indicates that elevated levels of IGF-1 are associated with lower erythrocyte deformability at high shear rates [33].

Apelin is a cytokine that is predominantly secreted by adipocytes [1]. In rats with reduced erythrocyte deformability due to the experimental induction of diabetes and ischemia-reperfusion injury of the heart, apelin-13 has been shown to restore this loss of erythrocyte deformability [40].

Melatonin can elevate the erythrocyte deformability in experimental sepsis due to its nitric oxide scavenging activity and antioxidant effect [41]. However, pinealectomy alone did not lead to any statistically significant alterations in erythrocyte deformability, but when melatonin was added, a significant decrease was observed [42]. Therefore, this issue remains controversial and requires further study.

See Table 2 for hormones influencing erythrocyte flexibility.

OXYGENATION OF HEMOGLOBIN

The function of erythrocyte 2,3 diphosphoglycerate (2,3-DPG), an intermediate molecule of glycolysis, is to bind to deoxyhemoglobin and facilitate oxygen transport. Hormones may modulate hemoglobin's capacity to bind and release oxygen, by affecting the level of erythrocyte 2,3-DPG.

Thyroid hormones. Tokay et al. [43] showed that thyroid hormones upregulated the levels of 2,3-DPG in erythrocytes, thus implying a possible connection with the regulation of oxygen release from hemoglobin. The hormone's effects on 2,3-DPG synthesis may provide a biochemical explanation for the shift in the oxyhemoglobin dissociation curve seen in thyroid disorders.

Dehydroepiandrosterone (DHEAS) has been linked to changes in the deoxygenation rate of hemoglobin, which could influence hemoglobin's affinity for oxygen [17, 44, 45].

See Table 3 for hormones influencing oxygenation of hemoglobin.

ERYTHROCYTE ERYPTOSIS

Eryptosis refers to the premature, stress-triggered suicidal death of erythrocytes, which is distinct from accidental hemolysis or cellular senescence [2, 15].

Eryptotic effect is triggered by endocannabinoids. Anandamide, a type of endocannabinoid, has been reported to induce eryptosis, by increasing the activity of erythrocyte cytosolic Ca^{2+}, resulting in the cell shrinkage and, subsequently, the induction of eryptosis [46].

Anti-eryptotic hormones

Inhibition of eryptosis is crucial in certain therapeutic situations, such as in patients with sickle cell anemia, who experience elevated eryptosis levels that can exacerbate anemia [18]. Numerous hormones can inhibit eryptosis, some of which are mentioned bellow.

Erythropoietin not only stimulates erythrocyte development in the bone marrow (erythropoiesis), but also exhibits direct anti-eryptotic properties, as it reduces Ca^{2+}-mediated eryptosis by inhibiting non-selective cation channels [15].

Catecholamines also have an anti-eryptotic effect, by impairing the Ca^{2+} cation channels' ability to enhance the entry of Ca^{2+} ions [47].

Leptin and thyroid hormones have been associated with maintaining erythrocyte deformability, indicating a potential anti-eryptotic effect [16, 20].

Melatonin. While the effects of melatonin on erythrocyte deformability remain controversial, some studies suggest that melatonin may have an anti-eryptotic effect

Table 2. Hormones influencing red blood cells' flexibility

Improve RBC flexibility	Reverse the loss of RBC flexibility	Impair RBC flexibility	Unclear results on RBC flexibility
Cateholamines	Apelin	Catecholamines: supraphysiological levels – in untreated pheochromocytoma	Female sex hormones
Erytropoietin		Erytropoietin: subphysiological levels, in chronic kidney disease	Melatonin
TSH		Thyroid hormones	
Leptin		IGF-1	
		PGE2	

RBC – red blood cells; TSH – thyroid-stimulating hormone; IGF-1 – insulin-like growth factor 1; PGE2 – prostaglandin E2

Table 3. Hormones influencing oxygenation of hemoglobin

Decreases	Increases
Thyroid hormones	-
Dehydroepiandrosterone (DHEAS)	-

Table 4. Hormones influencing red cell eryptosis

Eryptotic effect	Anti-eryptotic effect
Endocannabinoids	Erythropoetin
	Catecholamines
	Leptin
	Thyroid hormones
	Melatonin

[41]. The beneficial effect of melatonin has been already proven to prevent oxidative stress-induced damage associated to lipid peroxidation [41].

See Table 4 for hormones influencing red cell eryptosis.

LIMITATIONS

This literature review examines the role of hormones in regulating erythrocyte survival and functionality.

The action of hormones on mature (and immature) erythrocytes involves a complex interplay between various signaling pathways and receptors, influencing erythrocyte function, survival, and responses to different physiological stressors. However, this review does not address two key points. Firstly, it does not explain the mechanism by which certain hormonal receptors are spared from removal during terminal erythrocyte maturation – specifically, how some receptors avoid the "tagging" process that leads to their autolysis (via an autophagy/exosome-mediated pathway tied to membrane remodeling). Secondly, it does not explain the complex interplay among the various signaling pathways and receptors involved. Due to these limitations, the review cannot be considered a fully "causal literature review."

This literature review can neither be considered a "systematic literature review," since it does not have strict inclusion and exclusion criteria. Compared to a systematic literature review on the same topic, this review is more subjective, as we have constructed a narrative based on selected relevant studies in accordance with our own criteria. Our focus is on interpreting results and conceptualizing ideas rather than on providing a comprehensive, objective analysis of all relevant studies.

By integrating findings from different research endeavors, we aimed to present a coherent narrative that highlights the broader picture. Thus, this literature review paper should be classified as a "narrative (contemplative) literature review." To the best of our knowledge, there is no similar integrative interpretation of this intriguing "intelligent design" that enhances the physiological plasticity of mature erythrocytes.

CONCLUSION – CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Hormonal receptors on mature erythrocytes prevent the premature, stress-induced death of erythrocytes (eryptosis) and protect the erythrocytes. Some hormonal receptors, such as those for TSH, angiotensin II, cortisol, and endothelin-1, are essential for maintaining erythrocyte volume homeostasis and osmotic resistance. Others, including receptors for catecholamines, erythropoietin, insulin, leptin, somatostatin, and thyroid hormones, regulate erythrocyte membrane deformability (flexibility) and rheology. In addition, receptors for thyroid hormones (T_3, T_4) and DHEAS mediate adjustments in the affinity of erythrocyte hemoglobin to oxygen, depending on the intensity of tissue metabolism.

When the supportive function of hormones and their receptors is not effective, eryptosis increases and, consequently, the number of mature erythrocytes in the circulation decreases. Addressing the issue of anemia is a significant challenge in modern medicine, as it is a highly complex condition involving numerous underlying pathophysiological mechanisms. Future research is needed to determine whether introducing new technologies and the development of specific hormonal receptor antagonists/agonists could prolong the life and potentially enhance the well-being of individuals with different types of anemia.

ACKNOWLEDGMENT

The authors would like to thank Ana Simović for her invaluable help in preparing the manuscript.

Funding: Ministry of science, technological development and innovation Serbia; project no. 451-03-66/2024-03/200110.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

Conflict of interest: None declared.

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Како хормони посредством својих рецептора утичу на зреле еритроците

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САЖЕТАК

Анемија је најчешћи поремећај здравља свуда у свету и једно од стања са којима се лекари опште праксе најчешће сусрећу. Еритроцити су изложени сталном стресу док циркулишу у крви (нпр. трпе стрес услед сила смицања, осмотски стрес, оксидативни стрес).

Циљ овог прегледног чланка је био да анализира литературне податке о томе шта хормонски рецептори раде на зрелим еритроцитима и како су они повезани са ризиком од настанка анемије.

Истраживали смо литературне податке објављене током претходних пет година (*PubMed*, *Google Scholar*) и анализирали ефекте које хормонски рецептори имају на четири специфичне карактеристике зрелих еритроцита: на осмотску отпорност, деформабилност/реологију, афинитет хемоглобина према кисеонику и ериптозу еритроцита.

Утврдили смо да хормони имају снажан утицај на регулисање преживљавања и функционалност еритроцита. Ови рецептори повећавају физиолошку пластичност зрелих еритроцита и служе као ефикасно средство за дубље деловање интегралних регулаторних механизама, који промовишу опстанак еритроцита и хомеостазу целог тела. Додатно, ови хормонски рецептори су уско повезани са ризиком од настанка анемије: када супортивна функција хормона и њихових рецептора није ефикасна, ериптоза се повећава и, као последица тога, смањује се број зрелих еритроцита у циркулацији.

Кључне речи: физиолошке појаве; крвне ћелије; хемикалије и лекови – хормони; осмотска фрагилност/отпорност; болести, хематолошке – анемија

DOI: https://doi.org/10.2298/SARH230812095P
UDC: 001.891-055.2(497.11)

REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

Women in science and equity in Serbia – so near, yet so far

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SUMMARY
The concept of diversity, equity, inclusion and belonging is essential for research and academic programs and institutions worldwide, but although women do not lag behind men at entry and graduation from Serbian universities, equitable leadership does and it further hinders outcomes in every way: from translational science via healthcare up to legislative efforts to protect children, women and elderly. Although all these may seem as *l'art-pour-l'art* issues when compared to mere survival in war zones on two continents and all issues women face under circumstances of displacement and bans on rights to education, healthcare and sounds of their own voices in public, still it is the ongoing fight for rights lost in silence and where one least expects it that has to push every human being to fight for the oppressed and underprivileged.
Keywords: COVID-19; sex differences; gender differences; women in medicine; women in cardiology; women in STEM

Received • Примљено: August 12, 2023
Accepted • Прихваћено: December 19, 2024
Online first: December 24, 2024

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INTRODUCTION

The close of the second decade of the 21st century, marked by the and the SARS-CoV2 (COVID-19) pandemic, unveiled another Pandora's box – one highlighting the pervasive inequities faced by women. These ranged from adequate treatment as patients, initially underestimated due to erroneous assumption that their sex offered protection against the disease [1, 2, 3], to the harsh working conditions endured by women in the healthcare sector, who bore the brunt of the pandemic's first wave [1–6], and culminating in the widening of gaps in research opportunities and academic promotions [1, 2, 3].

The fight against "bikini medicine" in the United States has been gaining momentum in crossing borders with global campaigns teaching patients, physicians, researchers, legislators and other advocates that heart disease does take more lives of women than all cancers combined not just in the United States [2], but worldwide as well, as it does in Serbia [7],

Figure 1. NOVAK 2022 and Women's Heart Programs: A Bare Necessity of Diversity and In-clusion, not a Fashion Accessory of Innovation (October 29, 2022, Novi Sad, Serbia)

although different practices and legislation in healthcare tend to hinder progress in that regard and the pandemic has, actually, emphasized the necessity of tailored comprehensive care for women [2, 3, 8. 9, 10]. On the other hand, as history has taught us before, all times of crises – such as the COVID-19 pandemic and ongoing warzones on two continents – lower the threshold for violence, not only displaced women, and in particular women of color suffer the most [11, 12], but in the least expected places and sociodemographic strata [2, 13–16]. This, in turn, brings us back to the necessity of diversity, equity, inclusion and belonging (DEIB) programs of academic institutions and that of Women's Heart Centers/Programs [2, 17, 18] that should follow the needs of the underserved population that women remain, especially where they suffer most discrimination [2]. Despite different models of the women's heart centers [2, 17, 18], the Serbian one [2] proposed positioning of its program aiming to a broader reach for socially-responsible and equitable healthcare, teaching, research and advocacy, which was also reaffirmed by the latest Presidential Advisory of the American Heart Association [9].

Taking it all in consideration, likeminded research groups continue to endeavor to fill the growing gaps that have heavily influenced Serbian scientific and healthcare landscapes, for the growing number of recorded femicides in Serbia [19] – where femicide is still not recognized as a criminal offense, yet prosecuted as an aggravated murder – are facilitating normalization of all lesser forms of violence women are subject to: women who report bullying and harassment are discouraged to do so via social media, social pressures and lack of diligence by the police and justice departments while lengthy proceedings end up with none whatsoever or mediocre sanctions for the perpetrators whom everyone else sees still flourishing in their professional and social roles.

SERBIAN EQUITY SCENE: 2022–2024

United around the same idea that equity and meritocracy – and not patriarchal personal preferences – share the keychain for a thriving society our group continued organizing educational events targeting a wide population.

NOVAK 2022: the "Dr Nanette Kass Wenger" Women's Heart Program session

With SARS-CoV-2 pandemic approaching its end, gathering a variety of experts [1, 2, 20, 21, 22] of different fields (Figure 1),we re-addressed the issue of women's health aiming to dispel myths that keep hindering long term cardiovascular health of women in Serbia where – among other issues – vaccination rates of pregnant women were low, while data on newborns' COVID-19 infections unknow, although our microbiologists were among pioneers in the field starting from the first wave[23]. During the first year of pandemic, pregnant women lacking previously acquired immunity had an increased risk for both severe morbidity and mortality following SARS-CoV-2 infection when compared to non-pregnant [24, 25, 26], although infection was associated with higher risk of preterm delivery [27]. Still, in most neonates and infants SARS-CoV-2 infection was either asymptomatic or mild [28]. However, as studies showed that anti-SARS-CoV-2 antibodies are detected in cord blood of women infected with SARS-CoV-2, it is likely that some degree of protection against infection

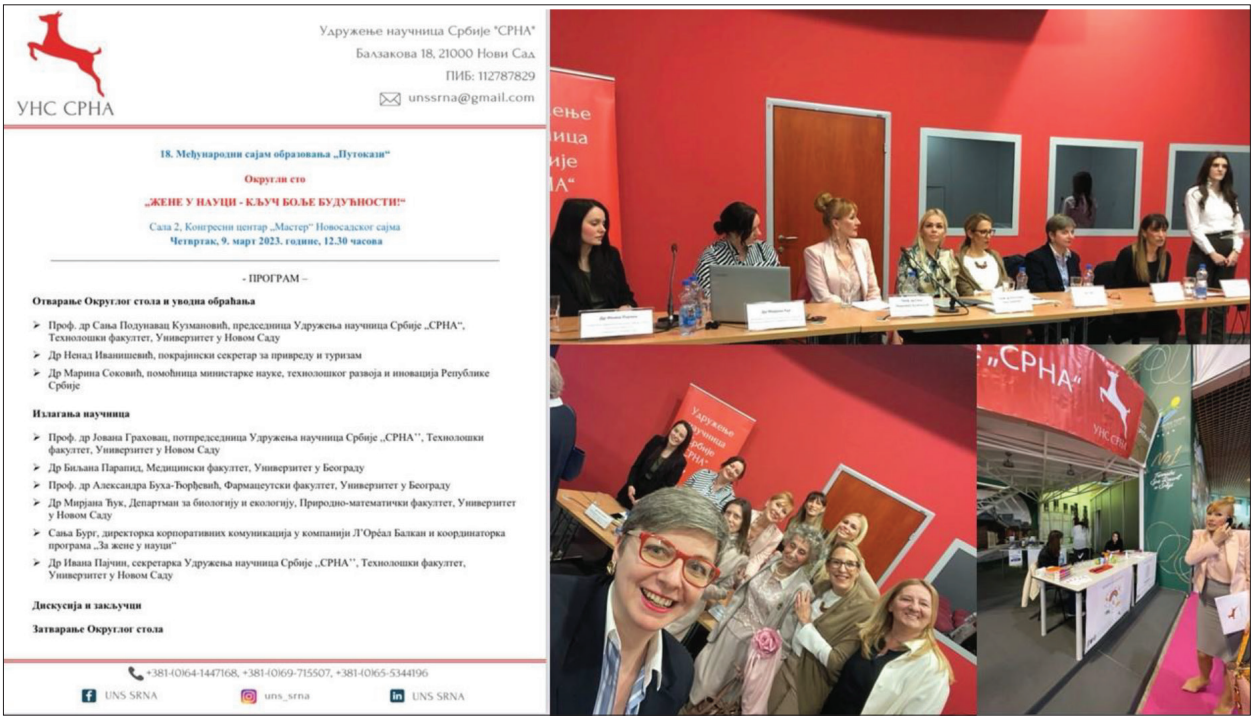

Figure 2. 18th International Fair of Education and SRNA's roundtable "Women in Science – Key to a Better Future" (March 9, 2023, Novi Sad, Serbia)

and/or risk reduction of developing severe COVID-19 in infants may be expected if the infants are born to women with pre-existing immunity [26, 29]. In order to beat the pandemic, the first COVID-19 vaccine based on messenger RNA technology was approved in December 2020 by the Food and Drug Administration and although this vaccine has been shown to be highly effective in real world setting, pregnant individuals were not included in the initial vaccines' efficacy trials [30]. For several months a clear universal evidence-based recommendation was expected for the immunization of this vulnerable population, which led to lesser acceptance of the vaccine in the pregnant population [31]. Also, it is considered that the benefits of vaccination have been communicated "confusedly" with lack of data about COVID-19 vaccine safety [26, 32]. Finally, in mid-2021 it was reported that of the top 20 countries affected by pandemic, 11 allow vaccination of pregnant women, of which two have classified pregnant women as a high-risk group for which vaccination is safe. On the other hand, only five of the 20 countries with high maternal mortality allow vaccination of pregnant women but none of these countries prioritized vaccination of pregnant women [33]. Pointing out the safety as the most challenging issue when it comes to vaccinating pregnant women, it is stated that prenatal mRNA COVID-19 vaccination did not show association with adverse immediate pregnancy outcomes or newborn complications [34]. Injection-site pain, fatigue and myalgia, as the most frequent reactions after COVID-19 vaccination in pregnant women, were reported at the same level among non-pregnant women [35] and more frequent after the second dose of mRNA vaccines. Moreover, the incidence rates of adverse pregnancy and neonatal outcomes (fetal loss, preterm birth, and neonatal death) were similar between vaccinated pregnant women and the same population before the pandemic, but also between vaccinated and unvaccinated pregnant women during the pandemic [30, 34]. Safety concerns of COVID-19 vaccines' components and technological platforms were in detailed described by Ciapponi et al. [36], whose team did not find any evidence of pregnancy-associated safety concerns of COVID-19 vaccines (selected for review by the COVAX MIWG, COVID-19 Vaccines Global Access-Maternal Immunization Working Group) or their components and platforms when used in other vaccines. Still, vaccine naïve and sceptics were mostly encountered amongst nurses in our healthcare sector, even outside family planning concerns, although effects of repeated infections have been demonstrated to influence cardiovascular morbidity, extended absences from work, reassignment requests that hospital systems sometime cannot fulfill, which overall increases burnout [2, 8, 37] of an already exhausted workforce they represent.

SRNA roundtable: March 2023

As the educational fair coincided with the International Women's Day, SRNA – the pioneering #SheForShe team of Serbian academia – organized a roundtable (Figure 2) that gathered women researchers from different areas who discussed not only importance of their research fields in which both their sex is rare, but sex disparities tend to be neglected even when they influence the outcomes of their research: biology and biodiversity[38], medicine [2], pharmacy [39], sociology [15, 16, 40] and so many more. From the medical standpoint, it is well know that anatomy [41, 42, 43] and physiology mandate the response

Figure 3. The First Continuous Medical Education (CME) at the University of Belgrade, Faculty of Medicine "Gender differences recognition as a road to improving healthcare of women" held on February 22, 2024 (Belgrade, Serbia) was offering a six-hour-long CME and as refreshments muffins from MuffinStore (Belgrade, Serbia) as the first family-owned catering company in Serbia that hires only women over 40 years who were fired and cannot find employment elsewhere

to disease, as well as treatment, but still, women remain under-represented in research trials even when women are principal investigators [44] and despite ongoing era of modern pharmacology in cases of drugs that exhibit clear benefit for men in terms of long term survival and complications' free follow up [45] and even in fields that should be in the scope of growing research as lactating mothers [46]. Yet, as we live in the era of sustainable development and modernizing legislations to keep up the pace with research and technology who are expected to further their collaborations in every way and to which Serbia has committed [47], equity is also invited to this party. Fortunately, challenging fields of under-financed research and research talents, has found one of its loudest advocates in the L'Oréal Fund for Women that has selflessly endorsed research led by women in Serbia and some of the panelists shared their own experience as laureates or mentors of mentees whose research projects were supported by L'Oréal in Serbia via their annual grants.

CME at FMUB: 2023/2024

For the first time at the Faculty of Medicine of the University of Belgrade (FMUB), during the school year 2023/2024, a continuous medical education (CME) program (Figure 3) designed by basic science researchers [41, 42, 43, 48, 49], clinicians [1, 3, 13, 18, 20, 21, 22, 45, 50–61], public health [62] and legal [63] experts was proposed and approved as a six-hour-long CME credits aiming to help recognize and fight discrimination of different

patients' populations who often carry a stigma of their sex, gender, age, social determinants of health and personal choices that are not judged in other parts of Europe and the world: women, elderly, displaced people with emphasis on women and children, different addicts, prostitutes and LGBTQIA+ who face endless forms of discrimination from both medical and legal perspectives when seeking medical help for themselves or as caregivers/partners of ill or hospitalized LGBTQIA+ patient. The first, inaugural CME had been planned to be held during the "16 days of activism" of 2023 at the Ceremonial Hall, but eventually pushed for Heart Month of the AHA, i.e., February 2024, due to logistic reasons and it scored a remarkable 4.93/5 per FMUB's reports in Summer 2024 which encouraged the team to pursue re-accreditation in the 2024/2025 and promote further the round-table concept that encourages participants to exchange more easily on experience, advice seeking and ideas for improvement needed in their respective areas and medical and legal practices. The CME was endorsed by the Ministry of Education of the Republic of Serbia led by Professor Slavica Đukić-Dejanović, the Office of the Commissioner for Protection of Equality of the Republic of Serbia Ms. Brankica Janković and office of UN WOMEN in Serbia in particular Ms. Milana Rikanović and Ms. Nevena Marčeta.

"AND, WHAT NOW?" *EN LIEU DE* DISCUSSION

Discrimination in all walks of life comes in all sizes, shapes and colors and never goes under the DEIB radar where one is fully in function. Regrettably, in different corners of the world where one lacks in function of local politics, we – on the verge of the second quarter of the 21st century – witness girls and young women being stripped off their basic human rights as rights to education and healthcare, which then makes misogyny in academia [44] and hospital corridors [64] almost seem like a ridiculous complaint of the "privileged". Yet, one cannot be considered privileged if all his or her peers do not share the same privileges worldwide. From a broader research perspective, inclusion must start from female mice in our labs – for they exhibit behavior more stable than that of their male counterparts in neuro-science research [65] – up to leadership positions free of covert misogyny that surely plays a yet not quantified role in science, technology and engineering and mathematics (STEM), so that #WomenInSTEM would not remain a mere hashtag trending on social media outlets on themed occasions together with #WIM (women in medicine).

CONCLUSION

DEIB is an everyday necessity that ensures all living in the 21st century with rights achieved in the previous one, while equality and equity need to start walking hand in hand whatever the journey might be called – research, education, healthcare or politics – for a society to thrive for the benefit of all.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

Conflict of interest:
BP: Boston Scientific EMEA (DE& I, 1st Female Cardiologist Advisory Board, position accepted Nov 30, 2021); THEMIS Foundation (Belgrade, Serbia), Founder. **DB, MM**: THEMIS Foundation (Belgrade, Serbia), Research & Development council.

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Жене у науци и равноправност у Србији – тако близу, а тако далеко

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САЖЕТАК

Концепт разноликости, једнакости, инклузије и припадности кључан је за истраживачке и академске програме и институције широм света. Међутим, иако жене не заостају за мушкарцима приликом уписа и дипломирања на универзитетима у Србији, праведно лидерство то чини, што додатно отежава исходе на сваки начин: од транслационе науке, преко здравствене заштите, па све до законодавних напора за заштиту деце, жена и старијих доба. Иако наведени појмови могу изгледати налик *l'art-pour-l'art* проблемима када се упореде са пуким преживљавањем у ратним зонама на два континента и свим проблемима са којима се жене суочавају током расељавања, као и ускраћивањем права на образовање, здравствену заштиту и слободно изражавање мишљења на јавним местима, борба је непрестана за сва права која се губе у тишини и то на местима где се то најмање очекује. Свако људско биће мора да се бори за угњетене и обесправљене.

Кључне речи: ковид 19; полне разлике; родне разлике; жене у медицини; жене у кардиологији; жене у науци

DOI: https://doi.org/10.2298/SARH240730081D
UDC: 616.8-009.1-053.2

REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

Developmental coordination disorder – clinical features and treatment options

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SUMMARY
Developmental coordination disorder (DCD) is a neurodevelopmental disorder that is usually recognized after the age of five but may have lifelong motor, coordination, and cognition consequences. The criteria for setting a diagnosis refer to the presence of the following: performance of coordinated motor skills below that expected for chronological age, a deficit of motor skills that significantly and persistently interferes with activities of daily living, the onset of symptoms in an early developmental period, and a lack of motor skills that cannot be explained by intellectual disability or other neurological conditions that affect movement. This clinical picture is often comorbid with attention deficit hyperactivity disorder, autism spectrum disorder, and some other neurodevelopmental disorders. Prevailing DCD management includes task-oriented interventions as well as interventions focused on reducing impairment and improving physical function. The aim of the paper is to summarize typical DCD features related to diagnostic criteria, epidemiology, etiology, and comorbidities, as well as to present current management options.
Keywords: developmental coordination disorder; diagnostic criteria; comorbidity; task-oriented intervention

INTRODUCTION

The criteria for defining developmental coordination disorder (DCD) (ICD-11 code 6A04) include limitations of motor activities that are not otherwise caused by cognitive, sensory, or neurological deficits and are identified in the early developmental period [1, 2]. DCD is a neurodevelopmental disorder characterized by deficit in performing fine (e.g. handwriting and tying shoelaces) and gross motor skills (e.g. playing sports and dressing) at a level appropriate for calendar age, but clinical presentation can be very heterogeneous [3]. Within the clinical picture of DCD there is also a motor and neurodevelopmental component of the diagnosis [4]. In the past, the terms "clumsy child syndrome" and "developmental dyspraxia" were associated with this clinical picture [5].

In some cases, it can be challenging to determine the extent to which typical difficulties seen in DCD affect child's daily activities and participation and meet criteria for diagnosis. Notably, the common DCD description seems to include a large group of children who have a variety of impairments. Structured observation and examination of movement specificity can help in deciding on the diagnosis of DCD in children who have difficulties in coordination, generalization, learning and transfer within motor skills [6].

The aim of this paper is to fuse the specificities of DCD related to diagnostic criteria, epidemiology, etiology, and comorbidities, as well as to present current options for management of this condition.

DIAGNOSTIC CRITERIA

Current diagnostic parameters for determining DCD described in ICD-11 [1] and DSM-5 [4] refer to four mandatory criteria that are detailed in Table 1.

Received • Примљено: July 30, 2024
Revised • Ревизија: October 2, 2024
Accepted • Прихваћено: October 12, 2024
Online first: October 24, 2024

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Table 1. Diagnostic criteria for developmental coordination disorder*

Criterion	Description of criteria
A	Acquiring and performing coordinated motor skills, as well as the possibility for motor learning, are significantly below expectations considering the chronological age of the individual. Difficulties are manifested as clumsiness (e.g., dropping objects, tripping over or hitting objects), as well as slowness and inaccuracy in performing motor skills (e.g., grasping objects, using scissors or cutlery, riding a bicycle or rollerblade, writing with a pencil).
B	The motor skill deficit described in the previous criterion significantly and persistently interferes with activities of daily living that correspond chronological age (e.g., self-care and self-aid) and affects productivity during academic learning, leisure, and play.
C	The onset of symptoms is in the early period of development.
D	Motor skill deficits cannot be explained by intellectual disability or visual impairment and cannot be attributed to a neurological condition that affects movement (e.g., cerebral palsy, muscular dystrophy and degenerative disorder).

*Adapted from World Health Organization [1] and Cunningham et al. [2]

Table 2. Symptoms and signs suggesting possible developmental coordination disorder in different age groups*

Age	Symptoms and signs indicating possible developmental coordination disorder
Preschool children	• Persistent delay in motor developmental milestones: sitting, standing, walking, toilet training, speaking • Difficulties with running, hopping and jumping • Difficulties with catching or kicking a ball • Trouble walking up and down stairs • Poor coordination and balance • Frequently tripping and/or falling over things, bumping into objects • Lack of interest in construction toys (e.g. building blocks, Lego®) • Poor at getting dressed, buttoning up clothes, combing hair • Clumsy when picking up small things, tends to break small toys • Poor pencil skills – drawing, holding a pencil (drawings seem very immature compared to those of other children) • Poor at using scissors, fork and other utensils • Poor at puzzles, jigsaws or shape-sorting games • Difficulties with brushing teeth, getting dressed, tying shoelaces and other self-care • Difficulties with oral motor coordination, such as closing lips to blow bubbles or blowing out birthday candles
Schoolchildren and adolescents	• Problems from preschool period may persist • Problems with copying text or drawings from the school board • Difficulties with math and writing • Appearing disorganized • Seeming unable to follow instructions • Avoiding physical education, sports and games • Slow and poor handwriting with higher percentage of errors compared to neurotypical children • Driving difficulties

*Adapted from Harris et al. [9], Morgan et al. [10], and Smits-Engelsman et al. [11]

Preschool children with DCD master key developmental motor milestones (crawling, standing, walking, climbing stairs, buttoning clothes) at a later age compared to children with neurotypical development [1]. For example, it has been reported that 23% of children with DCD assessed between the ages of seven and 10 have never learned to crawl [7]. Children with DCD also have limited mobility, but generally the limitations are less pronounced than in children with cerebral palsy [8]. During middle childhood, the symptoms of DCD can become evident in activities such as handwriting, playing with a ball or in tasks of visuo-constructive abilities such as jigsaw puzzles or constructing various models [9, 10, 11]. Deficits in motor coordination in adolescence and adulthood can manifest when trying to master new motor skills (e.g., driving a car, using various tools, or taking notes), but even when motor skills are acquired, movement performance in all developmental stages is generally imprecise and clumsy compared to peers with neurotypical development [1, 9]. Clinical symptoms and signs suggestive but not specific for DCD in different age groups are shown in Table 2.

The diagnosis of DCD is usually made after the fifth birthday when all diagnostic criteria can be met. Due to major changes occurring in the developing brain during the first postnatal years, a certain time must elapse before symptoms and signs become unequivocally noticeable [12]. Although DSM-5 [4] included a new diagnostic criterion for DCD related to the onset of symptoms in an early developmental period, the evidence supporting this criterion is limited since DCD is generally not diagnosed before the age of five, as young children with motor delays can show spontaneous developmental catch-up. Likewise, the difficulty of a young child's cooperation and motivation to carry out assessment tests in this domain can lead to problems in the interpretation and straightforward diagnosis [13].

Children with DCD show a various spectrum of difficulties in controlling, coordinating and planning motor responses, as well as sensory and perceptual processing, which affects their quality of performing gross and fine motor activities [14]. Given highly heterogeneous presentation of DCD, diagnosis may be particularly challenging, and the experts in this field have made efforts to categorize DCD in distinct subtypes. Three subtypes of DCD have been proposed [15]: ideomotor DCD, presenting with a difficulty in the perception, praxia, and imitation of gestures; visual-spatial/constructional DCD, characterized by serious difficulties in visual-motor integration and visual-spatial structuring, while the third subtype refers to a mixed presentation which is comprised of the first two subtypes. However, other authors suggest perceiving the categorization of DCD according to cognitive specificities, and point out six subtypes:

1. children at risk – difficulty with jumping, as well as minor problems with manual dexterity and simultaneous coding,
2. children with average values of all cognitive-motor assessments,
3. children with values of all cognitive-motor assessments above the average,
4. children with detected manual dexterity, planning and simultaneous coding problems,
5. children with detected manual dexterity, planning and dynamic balance problems,
6. children with values of all cognitive-motor assessments below the average [16].

Despite the existence of different categorizations of DCD, it could not be claimed that the subtypes are clearly related to specific interventions within the treatment framework. However, in most scientific sources it is considered that children who score below the fifth percentile on standardized tests for the assessment of motor abilities (for example Movement Assessment Battery for Children Second Edition – MABC-2) can be described as children with significant movement difficulties and with

the probable presence of DCD. Children who score in the fifth to 15th percentile are at risk for DCD [17]. The results of this assessment do not provide a diagnosis of DCD, but contribute to the fulfillment of diagnostic criterion A.

EPIDEMIOLOGY AND ETIOLOGY

The reported prevalence of DCD ranges 2–20% of children [18], the most frequently assessed to be 5–6% in school-aged children [13]. Male predominance is a constant finding in studies (two to three times), and the risk of developing DCD increases with lower gestational age at birth [13]. However, despite such a high prevalence, DCD is considered one of the most unrecognized neurodevelopmental disorders, with the least organized support in terms of treatment [18]. Although DCD has been traditionally considered a childhood neurodevelopmental condition, it is estimated that it occurs in about 5% of the general adult population [13].

There is very little data on the cause of DCD and its pathogenetic mechanisms, making it difficult to understand core pathological problems in motor skill learning in order to determine the optimal therapeutic interventions. Yet, the evidence indicates the etiology is multifactorial, with both environmental and genetic factors contributing [19]. In most children with DCD, no obvious brain lesion can be seen. However, neuroimaging studies suggest that the brains of the affected children may show minor structural and functional changes [20]. For example, there is evidence of altered white matter development, indicated by reduced axial diffusivity in motor and sensory tracts [21]. Dysfunction in several brain regions has been implied: the cerebellum, basal ganglia, parietal lobe, frontal lobe areas, and possibly the corpus callosum [22, 23]. Considering the influence of the cerebellum on movement, coordination, balance, learning and cognitive functions, it is expected that its atypical developmental may be noted [19]. Poorer quality of visuospatial processing is most often associated with dysfunction of the parietal lobe, the impairment of motor planning, memory and executive functions indicates problems originating from the frontal lobe, and dysfunction of eye-hand movements implies problems within the corpus callosum [23, 24]. Nevertheless, undoubtedly the neural substrates of DCD have yet to be fully described.

COMORBIDITIES

The heterogeneity of the DCD presentation, in addition to subtypes, also includes the occurrence of comorbidities. There is frequently an overlap with other neurodevelopmental disorders, especially attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [2, 25]. Motor impairments are an integral part of the clinical picture of numerous neurodevelopmental disorders [12, 26], and it is believed that over 50% of children with ADHD (primarily the inattentive type) or ASD may have a simultaneous diagnosis of DCD [19]. The possibility of a genetic etiology linking DCD and ADHD or ASD has been indicated [27].

When considering a dual diagnosis of DCD and ADHD, it is important to emphasize that the diagnostic criteria for each disorder must be met to officially establish diagnosis of comorbidity. For example, some people with ADHD may appear clumsy (e.g., tripping over obstacles, knocking over objects, dropping things) due to inattention, hyperactivity, and/or impulsivity [28]. DCD in such cases should not be diagnosed [1].

It is important to note that criterion D complicates the diagnosis of DCD in children with ASD because it implies that the motor difficulties must be greater or minimally different from what is expected in children with ASD. In the literature, one comes across a very small number of recommendations on how to determine with certainty whether criterion D for the DCD has been met. It is necessary to establish whether the motor difficulties detected in children with ASD are an integral part of the clinical picture [29] or are a consequence of the simultaneous occurrence of DCD, because each diagnosis, or comorbidity, affects the type of treatment offered to children and families. The authors of this paper did not find any studies that provide clear guidelines on when to diagnose DCD in children with ASD, although the literature suggests that this should be done when criteria for DCD are met. However, no formal recommendations can be found to help clinicians interpret when motor difficulties exceed those typically expected in children with ASD [14].

Specific language impairment (SLI) is a comorbid condition that can occur in DCD. It is thought that about a third of children diagnosed with SLI also have DCD [30]. Children with a dual diagnosis of SLI and DCD have an evident decline in the quality of abilities in several domains of quality of life, which is not so pronounced in children with SLI [31].

Children with DCD are also facing two to four times increased risk of mental health issues, with anxiety detected in 16.7–33.8% and depression in 9.1–11.8% of cases [9, 32].

Recent researches indicate that secondary psychological problems (lower quality of life, low self-esteem, poor social relations, abuse, self-isolation) can also be classified as additional difficulties experienced by children with DCD [33, 34]. Hence, DCD can hinder social inclusion of children, potentially leading to emotional and behavioral problems, especially internalizing ones. Research from Korea proves that eight and nine-year-old children with DCD struggle with initiating and maintaining friendships, not only at school, but also at home with their parents. A lack of positive self-regard and low confidence in personal decision-making are common. However, it is promising that emotional behavioral issues in these children were found to decrease when the quality of their motor coordination is improved [35], so it is important to monitor negative psychological and social manifestations into adulthood [34]. Given all of the above, psychological support is considered to be crucial for individuals with DCD as other types of treatment [33].

In terms of physical health, children with DCD are often overweight or obese (OR 1.79–4.23) with compromised

physical fitness and therefore body mass index should be part of their general physical exam [9]. In addition, parent-reported symptoms of DCD are common in childhood epilepsy, which may be associated with additional stigmatization early and later in life [36, 37].

In practice, DCD is usually not considered in people with intellectual disability, because in that case the motor deficit must be significantly greater than the deficit that would be expected in a certain category of intellectual disability (mild, moderate, severe, profound). Although this may pose a problem, a formal diagnosis of DCD facilitates access to appropriate support, interventions and treatment and may shed light on shared underlying mechanisms [2]. Procedural learning and motor control deficits in the DCD may be secondary to several neural network dysfunctions (cortico-striatal and cortico-cerebellar), which may have relevance in cognitive and motor functioning later in adulthood [38, 39]. Other comorbid conditions that occur with DCD include various problems in learning and behavior, difficult acquisition of academic skills of reading, writing and following spelling rules, deficit of social communication and social interaction in the sense of difficult social reciprocity and problematic non-verbal communication [40].

TREATMENT

Interventions designed to improve motor performance for children with DCD have numerous components and differ in type, intensity, duration and frequency. When planning the intervention program, it is recommended to take into account both the "strengths" and "weaknesses" of the child in order to improve the quality of motor functions and execution of activities. Such a protocol improves the chance for the most pronounced functional independence in self-care [41]. However, if not all criteria for DCD are met, but there are motor problems in performing activities, the child should be included in various developmental and stimulating activities within his or her environment. This is especially important for children younger than five years who show significant motor dysfunctions but do not meet all the diagnostic criteria needed to diagnose DCD [13].

Often recommended interventions for children with DCD include a combination of *task-oriented interventions and interventions focused on reducing impairment and improving body function and structure*. Combining these two types of interventions in the treatment has a greater effect on improving the quality of motor skills than any of the prevailing interventions implemented in isolation [42]. *Task-oriented interventions* are motor activities or motor programs designed to improve the adoption and performance of a specific functional motor task [42, 43]. These interventions are based on theories of motor control and motor learning, using the concepts of active participation and increasing task demands [44]. In the literature, there are four methods of task-oriented intervention related to DCD:

1. Motor Skill Training (exercise and repetition of voluntary body movements in order to achieve the correct execution of a motor task, which achieves functionality and maximum participation within the environment) [45];
2. Neuromotor Task Training (uses individualized simplification of fine or gross motor activities into smaller components, thus enhancing the success of the individually performed step, until the child generalizes the motor skills needed to achieve the goal) [46];
3. Cognitive Orientation to Daily Occupational Performance (acquiring motor skills through the formation of problem-solving strategies, using behavioral and cognitive learning theories) [47];
4. Motor Imagery (a new cognitive approach by which the child practices or simulates a targeted motor activity) [48].

Among the different treatment approaches, the most talked about is the importance of cognition for the effect of intervention in children with DCD. The most effective part of the intervention is a process that obligatorily includes cognitive engagement, that is, a process that enables children to acquire, process, combine, plan and construct information [49]. New cognitive training methods prove that appropriate exercise programs are important for the safe and efficient performance of activities of daily living in children with DCD. These methods include exercises related to mental processes such as perception, memory, attention and planning [50].

Interventions used to reduce impairment and improve body functions and structures are called process-oriented approaches. The strategy of these interventions is based on the fact that improvement in basic motor deficits will lead to changes in motor performance [45].

In the literature, there is no clearly prescribed dosage with which the intervention should be carried out. The dosage of interventions should be based on the ability of the child with DCD to exercise at home, in kindergarten/school and in a health facility. Achieving short-term goals requires a very frequent schedule of exercises, which is adapted to the complexity of the goal. The exercise schedule should be organized in the range of two to five times a week, so that the set individualized goal can be achieved in about nine weeks. The recommended duration of one intervention in the literature ranges from 10 minutes to six hours per day [42]. The treatment of fine motor skills is usually significantly more time-intensive than the training of gross motor skills [13].

Within the treatment, it is important to note that multidisciplinary collaboration with clinicians from different fields can be extremely beneficial for people with DCD [51]. A multidisciplinary model could allow experts from different fields to contribute to the creation of treatments for each of the different difficulties present in DCD, in relation to motor, cognitive and secondary symptoms. This approach would significantly help to better understand the DCD and finally confirm its extraordinary complexity [52].

CONCLUSION

DCD is a neurodevelopmental disorder that occurs in 5–6% of children. The exact etiology of DCD is unknown, but it has been proven that multiple areas of the brain are affected, with clear genetic and environmental contributions. To be diagnosed with DCD, all four ICD-11/DSM-5 criteria must be met. The effects of motor dysfunction are manifested in the poor performance of daily activities and academic tasks. Comorbid conditions that occur in DCD are ASD, ADHD, and SLI.

Task-oriented interventions and interventions focused on reducing impairment and improving body function and structure are first-choice interventions that should be implemented with high frequency with children with DCD. Given that DCD is a very complex condition, it is necessary to form a multidisciplinary team, which will treat the multiple consequences of DCD and other related problems through specialized interventions.

ACKNOWLEDGMENT

This paper was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (contract number 451-03-66/2024-03/200096).

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

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Развојни поремећај координације – клиничке карактеристике и терапијске опције

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САЖЕТАК

Развојни поремећај координације представља неуроразвојни поремећај који се углавном препознаје након пете године живота, али може имати целоживотне последице на моторику, координацију и когницију. Критеријуми за постављање дијагнозе односе се на извођење координисаних моторичких вештина испод очекиваног у односу на хронолошку доб, дефицит моторичких вештина који значајно и перзистентно омета активности свакодневног живота, почетак симптома у раном развојном периоду и недостатак моторичких вештина који се не може објаснити интелектуалном ометеношћу или неким другим неуролошким стањима која утичу на покрете. Ова клиничка слика често је коморбидна са поремећајем пажње, са хиперактивношћу, поремећајем из спектра аутизма и неким другим неуроразвојним поремећајима. Протежирајуће интервенције за развојни поремећај координације укључују интервенције оријентисане на задатак, као и интервенције фокусиране на смањење оштећења и побољшање телесне функције.

Циљ рада је да сумира специфичности развојног поремећаја координације везане за дијагностичке критеријуме, епидемиологију, етиологију и коморбидитете, као и да прикаже савремене терапијске опције.

Кључне речи: развојни поремећај координације; дијагностички критеријуми; коморбидитет; интервенција оријентисана на задатак

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 публиковање. Радови објављени у СА се не хонорарашу. 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 лењиру 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 користити 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. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). 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 Хелсиншком 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 *SCIndeks 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 синтагме 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 публиковање.

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 ± 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 (°*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 CA 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 прихватати 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 чланка 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 видеоприказа у *e*-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 сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене 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 графикона. 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 графикона 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 индексиран 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 разматран за објављивање у часопису *Српски архив за целокупно 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 целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

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ISSN 0370-8179
ISSN Online 2406-0895
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ISSN 0370-8179
ISSN Online 2406-0895
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Народна библиотека Србије, Београд

61(497.11)

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Двомесечно. - Текст на енгл. језику. - Има суплемент или прилог: Српски архив за целокупно лекарство. Суплемент = ISSN 0354-2793. - Друго издање на другом медијуму: Српски архив за целокупно лекарство (Online) = ISSN 2406-0895
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COBISS.SR-ID 3378434

The Journal Serbian Archives of Medicine is indexed in: Science Citation Index Expanded, Journal Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journal, DOI Serbia

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