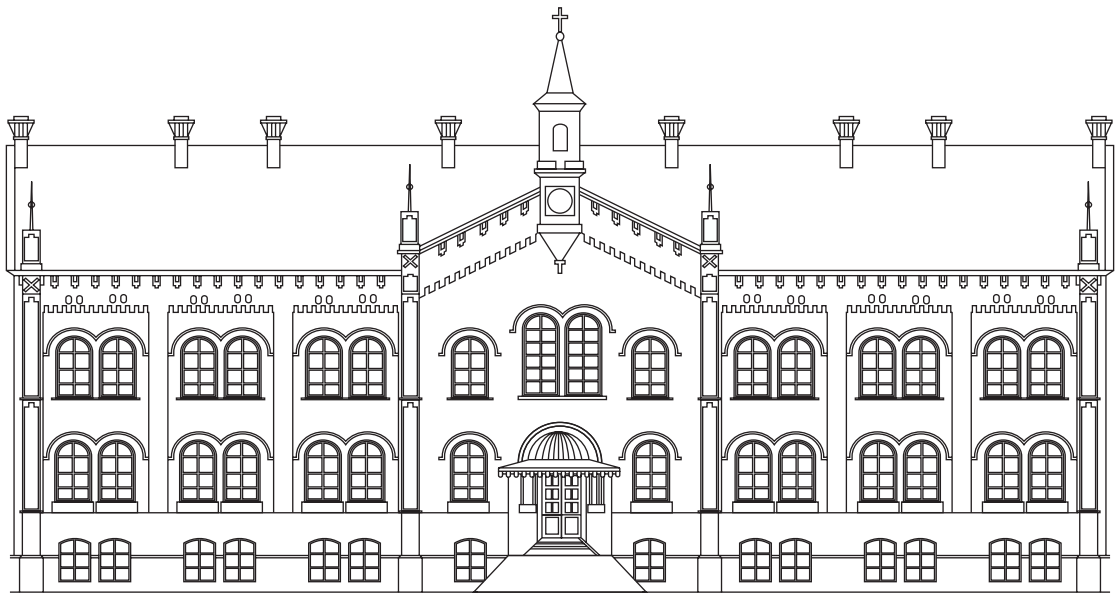
SRP ARH CELOK LEK

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

COBISS.SR-ID 3378434
UDC 61(497.11)

СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА



SERBIAN ARCHIVES
OF MEDICINE

JOURNAL OF THE SERBIAN MEDICAL SOCIETY

VOLUME 151 · MARCH–APRIL 2023 · ISSUE 3–4

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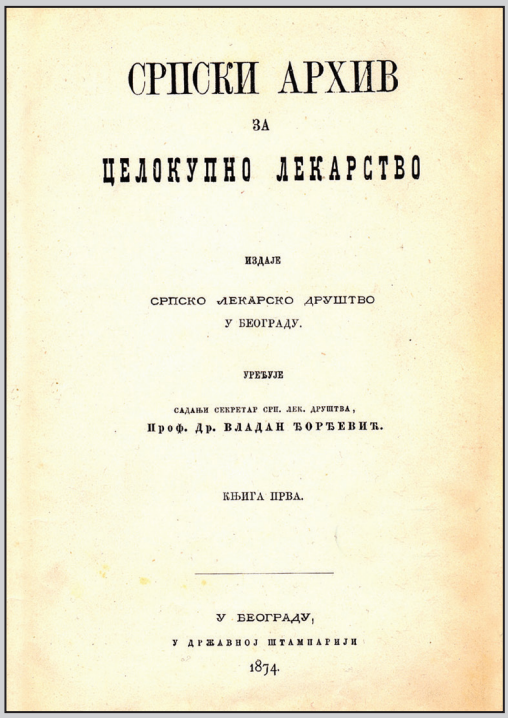

СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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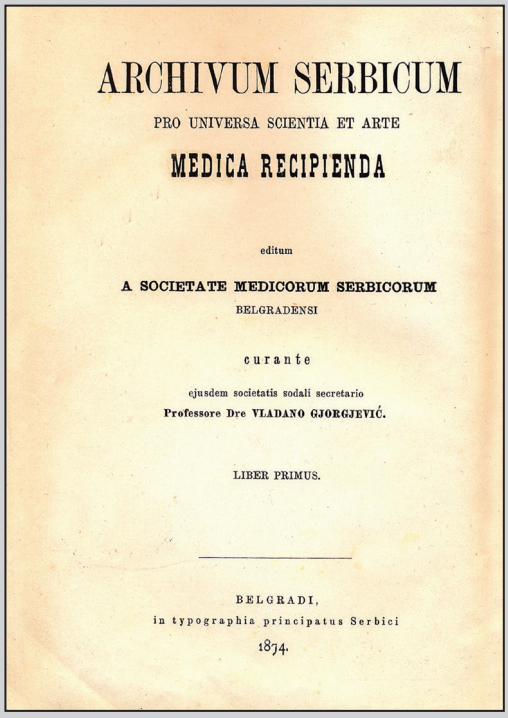
У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



ARCHIVUM SERBICUM

PRO UNIVERSA SCIENTIA ET ARTE

MEDICA RECIPIENDA

editum

A SOCIETATE MEDICORUM SERBICORUM

BELGRADENSI

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LIBER PRIMUS.

BELGRADI,

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1874.

The title page of the first journal volume in Latin

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

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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

Српски архив за целокупно лекарство

ГОДИШТЕ 151 МАРТ–АПРИЛ 2023. СВЕСКА 3–4

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.

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Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
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Српски архив
Краљице Наталије 1, 11000 Београд, Србија
Телефон: +381 (0)11 409 27 76
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ПРЕТПЛАТА И ЕКСПЕДИЦИЈА
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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 2023. године помогло је Министарство науке, технолошког развоја и иновација Републике Србије.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
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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 Миловановић
Корице: *MaxNova Creative*

Штампа: ЈП „Службени гласник", Београд

Тираж: 850 примерака

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

VOLUME 151 MARCH–APRIL 2023 ISSUE 3–4

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.

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Serbian language editor: Divna Prodanović
English language editors: Mirko Rajić, Ana Milovanović
Cover & Logo: MaxNova Creative

Printed by: JP "Službeni glasnik", Belgrade

Circulation: 850 copies

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EDITORIAL OFFICE
Serbian Archives of Medicine
Kraljice Natalije 1, 11000 Belgrade, Serbia
Phone: +381 (0)11 409 27 76
+381 (0)11 409 44 79
E-mail: office@srpskiarhiv.rs
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SUBSCRIPTION AND DISTRIBUTION
Serbian Medical Society
Džordža Vašingtona 19, 11000 Belgrade
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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 2023 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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ORIGINAL ARTICLES • ОРИГИНАЛНИ РАДОВИ

DOI: https://doi.org/10.2298/SARH221221022B
UDC: 331.225:614.253.5(470)"2020"; 616.98:578.834]:331.2

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

COVID-related incentive payments to healthcare workers

Irina Bocharova[1], Alexander Rymanov[2]

[1]Oryol State Agrarian University named after N.V. Parakhin, Oryol, Russia;
[2]Russian Presidential Academy of National Economy and Public Administration, Novosibirsk, Russia

SUMMARY
Introduction/Objective The study estimates the associations between the key pandemic indicators and the allocation of COVID-19-related bonus and welfare payments to Russian healthcare workers.
Methods The study uses regression analysis.
Results The study examines two consecutive types of COVID-19-related bonus payments: (1) incentive payments (in 2020) and (2) welfare payments (in 2020–2022). Concerning incentive payments (type 1), the study supports hypotheses regarding the association between the number of persons infected with COVID-19 in a relevant region and the actual/estimated amount of budget transfers to a relevant region for bonus payments to medical workers (a) for special working conditions and additional workload and (b) for performing particularly important work. As for welfare payments (type 2), the study supports hypotheses regarding the association between (1) COVID-19 cases, (2) COVID-19 recoveries, and (3) the fiscal year-end closeout and the amount of welfare payments.
Conclusion The main channel for financing payments to medical workers is a special welfare payment through the system of the Social Insurance Fund of the Russian Federation. This source exceeds the estimated total transfers and subsidies for similar purposes in 2020.
The study tests hypotheses regarding the association between the key pandemic indicators and the size of various types of budget transfers for bonus and welfare payments to medical workers.
Keywords: novel coronavirus infection; welfare payment; doctors; nurses; junior medical staff

INTRODUCTION

Incentives for health workers in connection with the spread of the novel coronavirus infection COVID-19 has been provided by the Russian authorities almost from the first months of the pandemic.

The maximum peak number of medical workers involved in the fight against COVID-19 was 550,000 people, including doctors – 156,000 people, a middle medical staff – 318,000 people, a junior medical staff – 76,000 people [1].

Russian regulations regarding the allocation of transfers to medical workers describe the methods of allocation transfers to the regions. The regulatory framework in this area has already been partially updated: some of the regulations in force in 2020 have lost their force [2, 3], other regulations, in contrast, have either replaced or expanded the scope of regulation of the issue under consideration, or continue to be in force [4, 5].

Academic papers reflect the issues under consideration.

Received • Примљено: December 21, 2022
Revised • Ревизија: February 11, 2023
Accepted • Прихваћено: February 28, 2023
Online first: March 3, 2023

Correspondence to:
Alexander RYMANOV
RANEPA Academy
Nizhegorodskaya ul. 6
Novosibirsk 630102, Russia
rymanov-ay@ranepa.ru

Best practices for paying COVID-19 bonuses to healthcare workers

Williams et al. [6] review the measures taken by European countries to pay bonuses to health workers involved in countering COVID-19. Payments are made either in the form of a one-time bonus, or in the form of monthly bonus payments. Reed [7] compares the level of bonuses paid to health workers and concludes that in the UK, doctors are paid more and nurses are paid at the OECD average.

Besley et al. [8] make policy recommendations to the UK government. They argue for the advisability of direct payments to health workers, dividing workers into those directly involved with the coronavirus and those not directly involved (GBP 1000 and GBP 500, respectively). Adeyemo et al. [9] report on the results of interviews with 45 health workers in the U.S. The study contains both positive and negative reactions from workers to bonuses received for emergency working conditions during the pandemic. Kovaleva et al. [10] study the stimulating component of remuneration in the healthcare institution.

Giubilini and Savulescu [11] advocate ethical principles (autonomy, fairness, responsibility, and utility) for bonus payments to healthcare workers for their work during the pandemic.

Bonuses for nursing staff

Gray et al. [12] identified motivators for nurses in the process of providing healthcare during the pandemic. A survey of 110 nurses at the

U.S. found that respondents were least motivated by hazardous work bonuses. Bitencourt et al. [13] examine the role of nurses in counteracting pandemic in a philanthropic clinic in Brazil and point to the payment of incentive bonuses. Hersh [14], based on a survey of nurses at U.S. hospitals, assesses the negative impact of COVID-19 on their working conditions.

Rural and remote areas

Strasser and Strasser [15] express concern that rural communities have limited access to resources and health services amid the pandemic. They advocate the need to stimulate health workforce in rural and remote areas in the form of providing guaranteed income, housing, various compensation packages, payment of bonuses and retention payments. Shrestha and Kunwar [16] report that frontline health workers in Nepal have not received government-promised payments and compensations for working amid the pandemic. In private clinics, the situation is even worse: medical workers are forced to either accept a pay cut or quit.

Medical students' motivational statements

Astorp et al. [17] conducted a survey of medical students at one of the Danish universities. The study assesses the motivational statements for their involvement as emergency workers. The students ranked 'salary' as one of the last motivational statements (10th out of 11 motivational statements).

Local practices for financing payments to health workers

Sumin et al. [18] consider the regulation of incentive, welfare, and insurance payments to medical workers in the context of COVID-19. Kadyrov [19] considers the legal regulation of special welfare payments to medical personnel. Shalberkina [20], Gubina [21], Puzin et al. [22] consider the legal regulation of welfare support for medical workers during the period of the novel coronavirus infection. Kadyrov and Chililov [23] consider the issues of informatization and information exchange in the process of supporting the implementation of welfare payments to medical workers in connection with COVID-19. Anisimova et al. [24] consider the implementation of social benefits paid to employees of medical organizations and employees of social service organizations in connection with COVID-19.

Underpayment and late payment of incentive payments to medical personnel

In connection with complaints from medical personnel about problems in receiving incentive payments in 2020, the Accounts Chamber of the Russian Federation, together with the control and accounting bodies of the constituent entities of the Russian Federation, conducted unscheduled inspections in 2020 [25]. As a result of the inspections, underpayments of 330.6 million rubles ($4.49 million) to medical workers were identified.

The main indicators of disease incidence recorded by sectoral agencies and organizations are the number of COVID-19 cases, the mortality rate, and others [26]. However, the use of these indicators in planning and allocating payments to health workers is somewhat difficult because they are not known in advance. The use of predictive statistical models (growth dynamics) that predict these indicators for planning and allocating incentive payments is also of little practical use, as these models have been (and continue to be) periodically reviewed and adjusted. In Russian practice, the historical level of average wages in a given region was used at the initial stage of planning the financing of payments to healthcare workers. As data become available on the current values of the COVID-19 indicators, retrospective estimates of the associations between these indicators (COVID-19 cases, recovering COVID-19 patients) and the volume of payments to health workers become possible. This study therefore aims to make such estimates.

METHODS

The study uses regression analysis in the field of health financing.

Allocations were set as a percentage of the average monthly salary in the region concerned (Table 1).

Table 1. Budget transfers for incentive payments (expressed as a percentage of the average monthly salary)

Healthcare professionals	Types of medical care		
	Emergency medical care	Primary healthcare	Specialized medical care in an inpatient setting
Doctors	80	80	100
Middle medical staff	40	40	50
Junior medical staff	20	20	30

The study is based on an analysis of observational data on payments to healthcare workers related to the coronavirus pandemic. Official data on estimated and actual payments to health workers are used in the study [2, 27, 28, 29].

Hypotheses to test

The study tests the following hypotheses (Table 2).

Hypothesis 1

H_1: the association between the number of people infected with COVID-19 in a relevant region in 2020 and the estimated amount of budget transfers to a relevant region for bonus payments to medical staff for special working conditions and additional workload in 2020 is statistically significant.

Table 2. Study hypotheses description

Hypotheses	Variables				
	Dependent				Independent
	Type of budget payment				
Bonus payments (2020)					
	Budget transfers to a relevant region for bonus payments to medical workers		Estimated or actual type of amount		
	for special working conditions and additional workload	for performing critical work	estimated	actual	
H_1	+		+		the number of persons infected with COVID-19 in a relevant region
H_2	+			+	
H_3		+	+		
H_4		+		+	
H_5	+	+		+	
Special Welfare Payment (SWP) (2020–2022)					
H_6	the total volume of payments of the SWP to medical workers in the whole country in a given calendar month			+	the number of people infected with COVID-19
H_7				+	the number of people recovered from COVID-19
H_8				+	the fiscal year-end closeout

Hypothesis 2

H_2: the association between the number of persons infected with COVID-19 in a relevant region in 2020 and the actual amount of budget transfers to a relevant region for bonus payments to medical workers for special working conditions and additional workload in 2020 is statistically significant.

Hypothesis 3

H_3: the association between the number of persons infected with COVID-19 in a relevant region in 2020 and the estimated amount of budget transfers to a relevant region for bonus payments to medical workers for performing critical work in 2020 is statistically significant.

Hypothesis 4

H_4: the association between the number of persons infected with COVID-19 in a relevant region in 2020 and the actual amount of budget transfers to a relevant region for bonus payments to medical workers for performing critical work in 2020 is statistically significant.

Hypothesis 5

H_5: the association between the number of persons infected with COVID-19 in a relevant region in 2020 and the actual amount of budget transfers to a relevant region for bonus payments to medical workers (a) for special working conditions and additional workload and (b) for performing critical work in 2020 is statistically significant.

Hypothesis 6

H_6: the association between the number of persons infected with COVID-19 and the total volume of payments of the Special Welfare Payment to medical workers in the whole country in a given calendar month is statistically significant.

Hypothesis 7

H_7: the association between the number of persons recovered from COVID-19 and the total volume of payments of the Special Welfare Payment to medical workers in the whole country in a given calendar month is statistically significant.

Hypothesis 8

H_8: the association between the fiscal year-end closeout and the total volume of payments of the Special Welfare Payment to medical workers in the whole country in a given calendar month is statistically significant.

Hypotheses 1–5 test the association between key indicators of the pandemic and incentive payments, hypotheses 6–8 test the association between key indicators of the pandemic and welfare payments (Table 2). The study was approved by the Ethics Committee of the SibMed Medical University (No. 9390) and conducted following the Declaration of Helsinki.

RESULTS

Hypotheses testing

Consider testing hypotheses (Figure 1).

Hypothesis 1

To test this hypothesis, a quadratic regression model was used:

$$y = \beta_0 + \beta_1 x_1 + \beta_{11} x_{11}^2 + \epsilon \quad (1)$$

where y is the share of the estimated amount of budget transfers to a relevant region for bonus payments to medical workers for special working conditions and additional workload in 2020, in the total amount of these transfers in the Russian Federation; x is the share of the number of people infected with COVID-19 in a relevant region in the total number of people infected with COVID-19 in the Russian Federation in 2020.

The fitted regression model is as follows:

$$y = -0.00482817 + 1.56884 x_1 - 0.11492\, x_{11}^2 \quad (2)$$

The model as a whole is significant (Table 3).

Table 3. Analysis of variance

Source	Sum of squares	df	Mean square	F-value	p-value, Prob > F
Model	53.49	2	26.74	36.08	< 0.0001
x	2.3	1	2.3	3.1	0.0819
x^2	5.82	1	5.82	7.85	0.0063
Residual	60.03	81	0.74	-	-

Table 4. Summary of fit

R^2	0.4712
R^2 adj	0.4581
Adeq precision	32.248
Std. dev.	0.86
Mean	1.19

Table 4 shows that 46% of the variability in the response variable is explained by the independent variable (Table 4, Figure 1).

The hypothesis H_1 is supported.

Hypothesis 2

To test this hypothesis, a quadratic regression model was used:

$$y = \beta_0 + \beta_1 x_1 + \beta_{11} x_{11}^2 + \epsilon \quad (3)$$

where y is the share of the actual amount of budget transfers to a relevant region in the total amount of transfers in the Russian Federation, x is the share of the number of persons infected with COVID-19 in a relevant region in the total number of persons infected with COVID-19 in the Russian Federation in 2020.

The fitted regression model is as follows:

$$\text{Ln}\, y = -1.39022 + 1.65447 x_1 - 0.16485\, x_{11}^2 \quad (4)$$

In this model, both the independent variable and the model as a whole are significant (Table 5).

Table 5. Analysis of variance

Source	Sum of squares	df	Mean square	F-value	p-value, Prob > F
Model	34.24	2	17.12	45.34	< 0.0001
x	8.03	1	8.03	21.26	< 0.0001
x^2	11.97	1	11.97	31.71	< 0.0001
Residual	30.59	81	0.38		

Table 6. Summary of fit

R^2	0.5282
R^2 adj	0.5165
Adeq precision	35.487
Std. dev.	0.61
Mean	-0.20

Table 6 shows that 52% of the variability in the response variable is explained by the independent variable.

The hypothesis H_2 is supported.

Hypothesis 3

To test this hypothesis, a quadratic regression model was used:

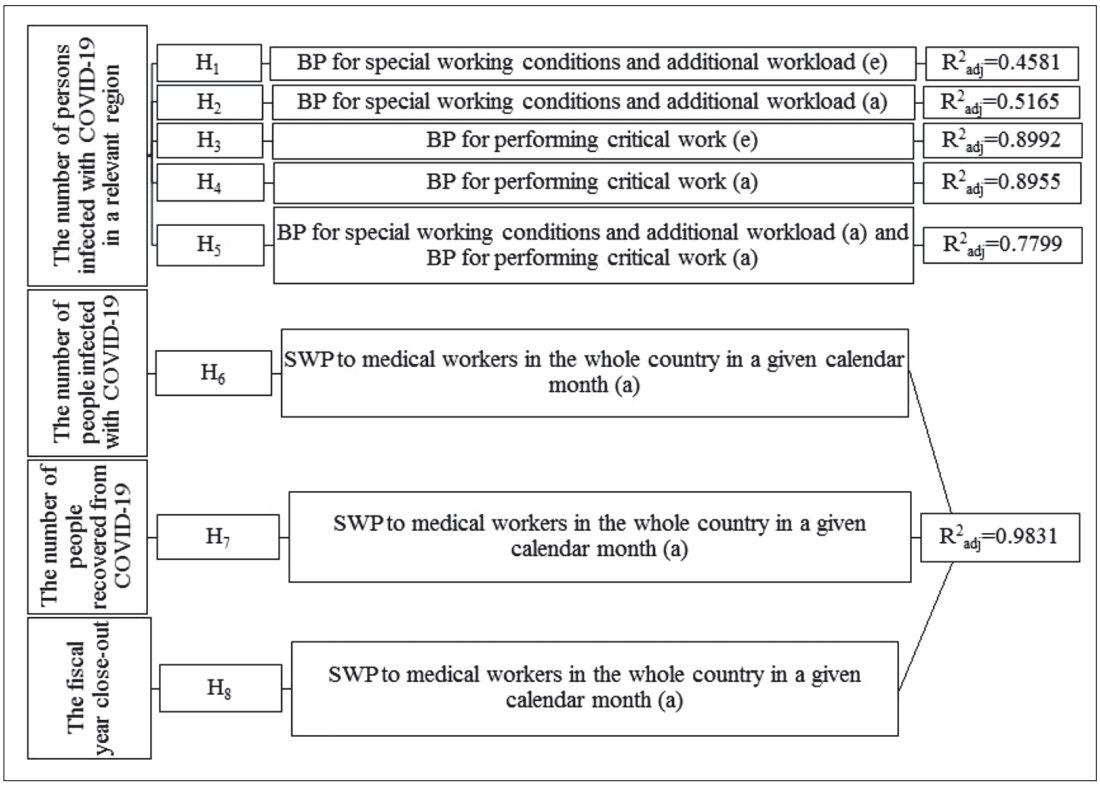

Figure 1. Hypotheses testing

BP – bonus payments; SWP – special welfare payment; e(a) – estimated (actual) type of amount

$$y = \beta_0 + \beta_1 x_1 + \beta_{11} x_{11}^2 + \epsilon \quad (5)$$

where y is the share of the estimated amount of budget transfers to a relevant region for bonus payments to medical workers for performing critical work in 2020, in the total amount of these transfers in the Russian Federation; x is the share of the number of people infected with COVID-19 in a relevant region in the total number of people infected with COVID-19 in the Russian Federation in 2020.

The fitted regression model is as follows:

$$y = +0.14615 + 1.06664 x_1 - 0.023904\ x_{11}^2 \quad (6)$$

In this model, both the independent variable and the model as a whole are significant (Table 7).

Table 7. Analysis of variance

Source	Sum of squares	df	Mean square	F-value	p-value, Prob > F
Model	176.12	2	88.06	375.74	< 0.0001
x	134.82	1	134.82	575.3	< 0.0001
x^2	15.22	1	15.22	64.96	< 0.0001
Residual	19.22	82	0.23	-	-

Table 8. Summary of fit

R^2	0.9016
R^2 adj	0.8992
Adeq precision	127.737
Std. dev.	0.48
Mean	1.18

Table 9. Analysis of variance

Source	Sum of squares	df	Mean square	F-value	p-value, Prob > F
Model	183.61	2	91.81	361.01	< 0.0001
x	135.33	1	135.33	532.16	< 0.0001
x^2	19.44	1	19.44	76.43	< 0.0001
Residual	20.85	82	0.25	-	-

Table 10. Summary of fit

R^2	0.8980
R^2 adj	0.8955
Adeq precision	122.815
Std. dev.	0.5
Mean	1.18

Table 8 shows that 90% of the variability in the response variable is explained by the independent variable (Table 8).

The hypothesis H_3 is supported.

Hypothesis 4

To test this hypothesis, a quadratic regression model was used:

$$y = \beta_0 + \beta_1 x_1 + \beta_{11} x_{11}^2 + \epsilon \quad (7)$$

where y characterizes the share of the actual amount of budget transfers to a relevant region for performing critical work, in the total amount of these transfers in the Russian Federation, x is the share of the number of persons infected with COVID-19 in a relevant region in the total number of persons infected with COVID-19 in the Russian Federation in 2020.

The fitted regression model is as follows:

$$y = +0.080773 + 1.14702 x_1 - 0.027010 x_{11}^2 \quad (8)$$

In this model, both the independent variable and the model as a whole are significant (Table 9).

Table 10 shows that 90% of the variability in the response variable is explained by the independent variable.

The hypothesis H_4 is supported.

Hypothesis 5

To test this hypothesis, a linear regression model was used:

$$y = \beta_0 + \beta_1 x_1 + \epsilon \quad (9)$$

where y characterizes the share of the actual amount of budget transfers to a relevant region (a) for special working conditions and additional workload and (b) for performing critical work, in the total amount of these transfers in the Russian Federation, x is the proportion of persons infected with COVID-19 in a relevant region in the total number of persons infected with COVID-19 in the Russian Federation in 2020.

The fitted regression model is as follows:

$$y = +0.23152 + 1.08314\ x_1 \quad (10)$$

In this model, both the independent variable and the model as a whole are significant (Table 11).

Table 11. Analysis of variance

Source	Sum of squares	df	Mean square	F-value	p-value, Prob > F
Model	88.81	1	88.81	295.15	< 0.0001
x	88.81	1	88.81	295.15	< 0.0001
Residual	24.67	82	0.30	-	-

Table 12. Summary of fit

R^2	0.7826
R^2 adj	0.7799
Adeq precision	97.853
Std. dev.	0.55
Mean	1.19

Table 12 shows that 78% of the variability in the response variable is explained by the independent variable.

The hypothesis H_5 is supported.

Hypotheses H_6–H_8

To test H_6–H_8 hypotheses, a linear regression model is used:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_1 x_2 + \beta_5 x_2 x_3 + \beta_6 x_1 x_3 + \epsilon \quad (11)$$

where y is the volume of payments of the Special Welfare Payment to medical workers in the Russian Federation as a whole in a given calendar month,

x_1 is the number of persons infected with COVID-19 in a given calendar month,

x_2 is the number of persons recovered from COVID-19 in a given calendar month,

x_3 is the indicator of the last two months of the fiscal year (the categorical variable describing the fiscal year-end closeout, $x_3 = 0$ or $x_3 = 1$),

x_1x_2 is the x_1x_2 interaction term,

x_2x_3 is the x_2x_3 interaction term,

x_1x_3 is the x_1x_3 interaction term.

The fitted regression model for the fiscal year-end closeout ($x_3 = 1$) is as follows:

$$y^3 = 284502 - 298.20371 \times x_1 + 80.33769 \times x_2 - 0.00276184 \times x_1 \times x_2 \quad (12)$$

The fitted regression model for the fiscal year (except the months of the closeout) ($x_3 = 0$) is as follows:

$$y^3 = 938.32682 + 2.78643 \times x_1 + 10.27625 \times x_2 - 0.00276184 \times x_1 \times x_2 \quad (13)$$

The power response transformation is used.

In these models, independent variables and interaction terms are significant (Table 13).

Table 13. Analysis of variance

Source	Sum of squares	df	Mean square	F-value	p-value, Prob > F
Model	16770000000	6	2795000000	184.69	< 0.0001
x_1	4133000000	1	4133000000	273.11	< 0.0001
x_2	365500000	1	365500000	24.15	0.0003
x_3	1705000000	1	1705000000	112.66	< 0.0001
$x_1 x_2$	88030000	1	88030000	5.82	0.0314
$x_1 x_3$	3973000000	1	3973000000	262.51	< 0.0001
$x_2 x_3$	311900000	1	311900000	20.61	0.0006
Residual	196800000	13	15130000	-	-
Cor total	16970000000	19	-	-	-

Table 14. Summary of fit

R^2	0.9884
R^2 adj	0.9831
Adeq precision	49.171
Std. dev.	3890.36
Mean	17565.94

Table 14 shows that 98% of the variability in the response variable is explained by independent variables.

The hypotheses H_6–H_8 are supported.

DISCUSSION

Inconsistent coverage of health workers with incentive payments in 2020 across regions

The Accounts Chamber of the Russian Federation [25] expresses concern about "significant disparities" (between regions) in the number of medical personnel receiving incentive payments. This is understandable, as the allocation of budget transfers is based on the number of people covered by compulsory health insurance in the respective region of the Russian Federation.

In the first months of the pandemic, in the conditions of insufficient information about the coronavirus itself, lack of time, lack of forecasts on the estimated number of cases in the relevant region of the Russian Federation, the use of this aggregate indicator was quite appropriate. The final recipients of incentive payments (medical workers) were set as a percentage of the average monthly salary in the relevant region of the Russian Federation according to the data for the previous year.

Bonus payments to Russian healthcare workers related to COVID-19 are consistent with general trends in the assignment of additional payments to healthcare workers for extraordinary working conditions in various countries [6]. National healthcare systems use both periodic and lump-sum payments to healthcare workers.

At the same time, this study examined two types of periodic payments to healthcare workers – earlier payments (incentive payments, 2020) and current payments (welfare payments, 2020–2022). The transformation of incentive payments into welfare payments was largely due to differences in their taxation and the more favorable tax status (for healthcare workers as their recipients) of welfare payments.

The results of this study confirm the association between the key pandemic indicators and the volume of incentive and welfare payments.

Remote territories of some countries during the pandemic (at least in the initial period of the pandemic) experienced some limitations in funding for health workers [15, 16]. This study used not only aggregate data at the national level, but also data from individual areas of the country, including remote areas. The findings on the existence of the association between the key indicators of the pandemic and the level of payments are also valid for the remote areas of Russia.

CONCLUSION

The study provides support for hypotheses regarding the association between the key pandemic indicators and the size of various types of budget transfers to cover bonuses and benefits paid to medical staff.

Conflict of interest: None declared.

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Подстицајне исплате здравственим радницима у вези са ковидом

Ирина Бочарова[1], Александер Риманов[2]

[1]Орјолски државни аграрни институт „Н. В. Парахин", Орјол, Русија;
[2]Руска председничка академија државне привреде и јавне управе, Новосибирск, Русија

САЖЕТАК

Увод/Циљ Студија процењује утицај кључних индикатора пандемије на доделу бонуса везаних за ковид 19 руским здравственим радницима.

Методе Студија користи регресивну анализу.

Резултати Студија испитује две узастопне врсте исплата бонуса везаних за ковид 19: (1) исплату подстицаја (у 2020. години) и (2) исплату социјалне помоћи (2020–2022. године). Што се тиче исплате подстицаја (тип 1), студија подржава хипотезе у вези са утицајем броја особа заражених ковидом 19 у релевантном региону на стварни/процењени износ трансфера буџета у релевантан регион за исплату бонуса медицинским радницима (а) за посебне услове рада и додатно оптерећење и (б) за обављање посебно важних послова. Што се тиче исплате социјалне помоћи (тип 2), студија подржава хипотезе у вези са (1) случајевима ковида 19, (2) опоравком од ковида 19 и (3) обрачуном на крају фискалне године и износом исплате социјалне помоћи.

Закључак Главни канал за финансирање плаћања медицинским радницима је посебна исплата социјалне помоћи путем система Фонда за социјално осигурање Руске Федерације. Овај извор финансирања премашује процењени укупан износ трансфера и субвенција у 2020. години у сличне сврхе. Студија тестира хипотезе о повезаности кључних индикатора пандемије и величине различитих врста буџетских трансфера за исплату бонуса медицинским радницима у 2020.

Кључне речи: нова инфекција вирусом корона; исплата социјалне помоћи; лекари; медицинске сестре; млађе медицинско особље

DOI: https://doi.org/10.2298/SARH220712030B
UDC: 616.31-089.5

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Evaluation of the success of the modified Vazirani–Akinosi technique in comparison to the standard Vazirani–Akinosi technique – a randomized clinical trial

Jovana Bakalović[1], Ljiljana Stojčev[2], Bojan Janjić[2], Bojan Gačić[2]

[1]University of Belgrade, School of Dental Medicine, Belgrade, Serbia;
[2]University of Belgrade, School of Dental Medicine, Clinic for Oral surgery, Belgrade, Serbia

SUMMARY

Introduction/Objective The correct choice of local anesthesia should imply choosing the simplest technique, with maximum anesthesia and minimal discomfort for the patient. The objectives of this research were to determine the efficacy of the modified Vazirani–Akinosi technique (mVAt) in comparison to the standard one (VAt) and to compare the techniques regarding clinically relevant parameters.

Methods The research was conducted at the Clinic for Oral Surgery, School of Dental Medicine, University of Belgrade. A prospective, randomized, single-blinded clinical trial included 60 patients scheduled for surgical extraction of mandibular third molars. The first group of patients was anesthetized using mVAt, while the second group received anesthesia using VAt. Pain during injection, onset time, duration of anesthesia, and width of the anesthetized area were the evaluated parameters.

Results Out of 60 performed injections, 42 were successful, which proved to be statistically significant in comparison to 18 unsuccessful injections ($p = 0.047$). The failure rate of the buccal nerve (BN) anesthesia was statistically significantly lower in the mVAt group ($p = 0.030$). There was no statistically significant difference among the groups considering pain ($p = 0.114$), onset time ($p = 0.370$), and duration of anesthesia ($p = 0.628$).

Conclusion mVAt proved to be more successful regarding BN anesthesia. Considering other examined clinical parameters, both techniques showed similar performance.

Keywords: Vazirani–Akinosi technique; mandibular anesthesia; oral surgery

INTRODUCTION

Attaining complete numbness prior to every surgical procedure is imperative, which unequivocally indicates that local anesthesia is an essential part of everyday oral surgery practice. The correct choice of local anesthesia technique should consider the simplest technique to perform, with the maximum effect of anesthesia and minimal discomfort for the patient. Many surgical procedures in the mandible require anesthesia of the inferior alveolar nerve (IAN), lingual nerve (LN) and buccal nerve (BN). Frequent use in everyday clinical practice has led to the discovery and description of various techniques and their variations for achieving anesthesia of the nerves mentioned.

Pioneers in achieving inferior alveolar and lingual nerve block were surgeons, William S. Halstead and Richard J. Hall. Their discovery was based on the injection of cocaine solution near mandibular foramen, back in 1884 [1, 2]. Ever since, Halstead's technique of performing inferior alveolar nerve block has been considered a conventional method and is well known as conventional inferior alveolar nerve block (CIANB). This technique takes into consideration intraoral parameters to determine the place of needle insertion. After administration of the anesthetic solution, it provides anesthesia of the inferior alveolar and the lingual nerve.

However, the success of the conventional technique requires not only the dentist's experience but also a high level of cooperation with the patient [1, 2]. Since patients usually face fear of both the procedure and anesthesia, the contemporary literature often states that the patient's overall impression of the doctor and the performed procedure is often and mostly determined by the success of anesthesia [3, 4].

The precision of determining the injection site vastly depends on the recognition of anatomical structures, which are prone to many variations among individuals. Edentulous patients with advanced bone resorption, patients with very strong cheek or tongue muscles, as well as large fat pads, are just some of the cases which may be encountered that can be more difficult to accurately determine the site of a needle insertion [1]. This extensively explains the data from the literature, indicating a relatively high failure rate of CIANB, from 15% to 25% [1, 5–12]. Frequent variability of the position, shape, and size of the mandibular foramen on the inner side of the mandibular ramus as well as the position and shape of the mandibular lingula may also contribute to the failure of CIANB [13]. Another factor which should be taken into consideration while applying this technique is the anteroposterior diameter of the ramus, and it's divergence [14]. Collateral sensory innervation of mandibular teeth, which in some cases

Received • Примљено: July 12, 2022
Revised • Ревизија: March 2, 2023
Accepted • Прихваћено: March 17, 2023
Online first: March 21, 2023

Correspondence to:
Correspondence to:
Bojan GAČIĆ
Clinic for Oral Surgery
Doktora Subotića 4
11000 Belgrade, Serbia
gacicb67@gmail.com

may originate from the mylohyoid nerve, can also affect the unpredictable outcome of CIANB [8, 9, 15, 16]. In addition, this technique often shows positive aspiration, since the inferior alveolar nerve is in close proximity to the inferior alveolar artery [1, 2, 7, 15, 17, 18, 19]. The artery is usually positioned posteriorly or posterolaterally in relation to the nerve, entering mandibular foramen together [15, 20].

Intending to improve on the Halstead's technique, which had been acknowledged as conventional, alternative techniques, commonly but inaccurately called mandibular anesthesia, have been described, among them the Vazirani–Akinosi (VA) technique. Vazirani introduced this technique into dental practice in 1960, while Akinosi presented a similar technique to the academic community in 1977 [1, 10]. In order to pay homage to Vazirani, the technique is known as the Vazirani–Akinosi technique.

Presenting the technique, in his original paper Akinosi [14] pointed out the ease of administration, shorter onset time, compared to other thus far described techniques, as well as the lowest intensity of pain during the injection and anesthetic solution deposition. The VA method has been described as a closed-mouth technique, which is stated to be an advantage when performed in patients with limited mouth opening [21, 22]. As stated by Akinosi, due to the closed-mouth position, the patient is unlikely to become apprehensive during the injection. In addition, a completely different approach and area of needle insertion reduce the possibility of provoking gag reflex in sensitive patients [1]. Unlike the conventional technique, it is stated that a correctly performed VA technique anesthetizes all three nerves important for surgical interventions in the mandible with a single injection [14]. Thus, additional injection for the BN is avoided, therefore additional traumatization of the tissues and the patient himself.

The often-mentioned information about the possible failure of anesthesia of the BN with the VA technique was the incentive to design a modification of this technique [8, 19, 23, 24].

The objectives of this research were to determine the efficacy of the modified in comparison to the standard VA technique, in terms of anesthesia of all three aforementioned nerves, and to compare the techniques regarding clinically relevant parameters such as pain during the injection, onset time, and duration of anesthesia.

METHODS

The research was conducted at the Clinic for Oral Surgery, School of Dental Medicine, University of Belgrade, Serbia, after the approval of the Ethics Committee was obtained.

Sixty adult patients who had been scheduled for surgical extraction of the mandibular third molars were included. Prior to the inclusion, all the patients had been informed about the procedure and written consent of participation was signed.

All participants were classified according to the American Society of Anesthesiologists (ASA) physical status classification system as ASA I and ASA II. Pregnant and breastfeeding women were excluded from the study, as well as patients who refused the consent to participate.

A prospective, randomized, single-blinded clinical trial was accomplished by patients randomly choosing number 1 or 2. Participants were allocated into two equal groups. The first group of patients was anesthetized using modified VA technique (mVAt), while the second, control group, was anesthetized using the standard VA technique (VAt).

All anesthetics were administered by the same doctor. The anesthetic of choice in all cases was 4% articaine (Septanest®, Septodont, Saint-Maur-des-Fossés, France) with epinephrine (1:100,000), and the needle gauge was 27G.

Standard Vazirani–Akinosi technique

With the mouth slightly open, the doctor palpates the front edge of the ramus with his finger (forefinger or thumb), while simultaneously retracting the cheek outwards. Before the insertion of the needle, the patient closes teeth lightly. The horizontally placed syringe is directed backwards and laterally as much as the maxillary dental arch and the alveolar ridge of the upper jaw allow. The needle is placed parallel to the occlusal plane, and at the height of the marginal gingiva of the teeth in the upper jaw. The puncture site is located in the mucosal fold between the maxillary tuberosity and the medial side of the mandibular ramus. After the puncture, the needle is directed laterally and parallel to the inner side of the ramus and inserted into the pterygomandibular space to a depth of 25–30 mm, where the anesthetic is deposited.

Modified Vazirani–Akinosi technique

The anatomical guidelines used to determine the puncture site as well as the method of needle insertion into pterygomandibular space do not differ from the described VAt. The difference between the mVAt and the VAt is reflected in the manner of anesthetic solution deposition. The mVAt implies deposition of the first dose of anesthetic solution (0.6 ml) at a depth of 25–30 mm. The needle is then withdrawn to a depth of 20–25 mm, where another third of the anesthetic solution is deposited. The last 0.6 ccm of the anesthetic is applied after withdrawing the needle another 5 mm, i.e., at a depth of 15–20 mm (Figures 1–4).

The parameters for evaluation were pain during injection, onset time, duration of anesthesia, width of the anesthetized area, and success of anesthesia. The pain was assessed by the patient using a numerical rating scale (NRS), from 0 to 10, with 0 meaning "no pain" and 10 meaning "worst pain imaginable." Additionaly, four-point verbal rating scale (VRS) was used (1 – no pain; 2 – mild pain; 3 – moderate pain; 4 – severe pain). The onset time was measured in seconds from the moment of the injection until the complete feeling of numbness was acquired. The duration of anesthesia was measured in minutes, from the moment of achieving complete anesthesia until the moment of sensibility restoration. The width of the anesthetized area was assessed subjectively, by the patient, stating the feeling of numbness in the innervation zones of the

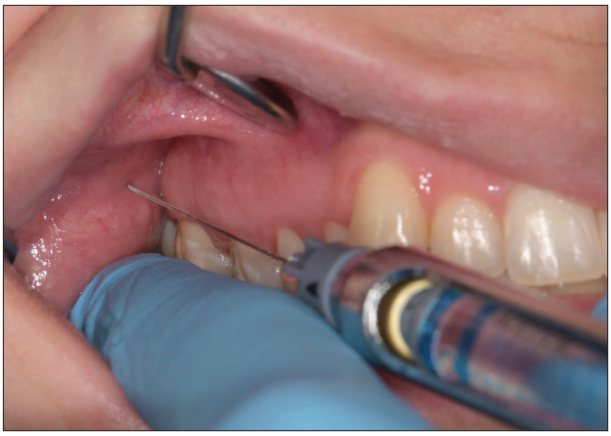

Figure 1. The puncture site and needle direction for modified Vazirani–Akinosi technique

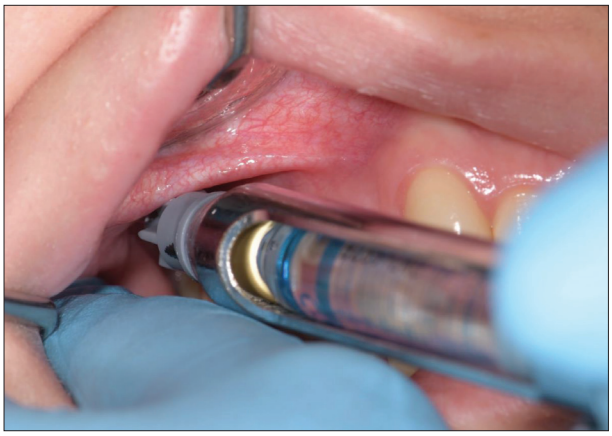

Figure 2. Deposition of the first dose of anesthetic solution (0.6 ml) at a depth of 25–30 mm within the pterygomandibular space

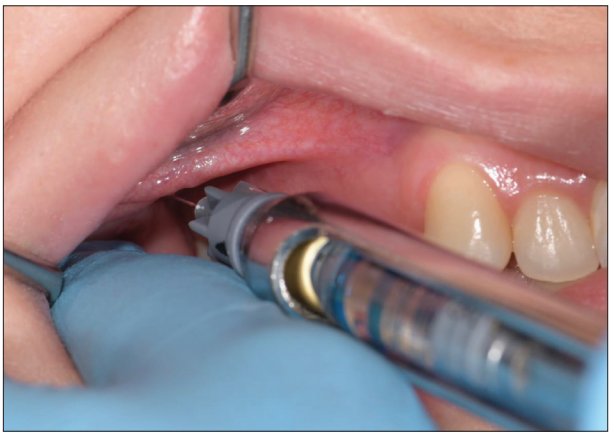

Figure 3. Deposition of the second dose of anesthetic solution (0.6 ml) at a depth of 20–25 mm within the pterygomandibular space

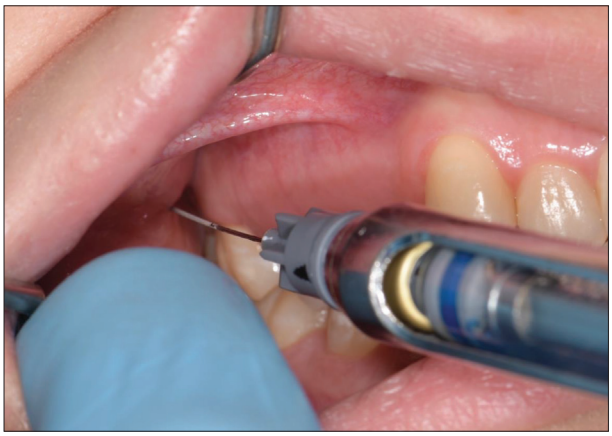

Figure 4. Deposition of the third dose of anesthetic solution (0.6 ml) at a depth of 15–20 mm within the pterygomandibular space

targeted nerves, and it was confirmed objectively, i.e., by a pin-prick test performed by the doctor. The test implied light pricks of mucosa in innervation zones of the targeted nerves with the dental probe. The width of the anesthetized area was considered adequate if the anesthesia included the innervation zones of IAN, LN, and BN. The injection was repeated before the surgery if failure to obtain adequate anesthesia occurred. If the failure implied only inadequate anesthesia in the BN innervation zone, only an additional BN block was administered. Cases that did not require any additional injection were considered successful.

Data analysis was carried out using IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY, USA). The level of significance was set at 0.05. Normality of distribution was tested using Kolmogorov–Smirnov test. Depending on the variable, parametric (t-test) or nonparametric (Mann–Whitney) tests were used, as well as measures of central tendency and dispersion. For categorical variables, the frequency and percentage in each category were presented and analyzed with a χ^2 test.

RESULTS

The study included 60 patients, aged 18–27 years. The average age of participants in the first group was 20.67 ± 2.4 years, and in the second group 21.50 ± 2.6 years, without a statistically significant difference (p = 0.224). There was a total of 33 female and 27 male patients, with no statistically significant difference regarding sex distribution within the groups (p = 0.604). The first group included an equal number of men and women, while the second group consisted of 18 women and 12 men.

The highest recorded value of pain intensity in both groups (in all 60 patients) using NRS was 4, and the overall mean pain score was 1.87 ± 1.2. Although there was no statistically significant difference between the examined groups (p = 0.114), patients rated mVAt as less painful (1.60 ± 1.3) compared to VAt (2.13 ± 1.2). The results of the VRS pain assessment are shown in Table 1.

Mean values representing the onset time measured in seconds are shown in Table 2. A slightly faster anesthetic effect was observed in the control group, i.e., after the application of the VA technique, without statistical significance (p = 0.370). Considering both groups, the shortest recorded onset time was 57 seconds, while the longest was 227 seconds. The mean onset time for all 60 cases was 138.20 ± 41.7 seconds.

Out of 60 performed anesthesia injections, 42 were successful, which proved to be statistically significant in comparison to 18 unsuccessful ones (p = 0.047). Details related to the success rate within the groups are shown in

Table 3. The number of unsuccessful injections, as well as the failure rate regarding individual nerves for each of the examined techniques, are shown in Table 4.

Table 1. Pain during the injection (verbal rating scale)

Group	No pain	Mild pain	Moderate pain	Severe pain	Total
Modified VA technique	7 (23.3%)	21 (70%)	2 (6.7%)	0 (0%)	30 (100%)
Standard VA technique	4 (13.3%)	22 (73.3%)	4 (13.3%)	0 (0%)	30 (100%)
Total	11 (18.3%)	43 (71.7%)	6 (10%)	0 (0%)	60 (100%)

VA – Vazirani–Akinosi

Table 2. Onset time of anesthesia measured in seconds

Group	Mean	Min	Max
Modified VA technique	140.37	57	227
Standard VA technique	136.03	65	187

VA – Vazirani–Akinosi

Table 3. The success rates within the groups

Group	Successful	Unsuccessful	Total
Modified VA technique	25 (83.3%)	5 (16.7%)	30 (100%)
Standard VA technique	17 (56.7%)	13 (43.3%)	30 (100%)
Total	42* (70%)	18* (30%)	60 (100%)

VA – Vazirani–Akinosi;
*statistically significant (p = 0.047)

Table 4. The failure rates within the groups

Group	Successful	IAN failure	LN	BN	Total
Modified VA technique	25 (41.7%)	1 (1.7%)	1 (1.7%)	3* (5%)	30 (50%)
Standard VA technique	17 (28.3%)	2 (3.3%)	0 (0%)	11* (18.3%)	30 (50%)
Total	42 (70%)	3 (5%)	1 (1.7%)	14 (23.3%)	60 (100%)

IAN – inferior alveolar nerve; LN – lingual nerve; BN – buccal nerve;
VA – Vazirani–Akinosi;
*statistically significant (p = 0.030)

A statistically significant higher success rate of BN anesthesia was observed in the mVAt group (p = 0.030). The success of anesthesia considering inferior alveolar and lingual nerve did not significantly differ among the groups (p = 0.554 and p = 0.313, respectively).

The duration of anesthesia in the first group averaged 172.87 ± 24.6 minutes and in the second group it was 176.93 ± 38.4 minutes. The values of this parameter did not show a statistically significant difference (p = 0.628).

DISCUSSION

Ensuring profound anesthesia is of great importance before every surgical procedure. Having in mind a wide variety of the described methods for achieving local anesthesia, modern dentistry should strive towards the improvement of techniques in terms of simplicity, effectiveness, and comfort. Obtaining numbness and a completely painless procedure may often present a great challenge, due to various above-mentioned difficulties. The ability to provide a successful nerve block by a single injection is, by all means, a key factor to consider when choosing the right technique.

Besides the overall success rate in this study, the results also show the ratio of failed injections, as well as individual nerves that, in case of failure, were not anesthetized. In total, 18 unsuccessful injections were reported. In 14 cases, the BN was not anesthetized. mVAt proved to be more effective in terms of BN anesthesia success, since only three failed injections were observed in this group, unlike the control group, where failure was noticed in 11 cases. Our results are in accordance with data from the literature where the Vazirani–Akinosi technique is presented as a technique of mandibular block that includes the IAN, LN, and very often BN [8, 19, 23]. In this study, failure to achieve anesthesia in the innervation area of the BN after the application of the VAt occurred in 36.7% of the cases. Studies conducted by Sisk [23] and Donkor et al. [19] reported 20% and 29% failure rates of BN anesthesia, respectively. Such cases require additional anesthesia for this nerve. Therefore, the main advantage of the Vazirani–Akinosi technique, which implies complete anesthesia of IAN, LN, and BN with a single injection, is devaluated. Namely, the IAN and the LN separate before entering the pterygomandibular space [20], through which they extend parallel to each other at an average distance of 5.3–8.5 mm [15]. The LN lies anterior and medial to IAN [9, 15]. The BN extends through the upper and anterior part of the pterygomandibular space, descending forward, towards the deep portion of the temporal muscle [20]. Due to the single-phase application of the entire dose of anesthetic solution at a depth of 25–30 mm, as the VA method suggests, the more anteriorly placed BN may not be anesthetized. As the modification of the technique implies – the sequential application of anesthetics to three different places within the pterygomandibular space – it is justified to expect successful anesthesia of all three targeted nerves (Figure 5).

As for the remaining four failed injections in both groups, three injections did not cover IAN innervation zone, while in only one case LN was not anesthetized. Presumably, the failure of anesthesia occurred due to poor assessment of the clinician when placing the needle into the pterygomandibular space. Since this technique relies mostly on the clinician's ability to make a good assessment and does not include any bony landmarks and endpoints, it is possible to deposition anesthetic solution outside the confines of the pterygomandibular space [1, 19]. Nevertheless, no statistically significant difference was observed among groups regarding these two nerves. In addition, a high rate of successful IAN and LN blocks was observed in both groups. These findings are in accordance with previously conducted studies that aimed to evaluate the efficacy of the VA technique. Based on the obtained results, Jendi and Thomas [2], Ravi Kiran et al. [5], Prabhu Nakkeeran et al. [7], and Akinosi [14] also indicated a high success rate and clinical efficacy of the VA technique.

Due to the lack of bony endpoint, while performing both examined techniques, it is possible to anesthetize the

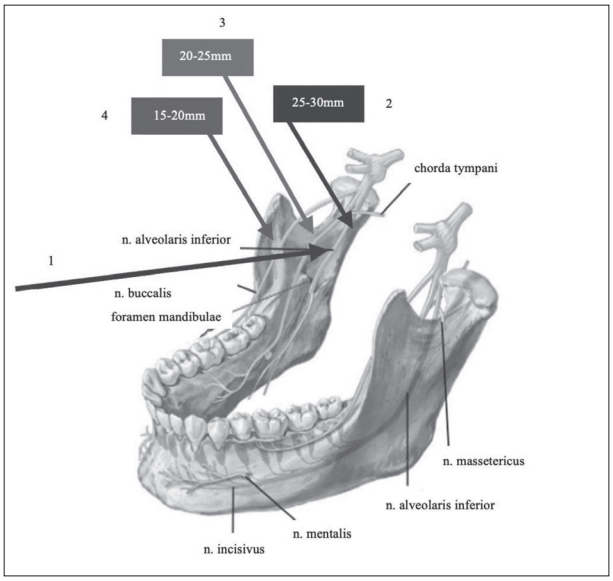

Figure 5. Scheme of needle insertion and anesthetic solution deposition depth for the modified Vazirani–Akinosi technique; 1 – direction of needle insertion; 2, 3, 4 – different depths of anesthetic solution deposition within the pterygomandibular space

auriculotemporal nerve, which happened in several cases during this research. This condition is not considered a complication but only an incidental anesthesia that will inevitably pass without any consequences.

The closed-mouth position, distinctive for the VA technique, ensures relaxation of the muscles and mucosa, which makes the needle prick, as well as the needle insertion, much less painful and unpleasant [14]. The puncture site and the anatomy of the upper parts of the pterygomandibular space also serve as a contribution to the low discomfort while performing this technique. After penetrating the oral mucosa and underlying buccinator muscle, the needle is inserted in the pterygomandibular space [14]. Having a fairly steady direction, it passes through the anterior entrance of the pterygomandibular space, i.e. between the deep tendon of temporal muscle externally, and the medial pterygoid muscle internally [20]. Following the medial surface of the ramus, the needle is inserted to a depth of approximately 25–30 mm. Extending upwards and medially, towards the lateral pterygoid process, the medial pterygoid muscle diverges from the mandibular ramus, giving greater width to superior parts of the pterygomandibular space [25]. The described manner of needle insertion together with advantageous anatomical relations result in negligible discomfort since excessive tearing of muscle fibers is avoided, thus minimizing tissue traumatization.

The specific puncture site, used in both mVAt and VAt, does not include insertion of a needle into sensitive areas that could provoke gag reflex, which makes them more comfortable for patients with severe gagging sensitivity [1, 26]. In addition, concentrating on the required closed-mouth position serves as a diversion, especially in apprehensive patients, shifting their thought focus from fear of the following injection [1]. Overall pain assessment in the present study showed low pain intensity among patients in both examined groups. Most patients evaluated the pain during the injection as mild, and no one reported severe pain. These findings are consistent with literature reports since Bhat et al.[1], Prabhu Nakkeeran et al. [7], Akinosi [14], Kota et al. [26], and Mishra [27] also stated low pain intensity and high comfort in their studies.

As one of the advantages of the technique, in his original work, Akinosi [14] points out a very short onset time, claiming that the altered sensation occurs 40 seconds after the injection, while the full effect of anesthesia is achieved after 90 seconds. In a study conducted by Jendi and Thomas [2], the mean onset time for the Vazirani–Akinosi technique was 104.24 seconds, Bhat et al. [1] reported the mean onset time of 1.98 minutes, and the study presented by Mishra [27] reported 1.6 minutes as the mean onset for this technique. In the present study, a slightly longer onset time was recorded, with the average of 136.02 seconds (2.26 minutes). Even longer onset time was observed by Ravi Kiran et al. [5], Todorović et al. [18], and Prabhu Nakkeeran et al. [7]. The time required for the anesthetic solution to achieve the effect mainly depends on the proximity of the anesthetic solution deposition to the targeted nerve trunk [2]. Since needle insertion while performing the VA technique is not determined by any bony endpoints, it is possible to inject the solution at an inadequate distance from the nerve trunk, i.e., more distant from the nerve. Such cases may require more time for the solution to take effect or even result in inadequate perfusion of the nerve trunk [1]. Besides the lack of bony landmarks, variations of the ramus anatomy should also be taken into account [2]. The anesthetic solution injected into the upper parts of the pterygomandibular space is able to diffuse targeted nerves under the influence of gravity [19]. Moreover, the diameter of nerve fibers may also affect the onset time, as stated by Mishra [27]. Namely, the diameter of the nerve trunk is larger in the superior parts of the pterygomandibular space, where the anesthetic solution is injected using the VA technique. This may cause a longer onset time since it takes more time for the anesthetic to diffuse and reach core nerve fibers.

In the study by Todorović et al. [18], the mean duration of anesthesia for the VA technique was 180 minutes, which is very similar to our findings. Bhat et al. [1] found the duration to be slightly longer, 3.69 hours on average. This may suggest that the duration of anesthesia is not a key parameter that should be considered when choosing the technique for IAN, LN, and BN block. Additionally, the duration of anesthesia largely depends on the pharmacological properties of the solution, as well as on the speed and the ability of the individual organism to metabolize and eliminate the solution, which certainly exceeds the goals and interests of this research.

CONCLUSION

Modified VA technique proved to be more successful regarding BN anesthesia. Considering other examined clinical parameters, both techniques showed similar performance.

Conflict of interest: None declared.

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Процена ефикасности модификоване технике у поређењу са стандардном техником Вазирани–Акиноси – рандомизована клиничка студија

Јована Бакаловић[1], Љиљана Стојчев[2], Бојан Јањић[2], Бојан Гачић[2]

[1]Универзитет у Београду, Стоматолошки факултет, Београд, Србија;
[2]Универзитет у Београду, Стоматолошки факултет, Клиника за оралну хирургију, Београд, Србија

САЖЕТАК

Увод/Циљ Правилан избор технике локалне анестезије подразумева одабир најједноставније технике за извођење, којом се постиже максимални ефекат анестезије уз најмању непријатност са становишта пацијента.

Циљ овог истраживања био је утврђивање ефикасности модификоване у односу на стандардну технику Вазирани–Акиноси, као и поређење наведених техника по питању клинички релевантних параметара.

Методе Истраживање је спроведено на Клиници за оралну хирургију Стоматолошког факултета Универзитета у Београду. Проспективна, рандомизована, једноструко слепа клиничка студија обухватила је 60 пацијената упућених на Клинику ради екстракције импактираних умњака у доњој вилици. Прва група пацијената анестезирана је применом модификоване, док је друга група пацијената анестезирана стандардном техником Вазирани–Акиноси. Праћени параметри били су бол током убризгавања анестетика, латентни период, ширина анестезираног поља и време трајања анестезије.

Резултати Од укупно 60 апликованих анестезија, 42 су биле успешне, што се показало као статистички значајно у поређењу са 18 неуспешних инјекција ($p = 0,047$). Проценат неуспеха анестезије образног нерва био је статистички значајно нижи у групи пацијената анестеризаних применом модификоване технике Вазирани–Акиноси ($p = 0,030$). Није било статистички значајне разлике међу групама по питању бола ($p = 0,114$), латентног периода ($p = 0,370$) и трајања анестезије ($p = 0,628$).

Закључак Модификована техника Вазирани–Акиноси показала је већу успешност анестезирања образног нерва. Узимајући у обзир остале клиничке параметре, обе технике су показале сличан учинак.

Кључне речи: техника Вазирани–Акиноси; мандибуларна анестезија; орална хирургија

DOI: https://doi.org/10.2298/SARH220227028D
UDC: 616.314.2-007-089.23; 616.314.2-77

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Assessment of condylar position in asymptomatic individuals before and after neuromuscular deprogramming with a stabilization splint

Kenan Demirović[1], Elma Demirović[2], Vildana Džemidžić[3], Enita Nakas[3]

[1]Demirović Private Practice for Orthodontics and Dentofacial Orthopedics, Sarajevo, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina;
[2]Prim. dr. Abdulah Nakas General Hospital, Emergency Department, Sarajevo, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina;
[3]University of Sarajevo, Faculty of Dentistry with Dental Clinical Center, Department of Orthodontics, Sarajevo, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina

SUMMARY

Introduction/Objective Deprogramming of the neuromuscular system with the use of stabilization splint might provide more precise evaluation of the centric relation (CR) – maximum intercuspation (MI) discrepancy.

The study aimed to evaluate the differences between the bite registrations obtained in the CR before and after the application of the stabilization splint therapy.

Methods The sample included 48 non-deprogrammed individuals without any apparent signs and symptoms of temporomandibular disorders (TMDs). The neuromuscular system was deprogrammed by employing stabilization splint therapy. A condylar displacement evaluation was performed on vertical, horizontal, and transverse planes of space, with the assistance of a condylar position indicator.

Results The mean values of condylar displacements, which were obtained after the deprogramming of the neuromuscular system, were significantly greater than those obtained before neuromuscular deprogramming for vertical condylar displacement ($p < 0.0001$). A greater degree of condylar distraction was observed on the left side of the vertical plane before ($p < 0.01$) and after neuromuscular deprogramming ($p < 0.05$). The highest level of condylar displacement occurred in the postero-inferior direction subsequent to the muscle deprogramming.

Conclusion It was observed that the level of average condylar displacements was significantly higher following the deprogramming of the neuromuscular system compared to that recorded before neuromuscular deprogramming using stabilization splint therapy. A more precise orthodontic diagnosis could have been obtained if the condyles were placed in a more exact CR position by muscle deprogramming.

Keywords: centric relation; maximum intercuspation; stabilization splint; condylar displacement

INTRODUCTION

From the perspective of condylar health, the centric relation is widely accepted as the most stable position of the condyles in the glenoid fossa [1–4]. Earlier studies concluded that the mandible in the centric relation (CR) is positioned by the elevator muscles in case no dental influences are present [1, 3, 5, 6, 7]. However, the actual condylar position is determined by the contact between the upper and the lower teeth in the maximum intercuspation (MI) position. Positions of CR and MI are rarely coincident, and small discrepancies are usually present between them. Discrepancies between the CR and MI can be evaluated at dental and condylar levels. Slides increased at the dental level should be confirmed through condylar measurement using the condylar position indicator (CPI) articulator. Significant slides might affect proper orthodontic diagnosis by changing the dentofacial features of dental malocclusions [2, 5, 7, 8]. Proffit [9] recommends mounting the orthodontic models on an articulator in case anterior slides of 2–3 mm and lateral slides of any range exist between the MI and the CR positions at the dental level. Values of dental CR–MI discrepancies do not usually correspond to discrepancy in values obtained at the condylar level for the asymptomatic population [2, 3, 4, 10]. Therefore, the mounting of diagnostic models is recommended by several clinicians before the start of orthodontic treatment. This enables the observation of the real difference between the CR and MI [2, 3, 7, 11, 12]. Furthermore, if the positions of the CR and MI are close to each other, the possibility of temporomandibular disorders (TMDs) development is lower [6]. The stability of condyles in the CR is most commonly worsened by the presence of occlusal interferences located in the area of the posterior teeth, which might increase the CR–MI discrepancy and cause development of TMD [2, 3, 9, 11, 13]. In order to reach the most stable intercuspal position, the mandible must avoid these prematurities that lead to mandibular shifts on all three spatial planes [11]. These deviated positions of the mandible coerce the related muscles to adapt to various neuromuscular patterns of activity,

Received • Примљено: February 27, 2022
Revised • Ревизија: January 26, 2023
Accepted • Прихваћено: February 21, 2023
Online first: March 8, 2023

Correspondence to:
Kenan DEMIROVIĆ
Demirović Private Practice for Orthodontics and Dentofacial Orthopedics
Bjelave 70
71000 Sarajevo
Federation of Bosnia and Herzegovina
Bosnia and Herzegovina
kenandemirovic@hotmail.com

causing condylar instability [2, 3, 11]. In order to relieve the muscles of inadequate activity, neuromuscular deprogramming is required. Several researchers recommend the application of stabilization splint therapy for deprogramming of the neuromuscular system prior to the registration of the CR position [12, 14, 15]. Also, when compared to other methods, the most consistent and reproducible results of CR bite registration were obtained after deprogramming was performed with the occlusal stabilization splint [15, 16]. Ideal protocol calls for complete neuromuscular deprogramming of all subjects, with increased CR–MI discrepancy at the occlusal level (horizontal or vertical discrepancy greater than 2.0 mm between the CR and MI position), using a stabilization splint therapy before the registration of the CR position. Roth [11] suggested that even if asymptomatic individuals were deprogrammed with an occlusal splint, greater difference between CR and MI would be observed in comparison with non-deprogrammed asymptomatic individuals. Regarding the impact of the neuromuscular system on CR bite registration, it was hypothesized that asymptomatic patients could show greater condylar distraction if the neuromuscular system was deprogrammed using the stabilization splint therapy, compared to the case of absence of such deprogramming. The purpose of this study was to compare the condylar displacements between the CR and the MI positions across three planes of space, when measured before and after the deprogramming of the neuromuscular system using a stabilization splint. Additionally, the condylar positions among males and females were compared both before and after the neuromuscular deprogramming.

METHODS

A total of 48 non-deprogrammed individuals in the aged 18–30 years (24 females and 24 males), who did not show any obvious signs and symptoms of TMDs, participated in the study. The study was carried out at the Demirović Private Practice for Orthodontics and Dentofacial Orthopedics located in Sarajevo.

Exclusion criteria included history of trauma involving the temporomandibular joints, history of orthodontic treatment or orthognathic surgery, history of temporomandibular joints treatment, presence of any past major prosthetic treatments and presence of rheumatoid arthritis or other rheumatic disorders. The study protocol was approved by the Ethics Committee, Faculty of Dentistry with Dental Clinical Center, University of Sarajevo, Bosnia and Herzegovina.

All the subjects included in the study had increased CR–MI discrepancy (greater than 2 mm) in the horizontal or vertical plane, measured at the level of occlusion. Horizontal (overjet) and vertical (overbite) values were measured in the positions of MI and CR, obtained before and after the deprogramming of the neuromuscular system with stabilization splint. The measurement of these parameters was recorded to the nearest 0.1 mm with the help of a digital ruler.

Evaluation of condylar displacement between the centric relation and maximum intercuspation

Bite registration in the MI position was obtained using a single layer of extra-hard Beauty Pink Wax (Moyco Techonologies Inc., Montgomeryville, PA, USA), prior to the deprogramming of the neuromuscular system. In order to register the CR position, blue bite registration wax (Delar Corp., Lake Oswego, OR, USA) was used in accordance with Roth's power-centric technique. Maxillary and mandibular diagnostic casts of all the participants were obtained before the neuromuscular deprogramming and mounted on an articulator (Panadent Corp, Colton, CA, USA) using an estimated face-bow and wax bite registered in the position of CR. The level of condylar displacement between the CR (Figure 1) and the MI (Figure 2) positions was evaluated before the neuromuscular deprogramming using initial CR and MI bite registration records. After the neuromuscular deprogramming with stabilization splint, newly obtained upper and lower diagnostic casts were mounted on an articulator using a new wax bite registered in the position of CR. The amount of condylar displacement between the CR and MI positions after the neuromuscular deprogramming was evaluated using the initial MI bite registration record, and the CR bite registration record taken after the neuromuscular deprogramming with stabilization splint.

Neuromuscular deprogramming with stabilization splint therapy

In order to find a more reliable CR position in patients with a large CR–MI discrepancy, neuromuscular system deprogramming was performed using an acrylic stabilization splint [7, 17] (Figure 3). This stabilization splint was constructed according to the principles of the mutually protected occlusion (Figure 4). All participants were instructed to wear the stabilization splints round the clock, except while eating and maintaining their oral hygiene. During each follow up, centric stops and the posterior eccentric disclusion were evaluated using 0.008 mm colored articulating paper Arti-Fol (Bausch Articulating Papers Inc., Nashua, NH, USA), and the splints were adjusted to optimum occlusal conditions for mutually protected occlusion. In order to track the condyles to a stable condylar position, centric relation records were taken every 15 days during the first two months of stabilization splint therapy and at one-week intervals during the third and/or fourth month of therapy. Stable condylar position was achieved when identical CPI values were obtained for three consecutive weeks. Neuromuscular deprogramming and stable condylar position in the fossa were obtained during the third or fourth month of splint application in all subjects. All mountings were performed on the same articulator. All the steps in this study were performed by the same trained operator. For statistical analysis, results were presented as mean ± standard deviation and median, while the testing of differences was performed with the nonparametric Mann–Whitney U test. Analysis was performed using

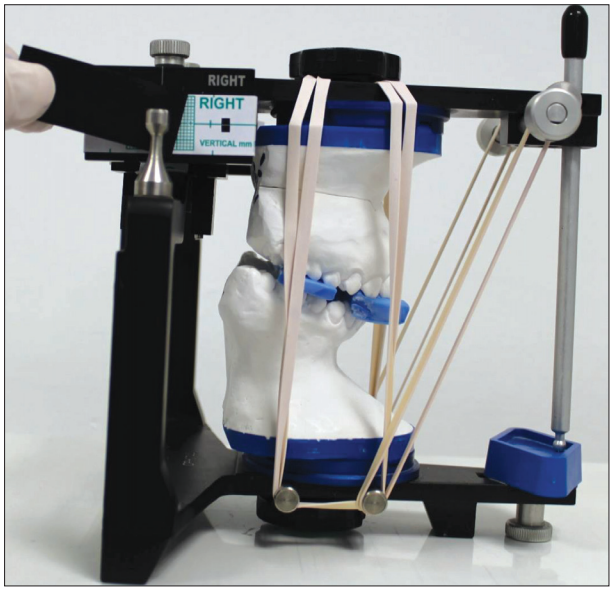

Figure 1. Centric relation position in condylar position indicator instrumentation determined by bite registered in centric relation position

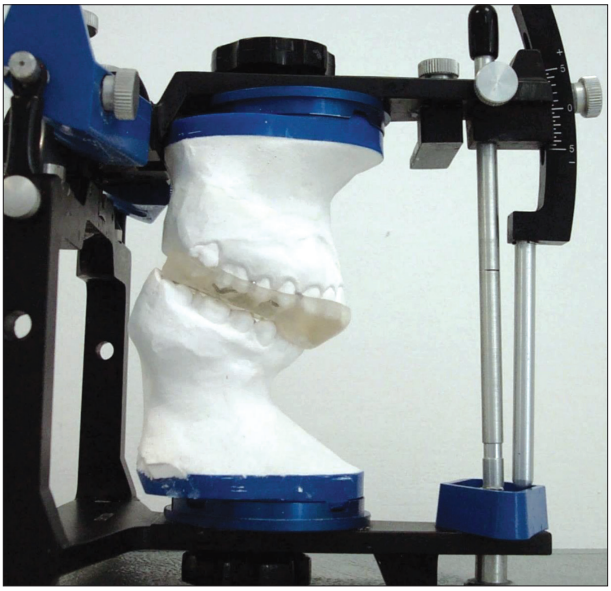

Figure 3. Acrylic stabilization splint constructed in a semi-adjustable articulator

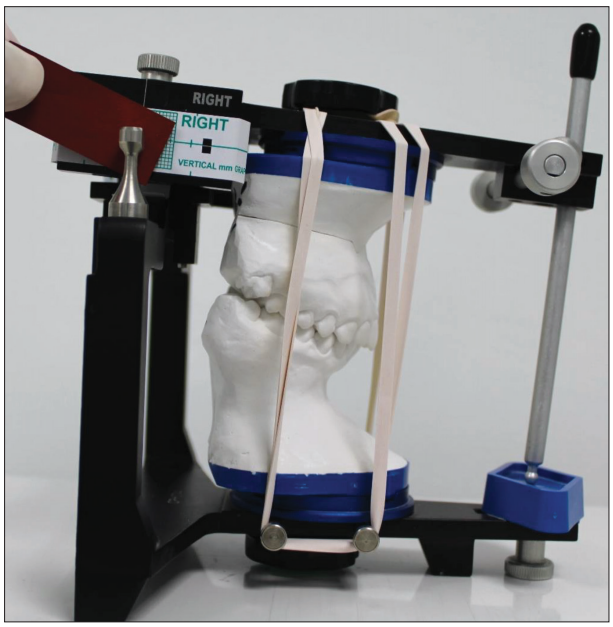

Figure 2. Maximum intercuspation position in condylar position indicator instrumentation determined by bite registered in the position of maximum intercuspation

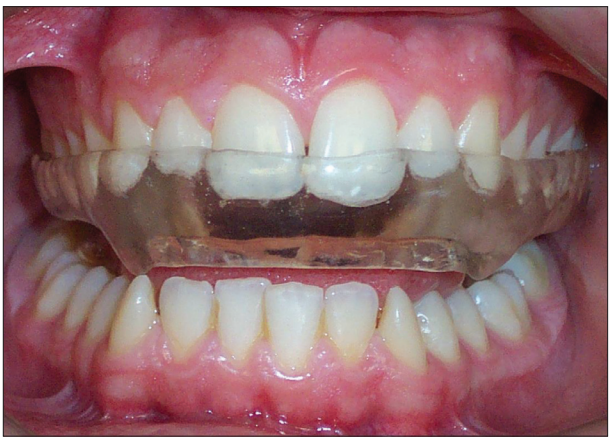

Figure 4. Occlusal scheme of the stabilization splint based on principles of mutually protected occlusion

the statistical package IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA).

The authors confirm that necessary patient's written consent has been obtained.

RESULTS

The mean values of condylar displacements obtained after the deprogramming of the neuromuscular system proved to be significantly greater than those attained before neuromuscular deprogramming in the case of CPI vertical right (Vert R) ($p = 0.0001$) and CPI vertical left (Vert L) ($p = 0.0001$) but not for the CPI horizontal right (Hor R) ($p = 0.144$), CPI horizontal left (Hor L) ($p = 0.171$) and CPI transversal (Transv) ($p = 0.203$) (Table 1).

Table 1. Comparison of mean values, standard deviations and median, in mm, of vertical condylar displacement on the right (CPI Vert R) and left (CPI Vert L) side, horizontal condylar displacement on the right (CPI Hor R) and left (CPI Hor L) side, and transversal condylar displacement (CPI Transv) before (B) and after (A) neuromuscular deprogramming with stabilization splint

Parameters (mm)	n	Mean ± SD	Median	Z	p
B – CPI Vert R	48	1.54 ± 0.47	1.60	-3.532	0.0001
A – CPI Vert R	48	1.97 ± 0.69	1.80		
B – CPI Vert L	48	1.82 ± 0.54	1.80	-3.912	0.0001
A – CPI Vert L	48	2.20 ± 0.63	2.20		
B – CPI Hor R	48	-0.32 ± 0.69	-0.50	-1.460	0.144
A – CPI Hor R	48	-0.49 ± 0.92	-0.8		
B – CPI Hor L	48	-0.41 ± 0.62	-0.50	-1.368	0.171
A – CPI Hor L	48	-0.56 ± 0.85	-0.65		
B – Transv	48	0.20 ± 0.25	0.20	-1.274	0.203
A – Transv	48	0.27 ± 0.30	0.20		

CPI – condylar position indicator; Z – standard score

Table 2. Comparison of mean values, standard deviations and median, in mm, of vertical condylar displacement according to right (CPI Vert R) and left (CPI Vert L) side, and horizontal condylar displacement according to right (CPI Hor R) and left (CPI Hor L) side before (B) and after (A) neuromuscular deprogramming

Parameters (mm)	n	Mean ± SD	Median	Z	p
B – CPI Vert R	48	1.54 ± 0.47	1.60	-2.577	0.010
B – CPI Vert L	48	1.82 ± 0.54	1.80		
B – CPI Hor R	48	-0.32 ± 0.69	-0.50	-0.757	0.449
B – CPI Hor L	48	-0.41 ± 0.62	-0.50		
A – CPI Vert R	48	1.97 ± 0.69	1.80	-2.313	0.021
A – CPI Vert L	48	2.20 ± 0.63	2.20		
A – CPI Hor R	48	-0.49 ± 0.92	-0.80	-0.530	0.596
A – CPI Hor L	48	-0.56 ± 0.85	-0.65		

CPI – condylar position indicator; Z – standard score

Greater left-side inferior and posterior displacement of the condyles was observed after the neuromuscular deprogramming. These differences were statistically significant before ($p = 0.010$) and after ($p = 0.021$) in the vertical but not in the horizontal plane, neither before ($p = 0.449$) nor after (0.596) (Table 2). No statistical differences were observed between the genders (all $p > 0.05$) (Figure 5). Before neuromuscular deprogramming was performed, 70.8% of the subjects in the study had postero-inferior displacement of the condyles, 22.9% antero-inferior and 6.2% straight inferior on the left side, while on the right side, condyles were displaced postero-inferiorly in 60.4%, antero-inferiorly in 25% and straight inferiorly in 14.5% of the subjects. Evaluation of the direction of condylar displacement, after the deprogramming of the neuromuscular system, showed that 81.2% of the condyles were displaced in the postero-inferior direction and 18.7% in the antero-inferior direction on the left side. On the right side, 77.1% of the condyles were displaced in the postero-inferior direction, 20.8% in the antero-inferior direction and 2.8% in the straight inferior direction.

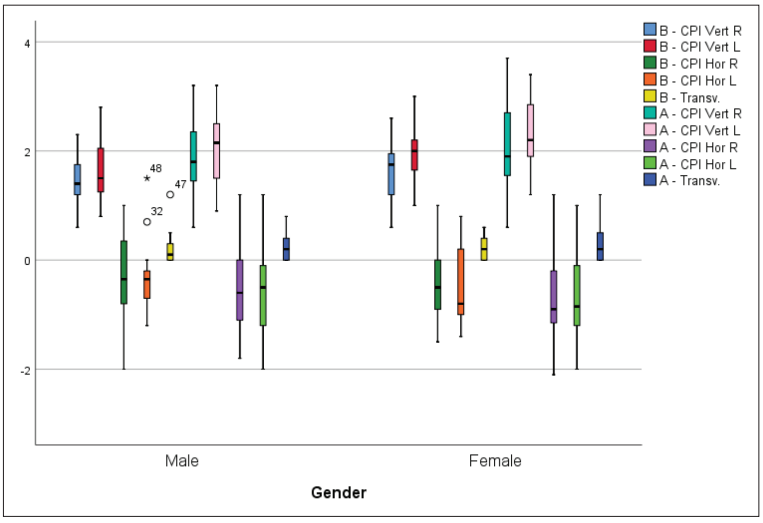

Figure 5. CPI – condylar position indicator; comparison of mean values, standard deviations and median, in mm, of vertical right (CPI Vert R) and left (CPI Vert L), horizontal right (CPI Hor R) and left (CPI Hor L) and transverse (Transv) condylar displacement between genders, before (B) and after (A) neuromuscular deprogramming with stabilization splint

DISCUSSION

It is considered that mandibular stability is realized when the positions of CR and MI coincide [11]. This means that orthopedic stability is guaranteed if the musculoskeletal position of the condyles in the fossa is as much as possible harmonized with the position of the teeth in MI [6]. In the studies that evaluated CR–MI discrepancy in asymptomatic individuals using just a CPI instrumentation, significant differences between the CR and MI were found [4, 17, 18]. Previous studies indicate that asymptomatic individuals with a higher occlusal CR–MI discrepancy (greater than 2.0 mm in horizontal and vertical directions) also showed significant condylar CR and MI differences [2, 10]. Most commonly, the presence of occlusal interferences increases discrepancy between the CR and MI, thereby leading the mandible to deviated positions, indirectly causing neuromuscular reprogramming of the related muscles. Deprogramming of the neuromuscular system is needed before CR bite registration, in order to detect a true discrepancy between the CR and MI. Although Roth's power centric technique was recognized as the most reliable and reproducible technique of CR bite registration, Roth [11] himself stated that clinical mandibular manipulation is not reliable in determining condylar position because of neuromusculature. In a very recent study, authors concluded that "Dentists and dental experts are dependent not so much on the head posture but on an acceptably reproducible horizontal jaw relation in order to be able to repeatedly check the occlusion in reconstructions of the mandibular posture" [19]. In most of the earlier studies, CR bite registration was recorded without previous muscle deprogramming, although the impact of the neuromuscular system on CR registration had already been proved [3, 4, 12, 18]. In a study by Fantini et al. [7] vertical and horizontal condylar displacements in asymptomatic patients were found to be greater after neuromuscular deprogramming with the stabilization splint in comparison with the results of previous studies, where no neuromuscular deprogramming methods were employed [12, 18]. In this study, it was hypothesized that stabilization splint therapy for approximately three months could lead to better seating of the condyles in the fossa, resulting in different CPI measurement results compared to those obtained before the deprogramming of the neuromuscular system in asymptomatic individuals. Statistically significant differences between the CR and MI were observed on the vertical plane. It was found that the mean vertical displacements on the right and left sides, obtained after the neuromuscular deprogramming, were significantly greater than those attained before the neuromuscular deprogramming (Table 1). These results are in close agreement with those derived in similar studies by Fantini et al. [7] and Yoon and Kim [17] who used identical methods. Vertical displacement of the condyles was more expressed on the left side before ($p < 0.01$) and

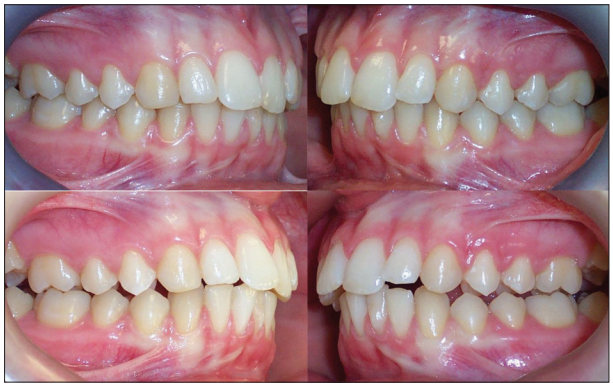

Figure 6. A – right lateral intraoral view of occlusion in maximum intercuspation before the stabilization splint therapy; B – right lateral intraoral view of occlusion after neuromuscular deprogramming with a stabilization splint; discrepancies between the upper and lower dental arch have increased in horizontal (overjet) and decreased in vertical (overbite) direction affecting the orthodontic diagnosis and plan of treatment; C – left lateral intraoral view of occlusion in maximum intercuspation before the stabilization splint therapy; D – left lateral intraoral view of occlusion after neuromuscular deprogramming with a stabilization splint; discrepancies between the upper and lower dental arch have increased in horizontal (overjet) and decreased in vertical (overbite) direction affecting the orthodontic diagnosis and plan of treatment

after ($p < 0.05$) the neuromuscular deprogramming (Table 2). On the other hand, Fantini et al. [7] found that after the neuromuscular deprogramming with the stabilization splint vertical condylar displacements were of greater magnitude on the right side. After the neuromuscular deprogramming, greater mean condylar displacements were observed on the horizontal plane too, but without statistical significance (Table 1). The condyles were displaced in postero-inferior, antero-inferior and straight inferior direction, which was corresponding with the findings of similar studies [2, 3, 11, 12, 18]. The results of this study are consistent with the findings of previous studies, confirming that the deprogramming with the stabilization splints significantly increases the amount of condylar distraction in vertical direction in asymptomatic patients [7, 17]. Also, before and after the neuromuscular deprogramming, patients showed higher mean values of condylar displacement than that it was found by other authors in non-deprogrammed asymptomatic groups [12, 18]. Statistically, no significant differences in condylar displacements were observed between males and females. In this study, it was shown that after the neuromuscular system was deprogrammed and the condyles were in a stable musculoskeletal position, the magnitude of discrepancy between the CR and MI at the level of occlusion might be significantly changed. The most common changes observed in inter-arch relations after the neuromuscular deprogramming included the following: the presence of localized occlusal interferences in premolar and molar areas, increased overjet, decreased overbite, and coincidence of transverse midlines (Figure 6 A–D), which corresponded with findings by other authors [2, 9, 5, 11, 20, 21]. These significant changes at the level of occlusion demonstrate the importance of neuromuscular deprogramming, especially from the aspect of making an accurate orthodontic diagnosis [2, 5, 7, 8, 21–25]. The use of occlusal splints for deprogramming of the neuromuscular system before orthodontic treatment is usually recommended for patients with signs and symptoms of TMDs. Earlier investigations have demonstrated the efficacy of neuromuscular deprogramming with occlusal stabilization splint in the reduction of signs and symptoms of TMD in patients with a large CR–MI discrepancy [3, 5, 15, 26]. Padala et al. [20] and Lim et al. [22] indicated that the signs and symptoms of TMDs are more significantly expressed in individuals with large CR–MI discrepancy. The latest studies confirmed that the most common type of occlusal splint used for treatment of the patients with TMDs is occlusal stabilization splint [26–29]. A study by Crawford [3] showed how anamnestic and clinical symptomatology drastically increase as the CPI values in vertical and horizontal direction rise from 1 mm to 2 mm. Accordingly, this implies that orthodontic models of asymptomatic patients with increased slide between the CR and MI at the dental level (greater than 2 mm) need to be mounted on an articulator and measured at the condylar level. If condylar measurements detect vertical and horizontal displacements larger than 1 mm and transverse condylar displacements larger than 0.5 mm, these patients may be at potential risk of developing TMD after the orthodontic treatment [30]. In this context, the deprogramming of the neuromuscular system with a stabilization splint and the consequent placement of temporomandibular condyles in a more correct and reliable CR position within the fossa could prevent a possible TMD in asymptomatic patients who showed greater CR–MI discrepancy between maxillary and mandibular dentition. The results of this investigation demonstrated that the mounting of orthodontic models in the CR on a semi-adjustable articulator and muscle deprogramming with a stabilization splint is recommended in asymptomatic patients who show increased discrepancy between the CR and MI. Moreover, it was assumed that a more accurate orthodontic diagnosis could be obtained if these asymptomatic patients were neuromuscularly deprogrammed and analyzed in the CR position in comparison with patients diagnosed based on hand-held casts articulated in MI.

CONCLUSION

Measured on the same group of patients, greater mean condylar displacements on the vertical plane were observed after the neuromuscular system was deprogrammed in comparison with condylar displacements recorded before muscle deprogramming. The more significant vertical displacement of the condyles was present on the left side before and after neuromuscular deprogramming. It is recommended that patients without any existing signs and symptoms of TMDs but with condyles in unstable musculoskeletal position should be neuromuscularly deprogrammed prior to the commencement of orthodontic treatment. The use of stabilization splint therapy in asymptomatic patients with increased CR–MI discrepancy could prevent orthodontic misdiagnosis and possible development of TMD during or after the orthodontic treatment.

Conflicts of interest: None declared.

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Процена кондиларне позиције код асимптоматских особа пре и после депрограмирања неуромишићног система помоћу стабилизационог сплинта

Кенан Демировић[1], Елма Демировић[2], Вилдана Џемицић[3], Енита Накас[3]

[1]Приватна специјалистичка ординација ортопедије вилица – ортодонције „Демировић", Сарајево, Федерација Босне и Хрцеговине, Босна и Херцеговина;
[2]Општа болница „Прим. др. Абдулах Накаш", Одељење за ургентну медицину, Сарајево, Федерација Босне и Хрцеговине, Босна и Херцеговина;
[3]Универзитет у Сарајеву, Стоматолошки факултет, Одељење за ортодонцију, Сарајево, Федерација Босне и Хрцеговине, Босна и Херцеговина

САЖЕТАК

Увод/Циљ Депрограмирање неуромишићног система помоћу стабилизационог сплинта даје могућност добијања прецизнијих резултата мерења приликом евалуације дискрепанци између центричне релације и максималне интеркуспидације.

Циљ ове студије је био да евалуирају разлике између загриза који су регистровани у положају центричне релације пре и после примене терапије са стабилизационим сплинтом.

Методе Ова студија је обухватала 48 болесника (старости између 18 и 30 година) који нису били депрограмирани на неуромишићном нивоу и који нису имали очигледних знакова и симптома темпоромандибуларних поремећаја. Депрограмирање неуромишићног система је извршено помоћу терапије са стабилизационим сплинтом. Евалуација степена кондиларних одступања је извршена у вертикалној, хоризонталној и трансверзалној равни, уз помоћ индикатора положаја кондила.

Резултати Просечне вредности кондиларних одступања у вертикалној равни добијене после депрограмирања неуромишићног система биле су значајно веће у односу на просечне кондиларне вредности добијене пре неуромишићног депрограмирања ($p < 0,0001$). Већи степен кондиларне дистракције примећен је на левој страни у вертикалној равни пре неуромишићног депрограмирања ($p < 0,01$), као и после њега ($p < 0,05$). После депрограмирања неуромишићног система највећи степен дистракције кондила забележен је у постероинферионом правцу.

Закључак У студији је утврђено да је ниво просечних кондиларних одступања био значајно већи после депрограмирања неуромишићног система у поређењу са нивоом кондиларних одступања забележених пре депрограмирања неуромишићног система. Постављањем кондила у правилнији положај центричне релације после депрограмирања неуромишићног система повећава се могућност за постављање прецизније ортодонтске дијагнозе.

Кључне речи: центрична релација; максимална интеркуспидација; стабилизациони сплинт; кондиларна одступања

DOI: https://doi.org/10.2298/SARH220210002J
UDC: 616.132.2-089.84

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Complete versus culprit-only revascularization in non-ST-segment elevation myocardial infarction and multivessel coronary artery disease

Milana Jaraković[1,2], Milovan Petrović[1,2], Dragan Ivanišević[3], Bojan Mihajlović[1,2], Mila Kovačević[1,2], Iva Popov[2]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia;
[3]University Clinical Center of Serbia, Clinic for Cardiac Surgery, Belgrade, Serbia

SUMMARY

Introduction/Objective The optimal percutaneous coronary intervention (PCI) in patients with non-ST-elevated myocardial infarction (NSTEMI) and multivessel coronary artery disease (CAD) is still not clear. The aim of our study was to examine intrahospital and long-term major adverse cardiovascular and cerebrovascular events (MACCE) in this group of patients.

Methods This retrospective study included 225 patients with NSTEMI and multivessel CAD treated with PCI at the Institute of Cardiovascular Diseases of Vojvodina. Three groups were formed: complete one-stage PCI; complete multi-stage PCI, and culprit-only PCI. We analyzed intrahospital and one-year follow-up MACCE and mortality after three years in all three groups.

Results Complete one-stage PCI was performed in 112 (49.8%), complete multi-stage PCI in 70 (31.3%), and culprit-only PCI in 43 (19.1%) patients. Patients with multi-stage complete PCI had the lowest mortality in comparison with one-stage and culprit-only PCI, both intrahospital (0% *vs*. 0.9% and 20.9%, respectively, $p < 0.0005$) and after one year (0% *vs*. 2.7% and 30.2%, respectively, $p < 0.0005$) and three years (4.3% *vs*. 5.4% and 32.6%, respectively, $p < 0.0005$). There was no significant difference in other MACCE between the groups, both intrahospital and after one year.

Conclusion In our study, multi-stage PCI significantly reduces intrahospital, one-year and three-year follow-up mortality in patients with NSTEMI and multivessel CAD.

Keywords: non-ST-elevated myocardial infarction; multivessel coronary artery disease; percutaneous coronary intervention; major adverse cardiovascular and cerebrovascular events; mortality

INTRODUCTION

The annual incidence of acute coronary syndrome (ACS) remains high and 70% of patients present as non-ST-elevated myocardial infarction (NSTEMI) and unstable angina pectoris [1]. Intrahospital mortality of patients with NSTEMI ranges 4–6% [2, 3]. Although the 30-day mortality in NSTEMI is lower than in ST segment elevation myocardial infarction (STEMI) and it ranges 3–5% [4], in long-term follow-up, patients with NSTEMI have a poorer prognosis in terms of one-year mortality of about 6%, reinfarction, and the need for repeated revascularization [1, 4]. Patients with NSTEMI are more likely to have multivessel coronary artery disease (CAD), which is associated with poorer clinical outcome [5].

The optimal therapeutic approach in patients with NSTEMI and multivessel CAD is less clear than in patients with STEMI or chronic CAD. In particular, with regard to percutaneous coronary intervention (PCI), there is a lack of randomized, prospective studies comparing revascularization of the infarct artery alone with complete revascularization of all blood vessels with hemodynamically significant stenosis [6, 7].

The aim of our study was to examine the in-hospital and long-term outcomes in terms of major adverse cardiovascular and cerebrovascular events (MACCE) in patients with NSTEMI and multivessel CAD, using three different revascularization strategies: PCI of the infarct artery alone, single-staged PCI and multi-staged PCI of all coronary arteries with hemodynamically significant stenosis.

METHODS

This retrospective observational study included 225 patients ≥ 18 years old, 160 (71.1%) male, with NSTEMI and significant multivessel CAD treated with PCI, admitted to the Institute of Cardiovascular Diseases of Vojvodina (ICVDV) from January 2011 to December 2017. The data was obtained from the ICVDV information system.

NSTEMI was defined according to the European Society of Cardiology fourth universal definition of myocardial infarction [8]. The definition of hemodynamically significant multivessel CAD involved stenosis of two or more large coronary arteries ≥ 75% [9].

Received • Примљено: February 10, 2022
Revised • Ревизија: October 17. 2022
Accepted • Прихваћено: January 3, 2023
Online first: January 10, 2023

Correspondence to:
Milana JARAKOVIĆ
Put dr Goldmana 4
21204 Sremska Kamenica, Serbia
milana.jarakovic@mf.uns.ac.rs

Patients who had previously undergone surgical revascularization of the myocardium, single-vessel CAD and chronic total occlusion verified by angiography, failed PCI of the infarct artery, candidates for surgical revascularization based on angiography, and patients who presented with cardiogenic shock were excluded from the study.

The study protocol was approved by the Ethics Committee of the ICVDV.

Three groups were formed: the first group consisted of patients with one-stage revascularization of all blood vessels with hemodynamically significant stenosis, the second group consisted of patients with multi-stage PCI, with culprit artery being revascularized in the first act and subsequent revascularization of the remaining blood vessels with hemodynamically significant stenosis, and the third group consisted of patients in whom revascularization of culprit artery only was performed. Patients with a residual synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score of 0 were defined as having undergone complete revascularization, and with a residual SYNTAX score > 0 as incomplete revascularization [10].

The method of revascularization depended on the decision of the interventional cardiologist during the procedure based on the type of lesion, suitability and feasibility of the intervention.

The use of anatomical or functional methods to assess the hemodynamic significance of the lesion, as well as the vascular approach, was at the discretion of the interventional cardiologist.

In the culprit-only group, we defined patients with poorer prognosis as those with residual SYNTAX score > 8 after the first intervention. In this group of patients, staged PCI was not planned for all the patients and the reasons for not performing PCI of the remaining significant lesions included the following: lesion not being suitable for PCI, stress test that did not indicate PCI of the remaining lesions, patients not being motivated for planned PCI or stress test, and death while awaiting intervention.

We examined intrahospital and the occurrence of MACCE one year after, which included death of cardiac origin, reinfarction, repeated revascularization, cardiac decompensation and stroke, as well as death of cardiac origin over a follow-up period of three years.

The following measures of the descriptive statistics were used: arithmetic mean, standard deviation, median, quartiles, frequencies, and percentages. The t-test for independent samples and the Mann–Whitney test were used to compare the mean values of the variables of the two populations. The correlation of categorical variables was examined using the χ^2 test for contingency tables or using the Fisher test. Kaplan–Meier survival analysis was used to determine survival length. The influence of variables on survival was performed using Cox regression analysis.

Statistical analysis and data processing were done using the Statistical Package for Social Sciences – SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA), in which the significance limit was $p < 0.05$.

RESULTS

The study included 225 patients with NSTEMI and multivessel CAD who were treated with PCI. The mean age of the patients was 62.8 ± 10.3 years.

There were 160 (71.1%) male patients, average age 61.3 ± 10.4 years, and 65 (28.9%) female patients, average age 66.5 ± 9.1 years, which showed to be statistically significant age difference ($p = 0.001$).

The first group, with complete one-stage PCI consisted of 112 (49.8%) patients; the second group, with complete multi-stage PCI, consisted of 70 (31.1%) patients, while the third group with culprit-only PCI consisted of 43 (19.1%) patients.

No significant difference between the groups in terms of demographic data, risk factors for the development of cardiovascular diseases, and previous diseases at admission was found, as shown in Table 1.

By analyzing laboratory parameters at admission, a statistically significant difference between the groups was found in terms of leukocyte count ($p = 0.01$) and neutrophil/lymphocyte ratio (NLR) ($p = 0.008$), as shown in Table 1.

In terms of clinical parameters analyzed at admission, the study groups were similar, and a statistically significant difference was found in terms of Killip class ($p = 0.045$) and cardiac arrest at admission ($p = 0.013$), as shown in Table 1.

During hospitalization, echocardiography was performed in all examined patients and a statistically significant difference in the left ventricular ejection fraction (LVEF) between the examined groups was found ($p = 0.005$), as shown in Table 1.

In terms of procedural characteristics, there was a significant difference between the groups in terms of the number of affected coronary arteries ($p < 0.0005$), culprit artery ($p = 0.008$), and the time elapsed from patient admission to PCI ($p = 0.002$), as shown in Table 2.

When clinical outcome was evaluated, intrahospital mortality in our study was 4.4%. Patients with culprit-only PCI had the highest intrahospital mortality (20.9%); intrahospital mortality among patients who underwent complete one-stage revascularization was 0.9%, while no intrahospital deaths were reported among patients who underwent complete multi-stage PCI, which represents a significant difference ($p < 0.0005$). Intrahospital outcome of the examined patients in terms of MACCE, including death, is shown in Table 3.

The rate of cumulative intrahospital MACCE including death was 9.8%, with the highest intrahospital MACCE in the group of patients with culprit-only revascularization (32.6%), followed by complete multi-stage revascularization (5.7%), and the lowest in the group of patients with complete one-stage revascularization (3.6%), which is a significant difference ($p < 0.0005$).

Cox's analysis for the occurrence of cumulative intrahospital MACCE, including death, has shown that the groups affected the occurrence of MACCE with a statistically significant difference (HR 0.387, 95% CI 0.208–0.720, $p = 0.003$), as presented in Table 4.

Table 1. Selected baseline and clinical characteristics at presentation in multivessel non-ST-elevated myocardial infarction patients

Baseline characteristics	Complete single-stage PCI	Complete multi-stage PCI	Culprit-only PCI	p
Age, mean ± SD	62.7 ± 10.2	61.4 ± 10.7	65.4 ± 9.8	0.137
Male sex, n (%)	83 (74.1)	46 (65.7)	31 (72.1)	0.472
Hypertension, n (%)	87 (77.7)	59 (84.3)	33 (76.7)	0.493
Risk factors, n (%)				
HLP	57 (50.9)	27 (38.6)	14 (32.6)	0.072
DM	30 (26.8)	22 (31.4)	14 (32.6)	0.700
Smoking	50 (44.6)	35 (50)	18 (41.9)	0.661
Alcohol	0 (0)	1 (1.4)	2 (4.7)	0.077
BMI > 30 kg/m^2, mean ± SD	29 ± 15	29 ± 4	30 ± 6	0.718
Disease history, n (%)				
COPD	8 (7.1)	5 (7.1)	2 (4.7)	0.841
CKI	4 (3.6)	3 (4.3)	1 (2.3)	0.861
Previous MI	17 (15.2)	15 (21.4)	14 (32.6)	0.054
Previous PCI	16 (14.3)	12 (17.1)	6 (14)	0.848
Previous CVI	7 (6.3)	5 (7.1)	4 (9.3)	0.803
Blood tests on admission				
Troponin, med (range) (ng/l)	48 (13–114)	27 (1–47)	42 (31.5–67.5)	0.509
Troponin max, med (range) (ng/l)	122 (65–295)	99.5 (51–286)	75 (32–114)	0.172
CK MB, med (range) (U/l)	33.5 (23–62)	33.5 (27–75)	26 (15.5–76.5)	0.642
Glucose, med (range) (μmol/l)	7.6 (5.7–10.5)	7.4 (6.1–14.1)	6.5 (6.2–8.4)	0.215
ALT, med (range) (U/l)	27 (19–35)	28 (16–55)	26 (15.5–35)	0.596
Creatinine, med (range) (μmol/l)	102 (92–116)	94.5 (85–105)	97 (86–114.5)	0.062
Uric acid, mean ± SD (μmol/l)	340 ± 92	329 ± 91	370 ± 106	0.079
Total bilirubin, mean ± SD (μmol/l)	12.3 ± 7.6	11 ± 5.6	12.6 ± 6.6	0.408
LDL, mean ± SD (μmol/l)	3.9 ± 1.1	3.7 ± 1	3.6 ± 1	0.384
Triglycerides, med (range) (mg/dl)	1.7 (1.2–2.4)	1.6 (1.1–2.8)	2.1 (1.4–2.4)	0.930
CRP, med (range) (mg/l)	5.7 (2.8–23.2)	8.3 (5.4–28.5)	8.3 (3–21.2)	0.296
Hemoglobin, med (range) (g/l)	143 (132–153)	146.5 (138– 162)	138 (120–144.5)	0.098
Leukocytes, med (range) (× 10^9/l)	7.75 (6.5–9.8)	9.05 (7.1–10.7)	8.5 (7.75–11.2)	**0.01**
Neutrophil/lymphocyte ratio, med (range)	2.3 (1.8–3.1)	3.25 (2.5–5.5)	2.8 (2.3–5.1)	**0.008**
Clinical parameters at admission				
Systolic blood pressure, med (range) (mmHg)	140 (130–160)	140 (130–150)	150 (142–165)	0.148
Diastolic blood pressure, med (range) (mmHg)	82 (80–95)	80 (70–90)	90 (80–90)	0.447
Heart rate, med (range) (beats/min)	85 (70–100)	87 (80–105)	75 (65–81)	0.590
Killip class				0.045
I, n (%)	93 (83)	55 (78.6)	26 (60.5)	
II, n (%)	12 (10.7)	9 (12.9)	12 (27.9)	
III, n (%)	7 (6.3)	6 (8.6)	5 (11.6)	
Cardiac arrest, n (%)	0 (0)	1 (1.4)	3 (7)	**0.013**
GRACE score, med (range)	121 (100–143)	107 (92–129)	115 (103–122)	0.212
Echocardiographic parameters				
EF (%), mean ± SD	53 ± 10	54 ± 8	48 ± 11	**0.005**
High degree MR, n (%)	0 (0)	0 (0)	2 (4.7)	0.064

PCI – percutaneous coronary intervention; HLP – hyperlipoproteinemia; DM – diabetes mellitus; BMI – body mass index; COPD – chronic obstructive pulmonary disease; CKI – chronic kidney insufficiency; MI – myocardial infarction; CVI – cerebrovascular insult; CK MB – MB isoenzyme creatine kinase; ALT – alanine transaminase; LDL – low-density lipoprotein; CRP – C-reactive protein; EF – ejection fraction; MR – mitral regurgitation

Kaplan–Meier analysis of survival has shown a significant difference in the occurrence of MACCE between the examined groups (p = 0.001), which is shown in Tables 5 and 6 and Figure 1.

The overall one-year mortality in our study was 16 (7.1%) and after three years it amounted to 23 (10.2%).

When MACCE after one year was analyzed, there was a statistically significant difference between the examined groups in terms of mortality (p < 0.0005), with the highest mortality among patients with culprit-only PCI (30.2%), followed by complete one-stage revascularization (2.7%), while there were no recorded deaths among patients in whom complete multi stage PCI was performed. There was no statistically significant difference in terms of other MACCE during the first year of follow-up, which is shown in Table 3.

In the three-year follow-up, a significant difference in mortality between the examined groups (p < 0.0005) was found, with the highest mortality among patients with culprit-only revascularization (32.6%); mortality in the group of patients with complete one-stage revascularization was 5.4%, and the lowest mortality was among patients with complete multi stage revascularization (4.3%).

When the predictors of intrahospital cumulative MACCE, including death, were analyzed, the results of multivariate binary logistic regression showed that, except examined patient groups, intrahospital MACCE was simultaneously influenced by the following: infarcted blood vessel, time elapsed since patient admission to revascularization, cardiac arrest by type of pulseless electrical activity/asystole, and hyperlipoproteinemia, which is shown in Table 7. The Hosmer–Lemeshow test shows that this model is good (p = 0.888).

The results of our study showed that in the culprit-only group, residual SYNTAX score affects neither mortality nor cumulative MACCE, both intrahospital and after one year of follow-up, which is shown in Table 8.

DISCUSSION

The prevalence of multivessel CAD in NSTEMI patients undergoing angiography is about 30–50% [11]. Higher

Table 2. Procedural characteristics of the patients with non-ST-elevated myocardial infarction and multivessel disease

Procedural characteristics	Complete single-stage PCI	Complete multi-stage PCI	Culprit-only PCI	p
Number of affected coronary arteries, n (%)				**< 0.0005**
Two	100 (89.3)	53 (75.7)	23 (53.5)	
Three	12 (10.7)	17 (24.3)	20 (46.5)	
Culprit artery, n (%)				**0.008**
Left main	1 (0.9)	0 (0)	4 (9.3)	
Left anterior descending	43 (38.4)	36 (51.4)	11 (25.6)	
Right coronary artery	26 (23.2)	16 (22.9)	14 (32.6)	
Left circumflex	41 (36.6)	18 (25.7)	14 (32.6)	
TIMI flow, pre-procedure, n (%)				0.285
0	11 (9.8)	14 (20)	5 (11.6)	
1	19 (17)	8 (11.4)	5 (11.6)	
2	49 (43.8)	27 (38.6)	24 (55.8)	
3	33 (29.5)	21 (30)	9 (20.9)	
TIMI flow, post-procedure, n (%)				0.052
0	1 (0.9)	1 (1.4)	4 (9.3)	
1	0 (0)	0 (0)	0 (0)	
2	3 (2.7)	1 (1.4)	1 (2.3)	
3	108 (96.4)	68 (97.1)	38 (88.4)	
Stent type, n (%)				0.171
Bare metal	44 (39.3)	36 (51.4)	19 (44.2)	
Drug eluted	65 (58)	31 (44.3)	23 (53.5)	
Drug eluted + bare metal	3 (2.7)	3 (4.3)	0 (0)	
Average stent length, med (range)	19 (5.5–112)	20.7 (5.3–70)	20.4 (5.5–43)	0.083
Average stent diameter, med (range)	2.75 (2.5–3.5)	2.75 (2.5–3)	2.75 (2.5–3.25)	0.857
Access site, n (%)				0.095
Radial artery	88 (78.6)	45 (64.3)	27 (62.8)	
Femoral artery	24 (21.4)	24 (34.3)	16 (37.2)	
Time from admission to PCI				**0.002**
< 24h, n (%)	24 (21.4)	30 (42.9)	12 (27.9)	
24–48 h, n (%)	23 (20.5)	20 (28.6)	6 (14)	
48–72 h, n (%)	13 (11.6)	2 (2.9)	8 (18.6)	
> 72 h, n (%)	52 (46.4)	18 (25.7)	17 (39.5)	

PCI – percutaneous coronary intervention; TIMI – thrombolysis in myocardial infarction

Table 3. Major adverse cardiovascular and cerebrovascular events

Variable	Complete one-stage PCI	Complete multi-stage PCI	Culprit-only PCI	p
Intrahospital				
Death, n (%)	1 (0.9)	0 (0)	9 (20.9)	**< 0.0005**
Reinfarction, n (%)	0 (0)	0 (0)	1 (2.3)	0.119
Repeated PCI, n (%)	2 (1.8)	4 (5.7)	4 (9.3)	0.104
Cardiac decompensation, n (%)	1 (0.9)	1 (1.4)	2 (4.7)	0.275
Stroke, n (%)	0 (0)	0 (0)	1 (2.3)	0.119
One-year follow-up				
Death, n (%)	3 (2.7)	0 (0)	13 (30.2)	**< 0.0005**
Reinfarction, n (%)	3 (2.7)	2 (2.9)	4 (9.3)	0.143
Angina pectoris, n (%)	6 (5.4)	6 (8.6)	2 (4.7)	0.610
Heart failure, n (%)	5 (4.5)	4 (5.7)	6 (14)	0.098
Stroke, n (%)	1 (0.9)	0 (0)	2 (4.7)	0.095
Two-year follow-up				
Death, n (%)	4 (3.6)	3 (4.3)	13 (30.2)	**< 0.0005**
Three-year follow-up				
Death, n (%)	6 (5.4)	3 (4.3)	14 (32.6)	**< 0.0005**

PCI – percutaneous coronary intervention

mortality in multivessel NSTEMI may be the result of different mechanisms, which include multiple vulnerable plaques and abnormalities in myocardial perfusion and contractility [9, 12]. Determining the culprit lesion can be challenging in NSTEMI and culprit-only PCI may result in unintentional treatment of a non-culprit lesion rather than a less apparent culprit plaque rupture or erosion [5, 13].

Our study shows a protective effect of complete multi stage PCI in multivessel NSTEMI compared to one stage complete PCI or culprit-only PCI with regard to occurrence of mortality both intrahospital (0% *vs.* 0.9% and 20.9%, respectively, $p < 0.0005$) and after one year (0% *vs.* 2.7% and 30.2%, respectively, $p < 0.0005$) and three years (4.3% *vs.* 5.4% and 32.6%, respectively, $p < 0.0005$), but with no significant impact regarding other MACCE.

According to the results of our study, patients who underwent complete multistage PCI had a lower risk of developing intrahospital MACCE by 62% compared to patients who underwent complete one-stage PCI, who had a 62% lower risk of developing intrahospital MACCE compared to patients who underwent culprit-only PCI (HR 0.387, 95% CI 0.208–0.720, $p = 0.003$).

There is a number of retrospective observational studies and registries that compared culprit-only with complete PCI in patients with multivessel NSTEMI with inconsistent results. According to the results of a large registry by Bauer et al. [14], no difference in intrahospital mortality was found between examined groups. When long term outcomes were analyzed, results of the TRANSLATE study failed to show statistically significant difference in mortality between examined groups during six months of the follow-up period [15]. In contrast to these results, registries conducted by Kim et al. [16] and Rathod et al. [17] showed better survival after one- and five-year follow-ups, respectively, of patients in whom complete revascularization was performed

The potential advantages of multivessel compared to culprit-only PCI include reduction of the myocardial territory at risk and improvement of myocardial function by increasing blood flow to the peri-infarct area, as described before [12]. This is how we explained

Table 4. Cox's analysis of intrahospital major adverse cardiovascular and cerebrovascular events

	B	SE	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Groups	-0.950	0.317	8.959	1	0.003	0.387	0.208	0.720

Table 5. Kaplan–Meier analysis of intrahospital major adverse cardiovascular and cerebrovascular events

Groups	Mean			
	Estimate	Std. error	95% CI	
			Lower bound	Upper bound
Culprit-only	20.5	3.47	13.7	27.3
One-stage complete	24.14	1.82	20.56	27.72
Multi-stage complete	22.3	0.82	20.68	23.91
Overall	27.84	3.05	21.85	33.82

Table 6. Kaplan–Meier (logrank) analysis of intrahospital major adverse cardiovascular and cerebrovascular events (overall comparisons)

Logrank (Mantel–Cox)	χ^2	df	Sig.
	14.988	2	0.001

Table 7. Predictors of intrahospital cumulative major adverse cardiovascular and cerebrovascular events (multivariate binary logistic regression)

Parameter	OR (95% CI)	p
Groups	0.155 (0.063–0.378)	**< 0.0005**
Time to revascularization	0.471 (0.278–0.797)	**0.005**
Culprit artery	0.201 (0.082–0.490)	**< 0.0005**
Hyperlipoproteinemia	0.208 (0.054–0.806)	**0.023**
Pulseless electrical activity/ asystole at admission	0.135 (0.028–0.656)	**0.013**

Table 8. Residual SYNTAX score as a predictor of intrahospital and one-year mortality and cumulative MACCE in the culprit-only group

Mortality	Residual Syntax score		p
	≤ 8, n (%)	> 8, n (%)	
Intrahospital mortality	5 (17.9)	4 (26.7)	0.696
Intrahospital MACCE	7 (25)	7 (46.7)	0.184
One-year mortality	8 (28.6)	5 (33.3)	0.742
One-year MACCE	12 (42.9)	9 (60)	0.347

MACCE – major adverse cardiovascular and cerebrovascular events

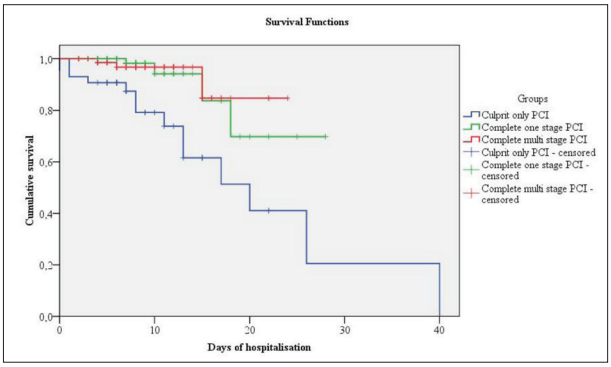

Figure 1. Kaplan–Meier analysis of intrahospital major adverse cardiovascular and cerebrovascular events;

PCI – percutaneous coronary intervention

significantly higher LVEF among patients with complete multi-stage PCI and one-stage PCI compared to culprit-only PCI, respectively (54 ± 8% and 53 ± 10% *vs.* 48 ± 11%, p = 0.005) in our study.

Most studies that compared complete with culprit-only revascularization excluded patients in whom complete multi-stage PCI was planned. SMILE was a randomized prospective trial which, after a one-year follow-up period, showed significant reduction of MACCE in patients with one-stage complete PCI in comparison with multi-stage PCI, mostly caused by a lower rate of repeated PCI, while it failed to show significant difference in reinfarction rate and mortality [18]. Recently, results of a small prospective study comparing total, staged, and fractional flow reserve-guided PCI were published in patients with NSTE-ACS and multivessel disease and they showed comparable effects between examined groups regarding the intrahospital and the six-month clinical follow-up mortality [19].

In previous studies comparing one-stage and multi-stage complete PCI in multivessel NSTEMI, it was hypothesized that a longer procedure duration, higher volume of contrast administered during the index procedure, possible complications (periprocedural myocardial infarction, procedure-related stroke, bleeding requiring transfusion, and contrast induced nephropathy requiring dialysis) could have an impact on higher rate of MACCE among patients with one-stage complete PCI at long-term follow-up [11, 17]. This could explain better long-term survival of patients with multi stage PCI compared to one-stage and culprit-only PCI in our study, but as this was a retrospective observational study, no valid data was available, so further research is needed.

Results of a multinational randomized COMPLETE trial of STEMI patients with multivessel CAD were recently published. This study showed that mortality of cardiovascular origin and reinfarction rate were lower among patients in whom complete revascularization was performed in comparison with culprit-only revascularization during three years of follow-up, regardless of performing complete revascularization during index procedure or as a planned multi-stage revascularization during 23 days [20]. If we were to transfer these results to NSTEMI patients, it would seem reasonable to consider interventions on non-infarct-related arteries in multiple acts, but further studies are needed.

Limitations

Our study has several limitations that could affect the results. Firstly, this was a retrospective observational study conducted at a single hospital, which involved a relatively small number of patients. Secondly, definition of the type of lesion and the method of revascularization depended on the decision of the interventional cardiologist during the procedure and there was no standard approach. Finally, the groups were not fully balanced in terms of the number of patients in each individual group and the existence of a broad composite target event.

CONCLUSION

In our study, in multivessel NSTEMI patients, complete multi-stage PCI is superior to complete one-stage and culprit-only PCI in terms of intrahospital and three-year follow-up mortality.

Conflict of interest: None declared.

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Комплетна реваскуларизација насупрот реваскуларизацији само инфарктне артерије код инфаркта миокарда без елевације СТ сегмента и вишесудовне коронарне болести

Милана Јараковић[1,2], Милован Петровић[1,2], Драган Иванишевић[3], Бојан Михајловић[1,2], Мила Ковачевић[1,2], Ива Попов[2]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Институт за кардиоваскуларне болести Војводине, Сремска Каменица, Србија;
[3]Универзитетски клинички центар Србије, Клиника за кардиохирургију, Београд, Србија

САЖЕТАК

Увод/Циљ Код болесника са инфарктом миокарда без елевације СТ сегмента (*NSTEMI*) и вишесудовном коронарном артеријском болешћу оптимални приступ перкутаном коронарном интервенцијом (ПКИ) још увек није јасан.
Циљ наше студије је био да се истражи појава интрахоспиталних и дугорочних нежељених кардиоваскуларних и цереброваскуларних догађаја (*MACCE*) у овој групи болесника.
Методе Ова ретроспективна студија је укључила 225 болесника са *NSTEMI* и вишесудовном коронарном артеријском болешћу код којих је учињена ПКИ на Институту за кардиоваскуларне болести Војводине. Формиране су три групе: комплетна ПКИ у једном акту, комплетна ПКИ у више актова и ПКИ само инфарктне артерије. Анализирали смо појаву *MACCE* интрахоспитално и после годину дана и морталитет после три године код све три групе болесника.
Резултати Комплетна ПКИ у једном акту урађена је код 112 (49,8%) болесника, у више актова код 70 (31,3%) и само инфарктне артерије код 43 (19,1%) болесника. Болесници са комплетном ПКИ у више актова имали су најмањи морталитет у поређењу са ПКИ у једном акту и ПКИ само инфарктне артерије интрахоспитално (0% насупрот 0,9% и 20,9%, $p < 0,0005$), после једне (0% насупрот 2,7% и 30,2%, $p < 0,0005$) и три године (4,3% насупрот 5,4% и 32,6%, $p < 0,0005$). Није било значајне разлике између група у погледу других *MACCE* интрахоспитално и после годину дана.
Закључак У нашем истраживању, ПКИ у више актова значајно смањује интрахоспитални морталитет после годину и три године код болесника са *NSTEMI* и вишесудовном коронарном артеријском болешћу.

Кључне речи: инфаркт миокарда без елевације СТ сегмента; вишесудовна коронарна болест; перкутана коронарна интервенција; велики нежељени кардиоваскуларни и цереброваскуларни догађаји; морталитет

DOI: https://doi.org/10.2298/SARH220929001J
UDC: 616-001-053.2/.6(497.6)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Characteristics of unintentional injuries in hospitalized children and adolescents – national retrospective study

Duška Jović[1], Snežana Petrović-Tepić[1,2], Darija Knežević[1], Aleksandar Tepić[2], Sanela Burgić[2], Vanja Radmanović[2], Marija Burgić-Radmanović[1]

[1]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[2]University Clinical Centre of the Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

SUMMARY

Introduction/Objective Unintentional injuries is a global health issue among children and adolescents. The aim of this study was to examine the characteristics of unintentional injuries divided according to different age groups and sex among the children and adolescents who have been hospitalized in public hospitals of the Republic of Srpska, Bosnia and Herzegovina.

Methods A retrospective analysis of the e-base of the Agency for Certification, Accreditation and Health Care Quality Improvement of the Republic of Srpska data were collected from 10 public hospitals for patients aged ≤ 19 years, who have been hospitalized for unintentional injuries in the period of January 2018 and December 2020.

Results The study identified 1336 patients who were hospitalized for unintentional injuries, most of whom were boys (67.4%). Falls were the most frequent cause of hospitalization in children of all age categories (aged 1 (70.6%), 1–4 (59.1%), 5–9 (68.5%)) and adolescents aged 10–14 (64.1%), while road traffic injuries were the leading cause of hospitalization in adolescents aged 15–19 (62.6%). The cause of injury for the hospitalized patients were significantly related to age ($p < 0.001$) and sex ($p < 0.05$) groups. According to the nature of the injury in relation to the area of the body, the most frequent injuries were to the head (41.1%), caused by traffic accidents and falls.

Conclusion Since falls and road traffic injuries were the leading causes of hospitalization, preventive measures should be taken to reduce the frequency of these injuries.

Keywords: unintentional injury; child; adolescent; hospitalization

INTRODUCTION

Injuries among children and adolescents are one of the main public health issues globally. Many of them result in pain, disability or death. The majority of these injuries falls into unintentional injuries (90%) [1]. Although these injuries are preventable, they are still prevalent especially in low-income countries where children are more likely to experience and die from unintentional injury [2]. An unintentional injury is defined as an "injury occurring due to non-premeditated acute transfer of mechanical, chemical, thermal or electrical energy or radiation" [3, 4], and the leading causes are road traffic injuries, falls, burns, poisonings and drowning [1, 5, 6, 7]. Over 40,000 children die every year in Europe due to an unintentional injury, with several thousand times more victims who live with varying degrees of disability or injury-related consequences [8]. On the other hand, according to the World Health Organization (WHO) data, it is estimated that tens of millions of children across the globe require hospital care for non-fatal injuries, with a large number of these injuries treated at home and as such remain unregistered [1]. Unintentional injuries that require hospital treatment of children leave consequences psychological, physical and economic for the family and society [9]. Those most at risk of injury are children aged 1–4 and adolescents aged 10–19. Small children, aged 1–4, are especially prone to injury due to their lack of experience, strength and physical skill, in combination with increased curiosity and hyperactivity, while the sudden increase in risk of injury in the age group of 10–19 is associated with engaging in risky behavior [10]. Since children and adolescents are vulnerable categories of population, the risk of unintentional injury in that period are mainly defined through individual factors such as age, development stages of growing up and sex. Additional risk factors that have a significant impact on the occurrence of injury include other factors in the child's social and physical environment [11, 12]. A comprehensive evaluation of the characteristics of unintentional injuries in hospitalized children and adolescents is vital and the foundation for assessing the size of this problem in our country.

The aim of this study was to examine the characteristics of unintentional injuries divided according to different age groups and sex among the children and adolescents who have been hospitalized in public hospitals (PHs) of the Republic of Srpska, Bosnia and Herzegovina.

Received • Примљено: September 29, 2022
Revised • Ревизија: December 27, 2022
Accepted • Прихваћено: December 29, 2022
Online first: January 10, 2023

Correspondence to:
Duška JOVIĆ
Faculty of Medicine
Save Mrkalja 14
Banja Luka
Republic of Srpska
Bosnia and Herzegovina
duska.jovic@med.unibl.org

METHODS

A cross-section study was carried out, including a retrospective analysis of the e-base of the Agency for certification, accreditation and health care quality improvement of the Republic of Srpska (RS ASKVA). A retrospective analysis of the RS ASKVA e-base collected data from all 10 PHs in the Republic of Srpska (eight PHs at the secondary and two at the tertiary level of health care), for the period of January 1, 2018 and December 31, 2020. The search included patients aged ≤ 19, both sexes, with at least one verified diagnosis of unintentional injury at reception. The unintentional injuries were identified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), marked with codes from group XIX (S00-T98) [13]. For patients who had at least one S or T code diagnosis, it was vital to search for additional diagnoses, which involved five external causes of unintentional injury from group XX – External causes of morbidity and mortality (V01-Y98), ICD-10. This study referenced causes the mechanisms of which brought about unintentional injuries according to WHO, so the search included: Road traffic injuries - RTI (V01–V04, V06, V09–V80, V87, V89, V99), Fire/Burns (X00-X09, X10-X19), Poisonings (X40-X49), Falls (W00-W19) and Drowning (W65-W74) [1]. The search excluded all patients whose injuries were verified as intentional (violence, suicide, self-harm). For the purposes of this study, the following data was collected: age, sex, level of health care according to the type of PH, clinic/department, treatment, characteristics of unintentional injuries, length of hospitalization and treatment outcome. The patients were categorized according to age groups into children (aged < 1, 1–4, 5–9) and adolescents (aged 10–14 and 15–19). The characteristics of unintentional injuries were defined according to external causes and nature of injury, and they were analyzed according to age groups and sex. The external causes included road traffic injuries, burns, poisonings, falls and drownings according to the ICD-10 codes mentioned earlier. The nature of the injury was classified according to the injured areas of the body (head; neck; thorax; abdomen, lower back, lumbar spine, pelvis and external genitals; upper limbs; lower limbs; multiple body regions; unspecified) for injuries caused by falls and road traffic injuries, then percentage of Total Burned Surface Area for burns (%TBSA: < 10%; 10–19%; 20–29%) and causes of unintentional poisoning (medication; non-medicinal substances). Treatment outcome was categorized into 1) healed, 2) transferred to another institution and 3) fatal.

The statistical processing of the data was carried out using SPSS Statistics for Windows Version 25.0 (IBM Corp., Armonk, NY, USA), with a 95% statistical significance confidence interval. The statistical analysis encompassed descriptive statistics (mean value, standard deviation, median, frequency, percentage). Differences among the causes of unintentional injuries and the groups of children according to age were tested using the Kruskal–Wallis test, and according to sex and nature of injury using the χ^2 test, while the correlation was tested using Cramer's – V and Contingency Coefficient – C.

The study was approved by the Ministry of Health and Social Welfare of the Republic of Srpska (no: 11/04-500-565/19, dated September 25, 2019), Agency for Certification, Accreditation and Health Care Quality Improvement of the Republic of Srpska (no: 11/2.01-801/19 dated September 26, 2019) and the Human and Biological Material Research Ethics Committee of the Faculty of Medicine at the University of Banja Luka (no: 18/4.3/20 dated February 7, 2020).

RESULTS

Over a three-year period (2018, 2019, and 2020), across ten PHs in the Republic of Srpska, the study identified a total of 1,336 (602, 521, and 213, in that order) children and adolescents hospitalized for unintentional injuries. The average age was 10.1 ± 5.9 years (ranging from 0–19). The largest patient group was in the age of 15–19 (29.4%). The group of adolescents aged 10–19, whose average age was 14.8 ± 2.9, was more frequently hospitalized (53.8%) than children aged 0–9. There was a difference according to sex when it comes to hospitalization, where boys were admitted more frequently (67.4%) than girls. The majority of the patients were treated in institutions of the tertiary level of health care (62.8%), in comparison to the secondary level. The majority of the children and adolescents were treated in surgical clinics/departments (85%). Out of a total of 1336 hospitalized patients, a little over a third required surgical treatment (n = 443, 33.2%), 19 cases required ventilation (1.4%), and 65.4% underwent non-surgical treatment. Over the three-year period, a total of 4,866 days of hospital stay was spent due to unintentional injuries/poisonings (2.163/1.809/914 days of hospital stay in the observed period, in that order), where the average length of hospital stay was 3.7 days (± 5.8 days), and the largest group was that with a stay of 1–7 days. The majority of children and adolescents recovered during hospitalization and were discharged home (95.1%), while there were 0.5% fatalities, all from road traffic injuries. General and clinical characteristics of patients who were hospitalized for unintentional injuries are presented in Table 1.

The leading causes attributed to hospitalization for unintentional injuries are falls (55.5%), followed by road traffic injuries (34%), burns (5.2%), poisonings (5.1%) and three cases of drowning (0.2%). The results showed that there are variations among causes whose mechanisms resulted in unintentional injuries, and age. In all age groups (< 1 year (70.6%), 1–4 yrs. (59.1%) and 5–9 yrs. (68.5%)), the highest number of hospitalizations were caused by falls, which is also true for adolescents in the age group of 10–14 (64.1%). In adolescents aged 15–19, of all the observed causes, the highest number of hospitalizations were caused by injuries sustained in road traffic injuries (62.6%), followed by those from falls (33.6%). The share of burns (5.2%) and poisonings (5.1%) in the overall sample of hospitalizations were equally distributed. Burns were more present among children aged 0–9 (84.3%), with the most cases occurring in those under the age of 1 (23.5%)

Table 1. General and clinical characteristics of patients who were treated for unintentional injuries

Variables	n	%
Age (years) (n = 1336; M = 10.1 ± 5.9)		
>1	51	3.8
1–4	252	18.9
5–9	314	23.5
10–14	326	24.4
15–19	393	29.4
Group (years)		
Children (0–9) **M = 4.6 ± 2.9**	617	46.2
Adolescent (10–19) **M = 14.8 ± 2.9**	719	53.8
Sex		
Male	900	67.4
Female	436	32.6
Level PH		
Secondary	497	37.2
Tertiary	839	62.8
Clinics/departments		
Surgical	1135	85
Non-surgical	177	13.2
ICU	24	1.8
Treatment		
Surgical intervention	443	33.2%
Non-surgical intervention	874	65.4%
Ventilation	19	1.4%
LOS (day) (M = 3.7 ± 5.8)		
1–7	1172	87.7
8–14	128	9.6
15–21	20	1.5
> 22	16	1.2
Outcomes		
Recovery/Home	1270	95.1
Transferred to another hospital	59	4.4
Fatal	7	0.5

M – mean value; SD – standard deviation; PH – public hospital; ICU – intensive care unit; LOS – length of hospital stay

and those aged 1–4 (16.3%). Hospitalization due to poisoning occurred more among children aged 0–9 (72.1%) than among adolescents. For children aged 1–4, poisoning is the number three cause of hospitalization (15.5%). Three cases of drowning were recorded for the age group of 5–9. In hospitalized patients, there is a statistically significant difference ($p < 0.001$) among causes that resulted in injury according to age groups of children and adolescents. The group of adolescents aged 15–19 was the most exposed to causes of injury with varying mechanisms which resulted in hospitalization (median = 5) in comparison with other groups. The causes of unintentional injuries which resulted in hospitalization according to age are presented in Table 2.

When it comes to distribution among the sexes, boys were treated in hospitals significantly more because of injuries caused by road traffic injuries (67.2%), burns (67.1%), falls (69.1%) and drowning (66.7%), while unintentional poisonings were evenly distributed in both sexes (50%). The obtained results have shown that there was a statistically significant difference between boys and girls when it comes to the causes whose mechanisms resulted in unintentional injuries ($\chi^2 = 10.3$, $p = 0.035$, $p < 0.05$).

When it comes to injuries caused by falls and road traffic injuries, three most common positions were found in relation to the area of the body: the head, upper extremities and lower extremities. In hospital treatment, head injuries had the highest percentage among all age groups at 41.8%, constituting 68.4% of the cases in children under the age of 1. Head injuries are followed by injuries of the upper extremities with a total share of 28%, with the highest percentage of such injuries in the group of children aged 5–9 (47.6%). The share of lower extremity injuries was 12.2%. There was a statistically significant correlation between the injured body area and the age of the children, where adolescents (aged 10–19) were more exposed to injuries in varying body areas which resulted in hospitalization ($p < 0.001$). Cramer's V coefficient indicates a weak correlation between the injured body area and the age of the children and adolescents ($V = 0.225$, $p < 0.001$), while the Contingency Coefficient speaks in favor of moderate correlation between the observed variables ($C = 0.411$, $p < 0.001$). The most frequent among burns were those that covered under 10% TBSA (61.4%), and the most vulnerable were children aged

Table 2. The causes of unintentional injuries which resulted in hospitalisation according to age

Variables			Age (in years)					Total	p value
			< 1	1–4	5–9	10–14	15–19		
			Children			Adolescents			
Causes of UI	ICD-10 code								p < 0.001
Road traffic injuries	V01-V04, V06, V09-V80, V87, V89, V99	n	2	23	81	102	246	454	
		%	3.9	9.1	25.8	31.3	62.6	34	
Fire/Burns	X00-X09 X10-X19	n	12	41	6	6	5	70	
		%	23.5	16.3	1.9	1.8	1.3	5.2	
Poisonings	X40-X49	n	1	39	9	9	10	68	
		%	2	15.5	2.9	2.8	2.5	5.1	
Falls	W00-W19	n	36	149	215	209	132	741	
		%	70.6	59.1	68.5	64.1	33.6	55.5	
Drowning	W65-W74	n	0	0	3	0	0	3	
		%	0	0	1	0	0	0.2	
Total		n	51	252	314	326	393	1336	
		%	100	100	100	100	100	100	

I – unintentional injury; ICD-10 – International Classification of Diseases – revision 10; p – Kruskal–Wallis test

Table 3. The nature of injury for hospitalized children and adolescents according to age

Nature of injury		Age (in years)					Total	χ^2 test p value
		< 1	1–4	5–9	10–14	15–19		
		Children			Adolescents			
Injured body area (road traffic, falls n = 1.195)								
Head	n	26	91	103	111	168	499	242.83 p < 0.001
	%	68.4	52.9	34.8	35.7	44.4	41.8	
Neck	n	0	2	0	4	14	20	
	%	0	1.2	0	1.3	3.7	1.7	
Thorax	n	0	1	4	11	14	30	
	%	0	0.6	1.4	3.5	3.7	2.5	
Abdomen, lower back, lumbar spine, pelvis and external genitals	n	0	8	15	15	42	80	
	%	0	4.7	5.1	4.8	11.1	6.7	
Upper limbs	n	0	34	141	121	39	335	
	%	0	19.8	47.6	38.9	10.3	28	
Lower limbs	n	2	16	16	39	73	146	
	%	5.3	9.3	5.4	12.5	19.3	12.2	
Multiple body regions	n	0	0	4	1	3	8	
	%	0	0	1.4	0.3	0.8	0.7	
Unspecified body or limb sites	n	10	20	13	9	25	77	
	%	26.3	11.6	4.4	2.9	6.6	6.4	
%TBSA Fire/Burns (n = 70)								7.47 p = 0.487
< 10% TBSA	n	10	23	2	5	3	43	
	%	83.3	56.1	33.3	83.3	60	61.4	
10–19% TBSA	n	2	14	3	1	1	21	
	%	16.7	34.1	50	16.7	20	30	
20–29% TBSA	n	0	4	1	0	1	6	
	%	0	9.8	16.7	0	20	8.6	
Causes of poisoning (n = 68)								1.75 p = 0.782
Poisoning by non-medicinal substances	n	0	17	5	5	4	31	
	%	0	43.6	55.6	55.6	40	45.6	
Poisoning by medication	n	1	22	4	4	6	37	
	%	100	56.4	44.4	44.4	60	54.4	

TBSA – total burned surface area

under 1 (83.3%) and 1 to 4 (56.1%), where the difference was not statistically significant (p = 0.487). Medication was the most common cause of poisoning (54.4%) resulting in hospitalization, in relation to non-medicinal substances (chemicals, pesticides, cleaning supplies and alcohol), but not at a statistically significant level (p = 0.782). Unintentional poisoning was most frequent in children aged 1–4, with a higher percentage of medication poisonings in the same group (56.4%). Since there were three cases of non-fatal drownings, further statistical analysis of the nature of the injury was not possible due to the sample size. The results of the nature of injury for hospitalized children and adolescents according to age are shown in Table 3.

With regards to sex, boys were more prone to injury in all body areas (68.4%): head (64.7%), neck (85%), thorax (76.7%), abdomen, lower back, lumbar spine, pelvis and external genitals (55%), upper limbs (74.3%) and lower limbs (74.0%), multiple body areas (87.5%) and unspecified body or limb sites (59.7%) in relation to girls ($\chi^2 = 24.8$, p = 0.001, p < 0.05). The difference between boys and girls in relation to %TBSA ($\chi^2 = 0.98$, p = 0.614) and causes of unintentional poisonings ($\chi^2 = 0.54$, p = 0.462) was not statistically significant (p > 0.05).

DISCUSSION

The conducted study found that the leading causes of hospitalization whose mechanisms resulted in unintentional injuries were falls, in 55.5% of the cases, followed by road traffic injuries 34.0%. That falls are the leading cause of hospitalization among children is corroborated by several prior studies [14, 15]. Looking at age groups, falls were identified as the leading cause of hospitalization in children (0–9 years) and adolescents aged 10–14. The obtained results are congruent with data from Scotland for 2020/21, where 43% of the hospitalizations for children aged under 15 for an unintentional injury were the result of a fall [16]. Our study also showed variations among the causes of hospitalization within adolescents. For adolescents aged 15–19, the leading cause of hospitalization is attributed to road traffic injuries, which constituted 62.6% of the total number of cases. The obtained results are similar to those of a national study conducted in Sweden, where the highest absolute differences in risk of traffic injuries were found precisely among adolescents aged 15 to 19 [17]. Road traffic injuries included in this study were responsible for all fatal outcomes which mostly affected adolescents aged 15–19

(85.7%). In Europe, road traffic injuries are the leading cause of death for children between 5 and 19 years of age. The European Academy of Pediatrics is putting in efforts to prevent morbidity and death in children, inviting policy creators to actively work on "vision zero", where no child would perish in traffic [18]. Injury patterns in adolescents differ from those in younger age groups, because the adolescence period is a developmental transition point for risk of injury, thanks to factors such as increased independence and increased tendency to assume risk [19]. The high incidence of injury in traffic in adolescents is partly the consequence of the lack of experience and maturity. In addition, adolescence is characterized by increased independence from parents, peer pressure, use of alcohol, use of mobile phones [20], as well as numerous other factors that include emotions, behavior, complex cognitive processes, culture, and other factors [21].

When it comes to differences among the sexes in all the age groups, our study showed that significantly more boys were hospitalized for unintentional injuries (67.4%) in comparison to girls, which is congruent with prior studies [22, 23].

Analyzing the nature of injury caused by falls and road traffic injuries, this study indicates that out of the total hospitalizations, the most frequent were head injuries (41.8%) compared to all other areas of the body, and that the most prone to such injuries were children under the age of 1 (68.4%). After head injuries, the next most frequent injuries were those of upper (28%) and lower extremities (12.2%). Prior studies showed that head injuries are a frequent cause of hospital admission, and that small children had a higher probability of sustaining a head injury compared to older children [24]. The size of the child's head, their soft and elastic bones in the skull, and weaker support structures of the neck, which contribute to head impact, are characteristics which distinguish them from adults, at the same time making them more susceptible to injury [25].

The results of the conducted study showed that the most hospital admissions for burns, out of the entire sample, were for those with under 10%TBSA (61.4%), which is congruent with prior studies [26, 27]. Children aged 0-4 were the group with the majority of hospitalization for burns, which were the second highest cause of hospitalization in the age group. Prior studies indicate that the first five years of childhood are at high risk for exposure to burns [28], which is often attributed to their curiosity to explore their environment, but also to their lack of instinct to understand danger from specific objects, and the lack of supervision by their parents/guardians [26].

Our data indicated that medication is responsible for 54.4% of unintentional poisonings, where the most exposed were children aged 0–4. This finding corroborates the results of several studies conducted in various countries and various scenarios, where this particular age group is dominated by accidental medication poisoning [29, 30]. The reasons could be that small children spend a significant portion of their time at home, where exposure to risk is associated with access to poisonous substances and medication. Improper storage of medication, lack of parental awareness of the toxicity of reagents, and carelessness with risks and the lack of supervision, all contribute to the incidence of accidental poisoning in childhood [30].

CONCLUSIONS

This study showed that among patients hospitalized due to unintentional injuries, there were significant differences in cause and nature of injury according to age groups and sexes. In children aged 0–9 and adolescents aged 10–14, the most frequent cause of hospitalization are injuries caused by falls, while traffic accidents are the leading cause of hospitalization among adolescents aged 15–19. Boys were significantly more hospitalized due to unintentional injuries caused occurring due to external causes. The most dominant injuries across all age groups were head injuries, caused by falls and traffic accidents. Therefore, undertaking preventive measures aimed at reducing injuries from falls and traffic accidents would be of crucial importance.

ACKNOWLEDGMENT

This paper is the part of Duška Jović doctoral thesis and presents some of the results that will be published in the thesis at the Faculty of Medicine, University of Banja Luka.

Conflict of interest: None declared.

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Карактеристике ненамерних повреда међу болнички леченом децом и адолесцентима – национална ретроспективна студија

Душка Јовић[1], Снежана Петровић-Тепић[1,2], Дарија Кнежевић[1], Александар Тепић[2], Санела Бургић[2], Вања Радмановић[2], Марија Бургић-Радмановић[1]

[1]Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина;
[2]Универзитетски клинички центар Републике Српске, Бања Лука, Република Српска, Босна и Херцеговина

САЖЕТАК

Увод/Циљ Ненамерне повреде представљају глобални јавноздравствени проблем међу децом и адолесцентима. Циљ истраживања је био испитати карактеристике ненамерних повреда према различитим добним групама и полу међу децом и адолесцентима који су болнички лечени у јавним болницама Републике Српске.

Метод Ретроспективном анализом е-базе Агенције за сертификацију, акредитацију и унапређење квалитета здравствене заштите Републике Српске прикупљени су подаци из 10 јавних болница за пацијенте доби ≤ 19 година који су хоспитализовани због ненамерних повреда у периоду од јануара 2018. до децембра 2020. године.

Резултати Идентификовано је 1336 пацијената, од којих су већина били дечаци (67,4%), који су хоспитализовани због ненамерних повреда. Падови су били први узрок хоспитализације деце свих добних категорија (< 1 године (70,6%), 1–4 године (59,1%), 5–9 година (68,5%)) и адолесцената 10–14 година (64,1%), док су саобраћајне незгоде биле водећи узрок хоспитализација у групи адолесцената доби 15–19 година (62,6%). Узроци повреда хоспитализованих пацијената значајно су повезани са добним ($p < 0,001$) и полним ($p < 0,05$) групама. Према природи повреде у односу на регију тела, најчешће су биле повреде главе (41,1%) настале услед саобраћајних незгода и падова.

Закључак С обзиром на то да су падови и саобраћајне незгоде водећи узроци хоспитализације, потребно је предузети превентивне мере за смањење ових повреда.

Кључне речи: ненамерне повреде; деца; адолесценти; хоспитализација

DOI: https://doi.org/10.2298/SARH221206031R
UDC: 616.36-008.6-053.2; 616.366-003.7-053.2

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Gilbert syndrome as a risk factor for the development of cholelithiasis in children

Vladimir Radlović[1,2], Zoran Golubović[1,2], Zoran Leković[1,2], Siniša Dučić[1,2], Nedeljko Radlović[3], Branislav Jovanović[1,2], Bojan Bukva[1,2], Polina Pavićević[1,2], Dejan Nikolić[1,2], Jovana Janković[1]

[1]University Children's Hospital, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Serbian Medical Society, Academy of Medical Sciences, Belgrade, Serbia

SUMMARY

Introduction/Objective Gilbert syndrome (GS) is the most common hereditary hyperbilirubinemia. As well as mild unconjugated hyperbilirubinemia, it is characterized by the excess of bilirubin monoglucuronide over diglucuronide in the bile and thus increases the risk of biliary calculosis. The aim of the study was to determine the importance of GS as a risk factor in the development of cholelithiasis in children.

Methods The study included a sample of 31 children (14 male and 17 female, mean age 12.16 ± 4.11 years, range 3–16.75 years) with symptomatic cholelithiasis. The diagnosis of cholelithiasis was based on an ultrasonographic finding, and for GS the diagnosis was based on at least a double increase of unconjugated bilirubin fraction after a three-day hypocaloric diet (400 kcal per day).

Results GS was confirmed in five or 16.13% of patients (three male and two female, mean age 14.71 ± 0.55 years, range 14–15.3 years). In addition to GS, in the history of the disease they all had some of the additional risk factors for the development of cholelithiasis. One of them had an identical problem as its mother, one had hereditary elliptocytosis, one had sudden weight loss, one was overweight, and one had premature birth and sepsis.

Conclusion GS registers in one-sixth of children with cholelithiasis, but in none of them as the only risk factor for developing this disease. This finding suggests that GS is a risk factor for the development of cholelithiasis, but not sufficient in itself in that respect.

Keywords: Gilbert syndrome; cholelithiasis; children

INTRODUCTION

Gilbert syndrome (GS) is the most common hereditary hyperbilirubinemia [1–4]. It is registered in 2–13% of the general population and characterized by a mild, intermittent unconjugated hyperbilirubinemia without evidence of hemolysis or liver injury caused by the autosomal recessive deficit of bilirubin uridine diphosphate glucuronosyltransferase (UGT1A1), a microsomal enzyme of the hepatocyte, which is of crucial importance in the conjugation of bilirubin with glucuronic acid [1–6]. The *UGT1A1* gene located on the long arm of chromosome 2 (2q37.1) is responsible for the expression of this enzyme [1]. The consequence of this genetic defect, the most common due to extra bases (TA) in the TATAA box sequence of the promoter region of the *UGT1A1* gene, is reduced synthesis of UGT1A1 by at least 50%, and consequently lower capacity of bilirubin conjugation and excretion [4, 6]. An additional pathogenetic significance in the occurrence of hyperbilirubinemia is a shorter lifespan of erythrocyte present in about one-half of cases, as well as the defect of the uptake and transport of unconjugated bilirubin at the hepatocyte level [4, 7]. Beside unconjugated hyperbilirubinemia, the UGT1A1 deficit is followed by the excess of bilirubin monoglucuronide compared to bilirubin diglucuronide in bile, which makes individuals with GS more prone to bilirubin (pigment) cholelithiasis [5, 7–14]. In the expression of GS, sex hormones, especially androgens, have significant effect, which explains its rare manifestation before puberty, and two to seven times higher incidence in males than in females [7, 11]. Higher erythrocyte count and muscle mass in men compared to women contribute significantly to this difference [7]. Earlier expression of GS is seen in young infants with hypertrophic pyloric stenosis, annular pancreas, congenital atresia and stenosis of small intestine, and other diseases accompanied with caloric deficits, as well as within the breastfeeding jaundice [1, 6, 15].

In GS without associated disorders, such as hemolytic and liver disease, serum bilirubin levels usually vary between normal values and 35–70 μmol/L, and rarely above that value [2]. Hyperbilirubinemia is precipitated and potentiated by low calorie intake, physical exertion, and fever [3, 7]. GS is not followed by other complications except for an increased risk for the development of biliary calculosis, significant involvement in incidence and degree of unconjugated hyperbilirubinemia in newborns and patients with hemolysis and hepatic impairment, as well as irinotecan intolerance [7].

Received • Примљено: December 6, 2022
Revised • Ревизија: March 18, 2023
Accepted • Прихваћено: March 19, 2023
Online first: March 21, 2023

Correspondence to:
Vladimir RADLOVIĆ
University Children's Hospital
Tiršova 10
11000 Belgrade, Serbia
vladar@beotel.net

The aim of the study was to determine the importance of GS as a risk factor in the development of cholelithiasis in children.

METHODS

The study was based on a sample of 31 children (14 male and 17 female, mean age 12.16 ± 4.11 years, range 3–16.75 years) hospitalized due to symptomatic cholelithiasis.

The diagnosis of cholelithiasis was performed by ultrasonographic examination of the abdomen. In addition to the details related to the symptoms and signs of cholelithiasis, as well as the presence of risk factors for its occurrence, all patients were subjected to a detailed physical examination and appropriate laboratory tests. In patients with unconjugated hyperbilirubinemia, in addition to insight into reticulocyte count and the appearance of erythrocytes, Coombs's test and measurement of osmotic resistance of erythrocytes were made. Since all patients had uncomplicated symptomatic cholelithiasis, all of them underwent laparoscopic cholecystectomy [16, 17]. According to the number of biliary concrements, cholelithiasis is classified into solitary and multiple, and, depending on their appearance, into pigment, cholesterol, and mixed [17, 16].

In all patients with unconjugated hyperbilirubinemia, verified during diagnosis of cholelithiasis or during recovery from cholecystectomy, tests for GS were performed. The diagnosis of GS is based on at least a double increase in the unconjugated serum bilirubin fraction after 72 hours of the hypocaloric diet (400 kcal per day), as well as its normalization or significant decrease after two to three days of administration of phenobarbitone (2–3 mg/kg) (Figure 1) [18]. This procedure was done in three patients before cholecystectomy and in two of them two months after surgery. The study was approved by the local ethics committee.

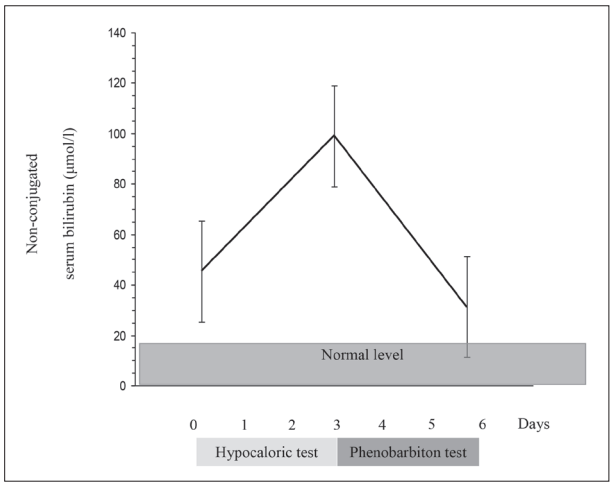

Figure 1. Serum non-conjugated bilirubin level after hypocaloric and phenobarbital test

RESULTS

GS and cholelithiasis association was established in five (16.13%) of 31 patients (three male and two female, mean age 14.71 ± 0.55 years; range 14–15.3 years) with cholelithiasis. Unconjugated hyperbilirubinemia was observed in three patients during the diagnosis of cholelithiasis and in two at the time of recovery from cholecystectomy. The underlying symptom that preceded the diagnosis of cholelithiasis was intense abdominal pain, recurrent in four and acute in one, localized in epigastrium and/or right hypochondrium, followed by emesis and occasional vomiting. All patients with cholelithiasis and GS had some of the additional risk factors for the development of biliary calculosis (Table 1). Except for a boy with hereditary elliptocytosis, with a transient choledocholithiasis and cholestasis three months before admission, other complications of cholelithiasis were not recorded.

Apart from palpatory pain and sensitivity in the epigastrium and/or right hypochondrium, which was present in all of the patients, a slight scleral icterus in three of them, palpable spleen by 1 cm in a boy with hereditary elliptocytosis, and being slightly overweight in one girl (+12.5%), other physical findings on admission were normal in all.

With exclusion of a boy with hereditary elliptocytosis, in whom, together with an unconjugated hyperbilirubinemia (114 μmol/L), characteristic erythrocyte appearance and significant reticulocytosis was found (4.2%), and two more with elevated unconjugated fraction of bilirubin in the serum (36 and 38 μmol/L), other laboratory analysis on admission, including blood hemoglobin values and additional liver tests, were normal in all.

Laparoscopic cholecystectomy was uneventful in all five patients. The number and appearance of their concretions are given in Table 1.

Table 1. Additional risk factors for the development of cholelithiasis in children with Gilbert's syndrome and appearance and number of biliary calculi

Patient	Risk factors	Appearance and number of calculi
1	Hereditary elliptocytosis	Black pigment, multiple
2	Cholelithiasis in mothers	Brown pigment, solitary
3	Premature birth (32 GW) neonatal sepsis	Black pigment, multiple
4	Overweight (+12.5%)	Black pigment, multiple
5	Reduction diet (sudden weight loss)	Black pigment, multiple

GW – gestational weeks

DISCUSSION

Thanks to ultrasound diagnostics, it is known today that cholelithiasis is not so rare in children, especially in those at the final stage of childhood [16, 17, 19]. Its prevalence in this age has been reported to be 0.13–0.22% [16, 19]. The main risk factors for gallstone formation in childhood, in addition to the family predisposition, are the diseases accompanied by reduced solubility of the biliary content,

such as hemolysis, obesity, anorexia nervosa, long-lasting total parenteral nutrition, hepatobiliary disorders, hypercholesterolemia, terminal ileum resection, cholecystitis, cystic fibrosis, and others, as well as premature birth and rapid weight loss [16, 17, 19–23]. With the onset of puberty, cholelithiasis is more common in girls than in boys [17, 20–23]. Due to the excess of the less hydrolysable bilirubin monoglucuronide to bilirubin diglucuronide and bile, GS is also ranked as the risk factor for the development of biliary calculosis [5, 7–14]. This fact is particularly present in the association of GS with hemolysis and other diseases accompanied by high inclinations to biliary calculosis [5, 16, 24].

The clinical picture of cholelithiasis in older children is similar to that of adults and is characterized by episodes of spasmodic postprandial pain localized in the right hypochondrium or epigastrium, accompanied by nausea, and often by vomiting [17, 20, 25]. However, in younger children it can be quite atypical, and resemble acute appendicitis, intussusception, volvulus and other acute surgical conditions that must be ruled out [25]. In a significant number of cases, cholelithiasis is complicated by cholecystitis, and rarely by gallbladder empyema and choledocholithiasis, followed by ascending cholangitis, and pancreatitis [16, 17, 19, 21]. Also, gallbladder perforation with bile peritonitis, and life-threatening sepsis is possible [26, 27].

Therapy of symptomatic cholelithiasis is surgical [16, 19, 28], and in uncomplicated cases the laparoscopic approach is preferred and widely adopted [16, 19, 28, 29, 30].

Symptoms and signs of cholelithiasis in our patients were quite characteristic [16, 23, 25]. None of them had complications of the disease, so laparoscopic cholecystectomy was performed in all of them, without conversion to open procedure.

Our data suggests that GS is a risk factor in the development of cholelithiasis, but not sufficient in itself in that respect. The presence of GS in patients with cholelithiasis is encountered more frequently (16.13%) in comparison to cholelithiasis prevalence in the general population (2–13%) and shows that GS can be considered a biliary lithogenic factor [1–5]. An additional argument in favor of this is the fact that out of five patients with cholelithiasis and GS three were boys and two were girls, while this relationship in the group of those without GS was reversed (11 *vs.* 15). Also, in four out of five patients, the biliary concrements were black-pigmented [5]. However, what disables this conclusion in the full sense is the fact that in all of them, besides GS, another risk factor for the development of cholelithiasis is also registered. In addition, patients with cholelithiasis and GS were on average significantly older than those without GS (14.71 *vs.* 11.67 years).

CONCLUSION

According to our study, GS registers in every sixth child with cholelithiasis, or more than twice as often compared to its average frequency in the general population, but never as the only risk factor for the development of this disease. This finding suggests that GS is a risk factor for the development of cholelithiasis, but not sufficient in itself in that regard.

Conflict of interest: None declared.

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Жилберов синдром као фактор ризика за развој холелитијазе код деце

Владимир Радловић[1,2], Зоран Голубовић[1,2], Зоран Лековић[1,2], Синиша Дучић[1,2], Недељко Радловић[3], Бранислав Јовановић[1,2], Бојан Буква[1,2], Полина Павићевић[1,2], Дејан Николић[1,2], Јована Јанковић[1]

[1]Универзитетска дечја клиника, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Српско лекарско друштво, Академија медицинских наука, Београд, Србија

САЖЕТАК

Увод/Циљ Жилберов (*Gilbert*) синдром (ЖС) представља најчешћи хередитарни поремећај метаболизма билирубина. Сем благе неконјуговане хипербилирубинемије, карактерише га ексцес билирубин-моноглукоронида у односу на диглукуронид у жучи и тиме повећан ризик од билијарне калкулозе. Циљ студије је био да се утврди значај ЖС као фактора ризика у развоју холелитијазе код деце.

Методе Студија је обухватала узорак од 31 детета (14 дечака и 17 девојчица, узраста три до 16,75 година, просечно 12,16 ± 4,11 година) са симптоматском холелитијазом. Дијагноза холелитијазе је заснивана на ултрасонографском налазу, а ЖС на најмање двоструком порасту неконјуговане фракције билирубина после тродневне хипокалоријске дијете (400 *kcal* дневно).

Резултати ЖС је доказан код пет или 16,13% болесника (три дечака и две девојчице, узраста 14 до 15,3 година, просечно 14,71 ± 0,55 година). Поред ЖС сви су у анамнези имали и неки од додатних фактора ризика за развој холелитијазе. Један болесник је имао идентичан проблем као мајка, један је имао хередитарну елиптоцитозу, један нагло мршављење, један вишак телесне тежине и један превремено рођење и сепсу.

Закључак ЖС се региструје код једног од шесторо деце са холелитијазом, али ни код једног од њих као једини фактор ризика за развој овог обољења. Овај налаз указује да је ЖС фактор ризика за развој холелитиазе, али не и да је у том смислу довољан.

Кључне речи: Жилберов синдром; холелитијаза; деца

DOI: https://doi.org/10.2298/SARH220708015L
UDC: 616.346.2-002(497.113)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparison of conservative and operative treatment of uncomplicated appendicitis in the pediatric population

Ivana Lukić[1,2], Jelena Antić[1,2], Veličko Trajković[1,2], Svetlana Bukarica[1,2], Jan Varga[1,2], Mihajlo Jecković[3]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Institute for Child and Youth Health Care of Vojvodina, Clinic of Pediatric Surgery, Novi Sad, Serbia;
[3]ST Medicina Institute of Occupation Health, Novi Sad, Serbia

SUMMARY

Introduction/Objective Studies about possibilities of conservative, i.e., non-operative management of acute uncomplicated appendicitis in adult and pediatric population have been published lately, considering benefits of preserving appendix and potential complications related to appendectomy.

Methods In this retrospective study, medical data of 76 patients treated at the Institute for Child and Youth Health Care of Vojvodina in Novi Sad for acute uncomplicated appendicitis in 2015 and 2016 have been analyzed, comparing length of stay, antibiotic therapy use, complications occurrence, as well as the financial burden depending of the type of therapy applied.

Results During this period, 76 patients (55 operated on and 21 treated conservatively) were treated for acute uncomplicated appendicitis. Conservatively treated children spent statistically significantly shorter period of time at the hospital compared to the ones operated on (4.24 *vs.* 5.76 days; $p < 0.001$). Early surgical complications occurred in 10.91% of those operated on and in 9.52% conservatively treated children, which was not a statistically significant difference ($p = 0.863$). The total cost of hospital stay was significantly lower in those who underwent non-operative management (10,340 RSD *vs.* 54,281 RSD; $p < 0.001$). The difference was significant even when analyzing costs related to rehospitalization and operative treatment of children initially treated conservatively ($p < 0.001$).

Conclusion Non-operative, i.e., conservative treatment of acute uncomplicated appendicitis in the pediatric population is safe and effective compared to the operative one, and it is not associated with more frequent occurrence of early surgical complications. Total costs for the non-operative treatment are significantly lower, even considering costs related to re-hospitalization of children initially treated conservatively.

Keywords: acute uncomplicated appendicitis; conservative treatment; antibiotics; children

INTRODUCTION

Acute appendicitis is the most common intra-abdominal condition in children that requires surgical intervention. It is considered to occur in approximately 4–8% of the pediatric population, with the pick incidence in the second decade of life, while it is extremely rare (incidence less than 0.5%) during the first year of life [1–4]. Appendicitis can be classified as complicated (appendicitis with generalized peritonitis or appendicitis abscess) or as an uncomplicated disease [5].

The role of appendix in the human body is still a subject of debate. It is believed that appendix is an important part of the immune system as a "safe-house" for beneficial microbiota, and therefore is important for recolonizing the bowel after gastrointestinal infections balancing between pathogenic and commensal bacteria [1, 6]. There is also evidence that mesenchymal cells of appendix can be a source for restauration of damages in intestinal tract during a lifetime. It can be used for performing vesicostomy (Mitrofanoff procedure) or appendicostomy for anterograde enemas (Malone procedure), and, in recent studies, decellularized appendix was used in a preclinical model for bladder augmentation [7].

Although operative management is the "gold standard" in treating acute appendicitis, conservative (non-operative) management for carefully selected children has been described as an efficient alternative [8]. Operative approach can be open (classical) or laparoscopic.

Evidence of conservative treatment of acute appendicitis has been found in a mummy from the Byzantine era. However, a significant improvement has occurred with the implementation of antibiotics in the 20th century [9]. This management can be applied if there are no certain indications for surgery, such as the presence of peritonitis or signs of perforation. At first, these studies were conducted only in adults, but recently a larger number of studies included pediatric patients as well [8, 10, 11].

There have been debates about the need for interval appendectomy after successful conservative management. Recently published studies claim that, considering the low risk of occult appendiceal neoplasm in young individuals, interval appendectomy is recommended

Received • Примљено: July 8, 2022
Revised • Ревизија: November 17, 2022
Accepted • Прихваћено: January 26, 2023
Online first: February 3, 2023

Correspondence to:
Ivana LUKIĆ
Hajduk Veljkova 10
21000 Novi Sad, Serbia
1412d20@mf.uns.ac.rs
ivana.lukic.md@gmail.com

in patients older than 30 and with complicated forms of appendicitis [12]. Considering potential risks related to surgery and/or anesthesia as well as potential benefits of appendix preservation, it is important to analyze safety and efficiency of conservative management of acute uncomplicated appendicitis in children.

METHODS

This study included 76 children treated between January 2015 and December 2016 at the Institute for Child and Youth Health Care of Vojvodina under the diagnosis of acute uncomplicated appendicitis. Respondents were divided into two groups: conservatively treated and operatively treated. The study was performed as a retrospective descriptive study. In the conservatively treated group there were children who had clinical, radiological, and/or laboratory signs of acute appendicitis, but were not operated on during their initial hospitalization according to the clinical monitoring of the patient. Patients with similar signs and symptoms who were selected by the attending surgeon for operative treatment were in the other group.

The diagnosis was made based on the patient's history, physical examination, laboratory tests, and ultrasound findings. The ultrasound examination results were categorized depending on the findings on the appendix and surrounding structures. A negative finding was labeled as U0, unspecified as U1, a positive finding limited to the appendix as U2, while a positive finding on the appendix associated with signs of inflammation of the surrounding adipose tissue and/or the presence of free fluid in the abdomen was labeled as U3.

Children who were operated on underwent either laparoscopic or open appendectomy. After hospital admission, oral intake was paused and parenteral rehydration was initiated. antibiotic therapy was administered 30–60 minutes preoperatively and surgery was performed under general anesthesia. Each removed appendix was sent for histopathological verification. Parenteral antibiotic therapy was continued postoperatively, observing postoperative recovery. Oral intake was paused as well in patients who were treated conservatively, followed by parenteral rehydration. If no progression of symptoms was observed during the clinical follow-up, conservative treatment was started, with only parenteral antibiotics 6–12 hours after admission. After 24 hours, if there was no progression of symptoms, oral intake was initiated. The duration of parenteral antibiotic therapy depended on the general condition of the patient, tolerance of oral intake, as well as laboratory analyses, i.e., (elevated) leukocyte values. Children from both study groups were discharged after the resolution of symptoms, the initiation of oral intake, and with established intestinal peristalsis; the antibiotic therapy was continued in the oral form.

The consent for conducting the research was obtained by the Ethics Committee of the Institute for Child and Youth Health Care of Vojvodina in Novi Sad. Reviewing patients' medical charts, we analyzed the occurrence of individual signs and symptoms of the disease, the presence of leukocytosis, ultrasound findings, as well as the duration of hospital stay, antibiotics' administration, and possible complications, including appendectomies performed in initially conservatively treated patients. Also, financial burden during the patients' stay in hospital conditions was analyzed.

Recorded data were analyzed using Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The data were described using frequencies, percentages, means, and standard deviations where appropriate. Between-group differences were analyzed using the independent-samples t-test, Mann–Whitney U test, and χ^2 test, while correlations between variables were estimated using Pearson's (r) and Spearman's (ρ) correlation coefficients. Calculated differences lower than the significance level of 0.05 were considered relevant.

RESULTS

During this period, 76 patients were treated for uncomplicated acute appendicitis at the Institute for Child and Youth Health Care of Vojvodina in Novi Sad. There were 55 children in the "operative treatment" group (30 males *vs.* 25 females) and 21 children in the "conservative treatment" group (14 males *vs.* 7 females). The mean age of children in the "operative treatment" group was 10.88 ± 3.801 years, while in the "conservative treatment" group it was 11.44 ± 3.398 years ($p = 0.539$) (Table 1). In the majority of children, symptoms did not last longer than 24 hours (71.43% in the group of conservatively treated and 80% in the group of operated). In the group of conservatively treated children there were no patients whose symptoms were present longer than a week, while in the group of operatively treated children there were 3.64% of such patients. This difference was not statistically significant ($p = 0.465$) (Figure 1). The groups were similar considering the age and sex of the patients, as well as the duration of their symptoms.

In the majority of patients (95.24% of conservatively treated and 83.64% of those operated on) leukocyte values (WBC) were above the reference values, although the difference between the groups was not statistically significant ($p = 0.232$) (Table 1).

Also, in the majority of children (80.95% in the group of conservatively treated and 72.73% in the group of those operated on) ultrasound findings corresponded to U3. A finding that corresponded to U2 was determined in 9.52% of patients in the "conservative treatment" group, and in 7.27% of those who had been operated on. An indeterminate finding (U1) was determined in 9.52% of children who were treated conservatively, and in 18.18% of the children who were operated on. Due to technical reasons, ultrasound diagnostics were not performed in 1.82% of the children from the group of surgically treated. The difference between these groups was not statistically significant ($p = 0.72$) (Figure 2).

Table 1. Differences in the age of patients, laboratory parameters (leukocytes – WBC), hospital stay, and the duration of antibiotic therapy

Parameters		Mean	Std. deviation	p
Age (years)	conservative treatment	11.44	3.398	0.539
	operative treatment	10.88	3.801	
WBC (10×10^9/l)	conservative treatment	16.438	3.7048	0.232
	operative treatment	15.005	4.9417	
Hospital stay (days)	conservative treatment	4.24	1.091	**0.0000**
	operative treatment	5.76	1.018	
Parenteral antibiotic therapy (days)	conservative treatment	2.86	1.558	**0.0000**
	operative treatment	5.29	1.536	
Enteral antibiotic therapy (days)	conservative treatment	6.19	2.4	**0.0000**
	operative treatment	1.64	2.256	

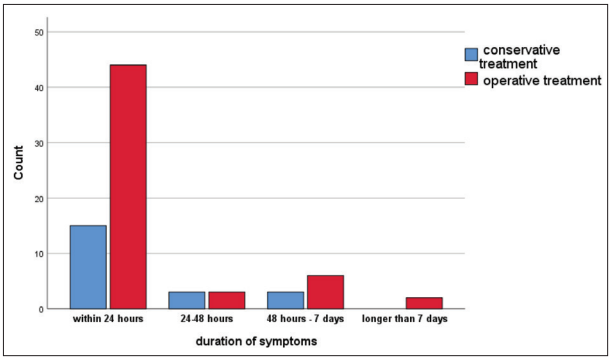

Figure 1. Duration of symptoms before hospitalization

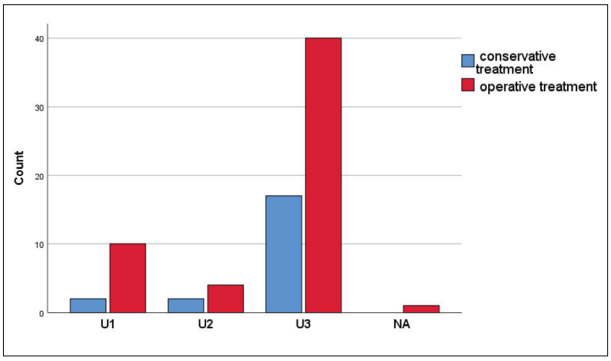

Figure 2. Ultrasound findings;
U1 – unspecified; U2 – a positive finding limited to the appendix; U3 – a positive finding on the appendix, associated with signs of inflammation of the surrounding adipose tissue and/or the presence of free fluid in the abdomen; NA – ultrasound not performed

Hospital stay was significantly shorter in conservatively treated children (4.24 ± 1.091 *vs.* 5.76 ± 1.018 days; p < 0.0001) (Table 1). These children were given parenteral antibiotic therapy significantly shorter as well (2.86 ± 1.558 *vs.* 5.29 ± 1.536 days; p < 0.0001) (Table 1).

After hospital discharge, except for two of them (9.52%), all the children continued to take oral antibiotics. Conservatively treated patients were taking oral antibiotics for an average of 6.19 ± 2.4 days, which is significantly longer (p < 0.0001) compared to 1.64 ± 2.256 days in the group of patients who were operated on (Table 1).

Analyzing all the children, early surgical complications were slightly more common in the group of patients who were operated on (in 10.91% compared to 9.52% in conservatively treated patients), but this difference was not statistically significant (p = 0.863). Within 10 months after successful conservative treatment, six patients (28.57%) came back due to abdominal pain and/or other symptoms that may have been related to appendicitis, but only in two of them (9.52%) complications really occurred, i.e., recurrence of acute appendicitis (Figure 3). These two children developed recurrent appendicitis four months after discharge, which was treated operatively (minimally invasive). One of them was uncomplicated and one was complicated appendicitis. Also, one month after the discharge, one child underwent elective appendectomy despite the absence of symptoms, on the parents' request. Postoperative complications were wound secretion, epigastric pain, obstruction, minor purulent collection in the ileocecal lodge, and the presence of an intra-abdominal abscess. No cases of ileus have been reported. Correlation analysis did not show an association between complications' occurrence and the duration of taking parenteral or oral antibiotics (Table 2).

Hospital costs during conservative and operative treatment were analyzed. Because of the high cost of drugs used due to the underlying disease (coagulation disorders), the costs of treating one child who was operated on had a value that stood out as extreme during the statistical analysis, which excluded this case from subsequent analyses that included this variable. The costs of hospital treatment

Table 2. Correlations between complication occurrence and duration of antibiotic therapy

Parameter				Parenteral antibiotic therapy	Enteral antibiotic therapy
conservative treatment	Spearman's ρ	complications	Correlation coefficient	-0.384	0.274
			Sig. (2-tailed)	0.086	0.230
operative treatment			Correlation coefficient	-0.186	-0.051
			Sig. (2-tailed)	0.173	0.709

Table 3. Hospital costs (including re-hospitalization in conservatively treated patients)

Parameter			Mean	Std. Deviation	p
hospital costs (RSD)	1st hospitalization	conservative treatment	10,340.41	3599.43	0.0000
		operative treatment	54,281.82	6242.02	
	2nd hospitalization	conservative treatment	20,845.56	28,533.75	0.0000
		operative treatment	54,281.82	6242.02	

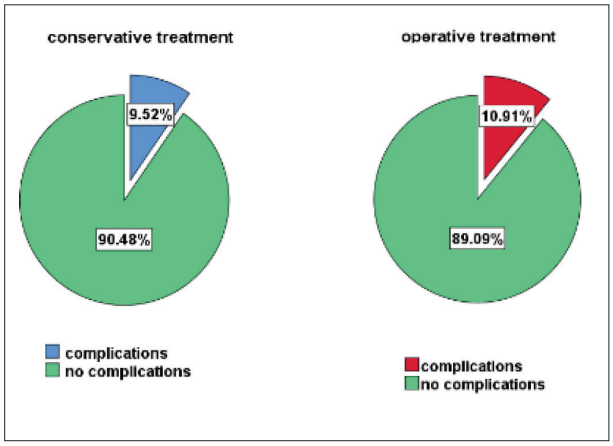

Figure 3. Rate of complications

for children undergoing conservative treatment were significantly lower (10340.41 ± 3599.43 RSD *vs.* 54281.82 ± 6242.02 RSD; $p < 0.0001$). The difference was significant even considering the costs related to a re-hospitalization for surgical treatment of children who were initially conservatively treated ($p < 0.0001$) (Table 3).

DISCUSSION

Suspected acute appendicitis is the most common surgical reason for visiting the emergency department in pediatric population. The clinical picture is primarily characterized by acute abdominal pain. Distinguishing acute appendicitis from other conditions that manifest with acute abdominal pain can sometimes be very difficult in childhood, both due to difficult examination and communication with the patient, and due to the fact that the manifestation of this disease in childhood can be very different. In our study, during the observed period, 76 patients were treated for acute uncomplicated appendicitis. Patients included in the study were approximately 11 years old, which is similar to peak incidence during the first two decades of life reported in literature [1, 2, 13]. Compared to children of preschool age or younger, school-age children are usually able to express their symptoms in an appropriate way, which might be the reason why majority of our patients referred to the emergency department within 24 hours after symptoms onset. A delay in presenting to the emergency department has been shown to harm the success of conservative treatment [14].

One of the most commonly used laboratory parameters when considering the diagnosis of acute appendicitis is the number of leukocytes. Some authors state that the number of neutrophils is a far more sensitive parameter and that neutrophil to lymphocyte ratio can be a useful predictor of complicated appendicitis forms [15, 16]. A significant percentage of our subjects (83.64–95.24%) had leukocyte values greater than 10×10^9/L, which is consistent with the diagnosis. Considering the fact that neutrophils and lymphocytes were not determined in the majority of our patients, in this study we did not analyze neutrophil count and lymphocyte to neutrophil ratio, but it remains as an interesting idea for future researches. The number of neutrophils is not routinely determined in most laboratories. In this regard, Kalan et al. modified the most commonly used Alvarado score by excluding neutrophilia as one of the score parameters, and thus adapted it to the pediatric population [17].

Frequent use of ultrasound imaging in diagnosis of acute appendicitis can be explained due to its high sensitivity and specificity, as well as its harmlessness [18]. Ultrasound sensitivity in the diagnosis of acute uncomplicated appendicitis is estimated at 62–100%, and specificity at 79.1–96.8% [18, 19]. Although the specificity of computed tomography (CT) in the diagnosis of acute appendicitis is considered to be 100%, and the sensitivity is about 90%, it is known that the CT method is more harmful due to the high dose of ionizing radiation. In addition, ultrasound diagnostics is far more accessible. In a recently published study by a group of Turkish authors, CT showed greater sensitivity and specificity in relation to ultrasound, although it did not lead to a reduction in the number of negative appendectomies in children [20]. However, an optimization of the ultrasound diagnostics quality resulted in a 67%-decrease in utilizing CT imaging in patients with suspected acute appendicitis, and consequently in a significant decrease in hospital costs [21]. In the study by Binkovitz et al. [22], in which ultrasound diagnostics were analyzed and compared to operative and histological findings, the categorization of ultrasound findings was performed. Ultrasound findings indicating acute uncomplicated appendicitis with signs of inflammation of the surrounding adipose tissue or the presence of free fluid in the abdomen were most commonly observed in this study, in 72.73–80.95% of children. In addition, less than 10% of children had signs limited to the appendix, which indicate its inflammation, such as an increase in the diameter of the appendix above 6 mm, an increase in the thickness of its wall, incompressibility, and the possible presence of an appendicolith. There were also several cases in which the finding could not be determined with certainty, because the appendix was not visualized. In reported literature, in approximately 10% of cases, the appendix cannot be visualized, and possible reasons for this are abdominal wall tension, obesity, air or fecal superposition, or atypical position of the appendix [19, 23, 24]. There were no patients in this study that underwent CT scans.

Analyzing hospital stay, patients included in our study who were treated with antibiotics only had significantly shorter hospital stay compared to the ones operated on (approximately four compared to six days). This finding is consistent with several reported studies in the pediatric population, but some studies reported shorter hospital stays for conservatively treated compared to the operatively treated adult patients with acute uncomplicated appendicitis, but not for children treated for the same condition. Also, there are studies which find no significant difference between these two therapeutic modalities [14, 25]. The length of hospital stays of patients operated on for acute appendicitis is significantly longer in our study possibly due to the different protocols considering the length of

hospital stay after appendectomy in our hospital, which differs from studies published world-wide [26, 27, 28].

The majority of published studies describe conservative treatment using parenteral antibiotic therapy for at least 48–72 hours, and until achieving clinical improvement. Therapy is then continued with enteral antibiotics for up to a total of 10 days [28]. A similar protocol was applied to our patients, and it was determined that the children treated operatively received parenteral antibiotics significantly longer compared to the ones treated conservatively. On the other hand, children treated conservatively were taking enteral antibiotics significantly longer after discharge from the hospital compared to those who underwent appendectomy. In this study, no differences were analyzed concerning the choice or the number of antibiotics, which is certainly material for some future research.

In our study, the success rate in the surgically treated children is 100%, because only children whose clinical diagnosis of acute uncomplicated appendicitis was confirmed intraoperatively and histopathologically were selected as patients in the control group. The success rate of the initial conservative treatment was also 100%. Considering that this was a retrospective study, the conservative treatment group selected patients with signs and symptoms of acute appendicitis who were not operated on during their initial hospitalization according to the clinical monitoring of the patient. It is possible that the patient selection process in some future studies could be different. For example, a prospective study with more detailed clinical, laboratory, and radiological assessment could allow us to determine patients that are safe to be treated conservatively. The percentage of complications observed in our patients was approximately 10% in each of the groups. As complications of the operation, we noticed wound secretion, epigastric pain, obstipation, a small purulent collection in the ileocecal region, and the presence of a small amount of free intraabdominal fluid. There were no cases of ileus reported. All postoperative complications were successfully treated conservatively. There were no complications during conservative antibiotic therapy. After initially successful conservative treatment, during a follow-up period of 10 months, six children (28.57%) were brought back to the surgeon suspected for recurrent appendicitis. Four of them did not have recurrent appendicitis, but two children (9.52%) did develop the disease again. One of these children again had uncomplicated appendicitis, while the other one was complicated. Both of these were recorded as a complication of conservative treatment, underwent laparoscopic surgery, and recovered without further complications. During the follow-up period, another child underwent surgery, also laparoscopically. This child was asymptomatic, but the surgery was performed at the request of the parents one month after the successful conservative treatment. Thus, success rate of the conservative management decreased to 90.48% after 10 months. The percentage of surgically treated recurrent appendicitis recorded in this study is slightly below the literature estimate of 16–21% [8, 14].

Complications were not associated with the duration of administering parenteral or enteral antibiotics. For future research, it could be interesting to analyze its correlation with the type of antibiotic used, as well as with combinations of antibiotics. It is reported in literature that larger outer appendiceal diameter and higher values of WBC are risk factors for recurrent appendicitis after initially successful conservative treatment, as well as that older children have grater chances of developing recurrent disease compared to the younger ones [29]. As previously reported, a delay in presenting to the emergency department has been shown to harm the success of conservative treatment [14]. All these statements could be an inspiration for our future research.

Considering the financial aspect of treatment, appendectomy is such a frequently performed operation that no matter how insignificant its monetary value may be, it cannot be completely neglected due to the significant burden on the health system. Most authors report that conservative treatment is to be significantly cheaper compared to operative one, especially if one keeps in mind the growing popularity of laparoscopic compared to open (classical) surgery. Certain studies reported significantly lower costs of conservative treatment during initial hospitalization, but due to the high percentage of recurrent appendicitis, with consequent appendectomies, this difference was lost during the follow-up period [30]. Our study showed that conservative treatment was significantly less expensive than surgery. The difference was significant even with rehospitalizations due to appendectomies performed during the follow-up period, including appendectomy performed on a child without recurrent appendicitis.

Based on all of the above, we came to the conclusion that conservative treatment of acute uncomplicated appendicitis in the pediatric population is not insufficient compared to surgery. Moreover, in certain aspects it proved to be better. Of course, the research has its limitations. The study was designed as a retrospective one, the analyzed sample was relatively small, but in terms of demographic characteristics of the respondents it was quite representative. It predominantly included children in the years when acute appendicitis is the most common, which is good on the one hand, but on the other hand it does not provide enough data on the applicability and safety of this therapeutic approach in children under five years of age. Also, the follow-up period was shorter compared to most studies published so far.

For our future research, it would be useful to construct a prospective study, expanding the investigation in terms of increasing the number of subjects, extending the follow-up period, more detailed analysis of the type and amount of antibiotics used, as well as attempts to determine factors that could predict complications of acute uncomplicated appendicitis in both operatively and conservatively treated children.

CONCLUSION

Conservative treatment of acute uncomplicated appendicitis in the pediatric population is legitimate and not insufficient compared to surgery. Moreover, in certain aspects

such as shorter hospital stay and lower financial burden, it seems to be superior. However, considering the limitations of our study, for our future research we should consider expanding the sample size and try to determine factors that could predict the safety of both conservatively and operatively treated children.

Conflict of interest: None declared.

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Поређење конзервативног и оперативног лечења акутног некомпликованог апендицитиса у педијатријској популацији

Ивана Лукић[1,2], Јелена Антић[1,2], Величко Трајковић[1,2], Светлана Букарица[1,2], Јан Варга[1,2], Михајло Јецковић[3]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Институт за здравствену заштиту деце и омладине Војводине, Клиника за дечју хирургију, Нови Сад, Србија;
[3]Завод за здравствену заштиту радника „СТ медицина", Нови Сад, Србија

САЖЕТАК

Увод/Циљ У последње време објављене су студије о могућностима конзервативног тј. неоперативног лечења акутног некомпликованог апендицитиса код одраслих и деце, с обзиром на предности очувања апендикса и могуће компликације везане за апендектомију.

Методе У овој ретроспективној студији анализирани су подаци из историја болести 76 болесника лечених на Институту за здравствену заштиту деце и омладине Војводине у Новом Саду због акутног некомпликованог апендицитиса током 2015. и 2016. године, упоређујући дужину хоспитализације, примену антибиотске терапије, учесталост јављања раних хируршких компликација, као и трошкове лечења у зависности од врсте терапијског приступа.

Резултати Током наведеног периода укупно је лечено 76 болесника (55 оперисаних и 21 конзервативно лечен) због некомпликованог акутног апендицитиса. Конзервативно лечена деца су краће боравила у болници (4,24 у поређењу са 5,76 дана; $p < 0,001$). Ране хируршке компликације су уочене код 10,91% оперисане и 9,52% неоперисане деце, што није статистички значајна разлика ($p = 0,863$). Трошкови хоспиталног лечења неоперисане деце били су значајно нижи (10.340 дин. у поређењу са 54.281 дин.; $p < 0,001$). Разлика у цени била је значајна чак и узевши у обзир трошкове настале услед поновне хоспитализације и оперативног лечења деце која су иницијално конзервативно лечена ($p < 0,001$).

Закључак Неоперативно тј. конзервативно лечење акутног некомпликованог апендицитиса у педијатријској популацији је безбедно и ефикасно у поређењу са оперативним лечењем и није праћено учесталијом појавом компликација. Трошкови неоперативног лечења у поређењу са оперативним знатно су нижи, чак узевши у обзир и поновне хоспитализације иницијално конзервативно лечене деце.

Кључне речи: акутни некомпликовани апендицитис; конзервативно лечење; антибиотици; деца

DOI: https://doi.org/10.2298/SARH221104123K
UDC: 616.29-073/-074

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Biochemical and ultrasonographic markers in fetal surveillance

Dušica Kocijančić-Belović, Jelena Dotlić, Slavica Akšam

University Clinical Center of Serbia, Clinic of Obstetrics and Gynecology, Belgrade, Serbia;
University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective Fetal growth restriction (FGR) is associated with increased fetal and neonatal mortality and morbidity. The study objective was to investigate the correlation of maternal blood biochemical markers routinely determined in the first and second trimester screening and ultrasound fetal surveillance parameters in the prediction of fetal growth and condition in singleton pregnancies.

Methods In the first trimester we measured serum levels of beta subunit of human chorionic gonadotropin (βHCG) and pregnancy-associated plasma protein A (PAPP-A). In the second trimester we measured values of chorionic gonadotropin (HCG), alpha fetoprotein (AFP), unconjugated estriol (E3) and inhibin A, also examined ultrasonographic biometric fetal parameters, amniotic fluid index (AFI) and Doppler resistance indexes. FGR was defined as ultrasonographically determined fetal weight and growth parameters below the 10th percentile for the gestational age. Obtained biochemical and ultrasonographic parameters were correlated.

Results Study included 104 singleton pregnancies. βHCG in the first trimester correlated negatively with fetal growth in the second and third trimester, and the second trimester AFI. Increased PAPP-A correlated positively with elevated resistance index in medial cerebral artery, lower biophysical profile scores, and intermediate type of non-stress test. Lower values of E3 were associated with FGR. Elevated serum AFP levels were linked to oligoamnion in the third trimester. There was no correlation of inhibin A levels with fetal condition.

Conclusion First and second trimester biochemical markers of pregnancy (βHCG, PAPP-A, HCG, AFP and E3) in combination with ultrasonographic biophysical parameters of fetus have predictive value for fetal growth and development.

Keywords: pregnancy; biochemical markers; ultrasound; fetal growth restriction

INTRODUCTION

Fetal growth restriction (FGR) is a progressive deviation from the growth curve below 10th percentile for the particular gestational week. The incidence of this disorder is 4–8%, in general population of pregnant women. It is considered pathological when followed by oligohydramnios - reducing the amount of amniotic fluid [the amniotic fluid index (AFI) below the value of 50 mm] and pathology of fetal Doppler findings [1]. FGR is associated with increased fetal and neonatal mortality and morbidity generally, while the greatest risk of poor perinatal outcome in fetuses with growth restriction is in the cases of superimposed hypertensive disorders. Fetal hypoxemia in these pregnancies is very often associated with subsequent polycythemia, hypercapnia and neonatal acidosis, lower levels of fetal glycemia, decreased glycogen reserves, decreased concentration of essential amino acids, increased fetal triglyceride concentration due to mobilization from fat reserves, as well as hypoinsulinemia [2].

One of the very common causes of growth restriction is the placental factor because placental structure and function affect the transport and exchange of gases and nutrients, as well as the products of metabolism at the level of uteroplacental circulation [3]. Ultrasound fetal measurements and other markers present the most common diagnostic method for prediction and diagnosing of FGR. Another proposed way of predicting fetal growth is placental assessment in terms of its volume and structure. In case of an incomplete trophoblastic invasion of the spiral arteries, the change from high to low resistance flow in maternal compartments does not happen which can cause preeclampsia and FGR. Therefore, the Doppler ultrasound examination is an additional useful non-invasive method for the assessment of the interaction between fetal and maternal hemodynamic compartment [4, 5].

Morphological changes in trophoblasts and placenta also affect changes in levels of synthesis and secretion of different biochemical placental markers, that are also part of screening in pregnancy [6, 7]. Screening of the first and second trimester of pregnancy is successfully applied in everyday clinical practice for early prediction and detection of fetal chromosomopathies. Furthermore, recent investigations proposed biochemical maternal screening as useful in prediction the risk of adverse fetal and maternal outcome. Some data imply that

Received • Примљено: November 4, 2022
Revised • Ревизија: December 26, 2022
Accepted • Прихваћено: December 27, 2022
Online first: December 30, 2022

Correspondence to:
Dušica KOCIJANČIĆ-BELOVIĆ
University Clinical Center of Serbia
Clinic of Obstetrics and Gynecology
Koste Todorovica 26
11000 Belgrade
Serbia
dusicakocijancic@yahoo.com

different biochemical markers could be useful for early detection of different fetal complications including FGR and preterm birth [8].

The aim of our study was to investigate the correlation of maternal blood biochemical markers routinely determined in the first and second trimester screening and ultrasound fetal surveillance parameters in the prediction of fetal growth and condition in singleton pregnancies.

METHODS

Healthy pregnant women who conceived naturally and had regular pregnancy check-ups at the Clinic of Obstetrics and Gynecology of the University Clinical Center of Serbia, were prospectively recruited in the study, during a three-months period (in 2018). All investigated women signed informed consent for the study, according to the Declaration of Helsinki. The study confirms to the legal standards and was approved by the Clinic Ethic Committee.

During the first pregnancy examination for every pregnant woman, we took detailed general medical, socio-epidemiological, and obstetric history (age, cigarette smoking, method of conception, hereditary and chronic illnesses, parity, gestational complications and outcomes of previous pregnancies such as hypertension, diabetes and pregnancy loss, gestational weeks of deliveries, Apgar score of previously born children). All pregnancies were dated by last menstrual period and fetal crown-rump length measured by the ultrasound. We also measured nuchal translucency according to Fetal medicine Foundation and Double test screening method.

Investigated women were regularly checked-up at least once per trimester throughout the pregnancy at our Clinic. They underwent regular screening for chromosomal abnormalities of the first and second trimester. All adverse pregnancy outcomes (miscarriage before 20th gestational week) were noted and those women were excluded from the study. Moreover, exclusion criteria for this study also included confirmed fetal genetic disorders and malformations, as well as severe chronic diseases of the mother that could influence pregnancy course and outcome: chronic hypertension, systemic lupus erythematosus, chronic kidney diseases, type 1 diabetes mellitus, disorders of thyroid gland.

On every examination we measured height and weight of pregnant women, and calculated their Body Mass Index (BMI), made clinical examination, took a detailed laboratory analysis. Moreover, in the first trimester at the time for mandatory Double test screening (11–14 gestational weeks) we determined levels of beta subunit of human chorionic gonadotropin (βHCG) and pregnancy-associated plasma protein A (PAPP-A). In the second trimester at the time of Triple test screening (16–19 gestational weeks), values of chorionic gonadotropin, (HCG), alpha fetoprotein (AFP) and unconjugated estriol (E3) were measured. In the case of indication for more detailed screening test we also performed Quadriple (Q) test, and measured values of inhibin A.

For the purpose of biochemical analyses, we used 10 milliliters of maternal blood, and it was drawn by venipuncture into nonheparinized tubes, for centrifuge process lasting 15 minutes. For results interpretation we used a reference software program SsdwLab 5 and a BRAHMS KRYPTOR analyzer, applying fluorocytometric immunoassay method. The measured serum concentrations (IU/L) of biochemical markers were converted into multiples of median (MoM) and adjusted for appropriate gestational week. We registered different categories of values from extremely low values below 0.5 MoMs and extremely high values above 2 MoMs. A value of 1 MoM represents the middle of the distribution. It is suggested that PAPP-A, βHCG and E3 should not be below 0.5 MoM while AFP should not be over 2 MoM to avoid adverse perinatal outcomes [9].

Fetal condition monitoring included antenatal ultrasound examinations in the period of combined screening of the first and biochemical screening in the second trimester, then control examinations every 4 to 6 weeks (at least once in each trimester). All gestational complications (gestational diabetes, hypertension, bleeding, contractions, premature membrane rupture, etc.) were regularly noted. In case of gestational complications, surveillance parameters were assessed according to the protocols for monitoring of high-risk pregnancies [10, 11].

In the first trimester ultrasound biometrics implied the crown rump length for the precise pregnancy dating, also measured nuchal translucency, while in later pregnancy we performed complete fetal biometry to see if there are the sings of growth restriction. We monitored the fetal biophysical profile (BFP) from the 28th week of gestation. Each ultrasound parameter was evaluated with grade from 0 to 2 - respiratory movements of the fetus, fetal movements with registration of flexion and extension, fetal tone, amount of amniotic fluid (by measuring AFI) or the largest pocket of amniotic fluid (below 2 and over 2).

The pathological finding of fetal BFP was set according to current standards 6 and below, while values of 8 were considered as good fetal condition [12]. Interpretation of the cardiotographic monitoring [non-stress test – (NST)] was performed according to the International Federation of Gynecology and Obstetrics criteria and divided into normal, intermediate and pathological record [13]. Normal NST means that the baseline is form 110–150 beats per minute, reactivity with adequate accelerations (at least two) for 30 minutes of monitoring, and changes in basal frequency with 5 up to 25 per minute. Intermediate NST record means basal frequency from 100 to 110, or from 150 to 170 beats per minute, with saltatory (over 25 beats) or silent (5 and under 5 beats per minute) type of oscillations. Pathological record means- basal frequency is around 150–170/min with reduced variability where the silent type of oscillations is registered or the sinusoidal type of variability.

Further ultrasound examination included measuring the resistance index in the umbilical artery (RiAu) and in middle cerebral artery (RiCm). The normal finding of the RiAu is 0.55–0.65, and in the RiCm 0.75–0.85 [14, 15].

Table 1. Ultrasound parameters of fetal monitoring

Parameters		Number of fetuses	Percent (%)	Pearson's χ^2 test	p-values
Fetal growth II trimester	< 5th percentile	1	1	161.139	0.001
	5th to 10th percentile	7	6.7		
	10th to 50th percentile	80	76.9		
	50th to 90th percentile	13	12.5		
	> 90th percentile	0	0		
Fetal growth III trimester	< 5th percentile	1	1	159.400	0.001
	5th to 10th percentile	16	15.4		
	10th to 50th percentile	69	66.3		
	50th to 90th percentile	13	12.5		
	> 90th percentile	1	1		
Amniotic fluid index (AFI) II trimester	< 5th percentile	2	1.9	140.782	0.001
	5th to 10th percentile	17	16.3		
	10th to 50th percentile	76	73.1		
	50th to 90th percentile	6	5.8		
Amniotic fluid index (AFI) III trimester	< 5th percentile	7	6.7	133.000	0.001
	5th to 10th percentile	25	24		
	10th to 50th percentile	63	60.6		
	50th to 90th percentile	4	3.8		
	> 90th percentile	1	1		
Umbilical artery resistance index (RiAu)	pathological	22	21.2	31.360	0.001
	normal	78	75		
Middle cerebral artery resistance index (RiCm)	pathological	5	4.8	81.000	0.001
	normal	95	91.3		
Biophysical profile (BFP)	4	2	1.9	178.160	0.001
	6	15	14.4		
	7	1	1		
	8	82	78.8		
Non-stress test (NST)	normal	81	77.9	108.510	0.001
	intermediate	13	12.5		
	pathological	4	3.8		

Fetal growth II trimester-normal growth for gestational age 50th percentile, extreme values –fetal growth restriction – below the 10th percentile, acceleration growth above the 90th percentile; amniotic fluid index – pathological below the 5 cm – oligohydramnion, above the 25 cm polihydramnion; biophysical profile – normal 8, pathological below 8; RiAu index – normal range from 0.55 to 0.65 (approximetly 50th percentile the in the third trimester) above the 0.65 – pathological; RiCm-normal range from 0.75 to 0.85 in the third trimester, above the 0.85 or under the 0.75 – pathological; non-stress test – classification of non-stress test according to the International Federation of Gynecology and Obstetrics recommendations

Pathological findings in Doppler sonography were increased resistance in the umbilical artery (more then 0.65 measured in the resistance index of the umbilical artery) and reduced resistance in the medial cerebral artery (below the 0.75, called the "brain sparing phenomenon") [14, 15]. After the 28th gestational week the AFI was determined to assess the sufficiency of amniotic fluid quantity. We measured the amount of amniotic fluid in the second and third trimesters by the classic way, by measuring all four quadrants of amniotic fluid. We checked the values also by measuring the deepest vertical fluid pocket. Based on the sum of the values, we obtained AFI for that gestational age. We compared the obtained values with the percentiles of the amount of amniotic fluid through nomogram tables.

If AFI was below 5 cm oligohydramnios were diagnosed, while AFI greater than 25 indicated polyhydramnios (above the nighty percentile) [16].

For the purpose of this study, we considered fetal growth as the main parameter in prenatal assessment of fetal condition. Fetal growth is obtained by computer generation of measured values of ultrasound biometry – biparietal diameter, head circumference, abdominal circumference and femur length. The individual parameters measured by ultrasound measurements together provide information on whether the size of the fetus corresponds to the given gestational age or whether there is restriction or acceleration of fetal growth. We also used percentiles of fetal growth in the nomogram tables.

FGR was defined as ultrasonographically-determined fetal weight and growth parameters below 10th percentile of those expected for the gestational age. Finally, upon birth, study authors noted the birth-weight and Apgar score of the child, as well as the gestational week (GW) of delivery (prematurity was considered if delivery occurred before the 37th gestational weeks).

Data were analyzed using methods of descriptive (number, percent, mean, standard deviation) and analytical statistics and applying the SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). The strength of correlation of maternal blood biochemical markers and ultrasound fetal surveillance parameters in the prediction of fetal condition, was assessed using Spearman's

Table 2. Correlation of fetal biometry, fetoplacental circulation and oxygenation with the maternal biochemical markers of first trimester screening

Parameters		DT HCG (MoM)	DT HCG category of MoM values	DT PAPPA MoM	DT PAPPA category of MoM values	DT NT (first trimester) MoM
Fetal growth II trimester	ρ	-0.228	-0.214	0.044	0.099	0.120
	p value	0.025	0.035	0.668	0.335	0.239
Fetal growth III trimester	ρ	-0.212	-0.170	0.139	0.130	0.086
	p value	0.037	0.096	0.177	0.205	0.402
Amniotic fluid index II trimester	ρ	-0.280	-0.249	-0.016	-0.002	0.130
	p value	0.006	0.014	0.880	0.985	0.202
Amniotic fluid index III trimester	ρ	-0.082	-0.092	0.144	0.057	0.005
	p value	0.425	0.371	0.162	0.582	0.964
Umbilical artery resistance index (RiAu)	ρ	-0.156	-0.155	0.147	0.102	-0.154
	p value	0.126	0.130	0.152	0.325	0.130
Middle cerebral artery resistance index (RiCm)	ρ	-0.146	-0.158	0.332	0.272	0.007
	p value	0.154	0.122	0.001	0.007	0.946
Biophysical profile (BFP)	ρ	-0.051	-0.027	-0.243	-0.127	-0.033
	p value	0.622	0.792	0.017	0.219	0.747
Non-stress test	ρ	-0.004	-0.107	-0.310	-0.224	0.178
	p value	0.970	0.303	0.002	0.030	0.082

DT – Double test; HCG – human chorionic gonadotropin; PAPPA – plasma protein A , NT – fetal nuchal translucency in the first trimester, MoM – multiple of median, ρ – Spearman's rho correlation coefficient

Table 3. Correlations of fetal biometry, fetoplacental circulation and oxygenation with the maternal biochemical markers of second trimester biochemical screening

Parameters		TT HCG MoM	TT AFP MoM	TT E3 MoM	QT HCG MoM	QT AFP MoM	QT E3 MoM	QT Inhibin A MoM
Fetal growth II trimester	ρ	-0.333	-0.141	-0.164	-0.258	0.258	-0.775	-0.775
	p value	0.152	0.565	0.516	0.742	0.742	0.225	0.225
Fetal growth III trimester	ρ	-0.184	-0.005	0.526	-0.632	-0.316	-0.316	-0.632
	p value	0.451	0.984	0.025	0.368	0.684	0.684	0.368
Amniotic fluid index II trimester	ρ	0.032	-0.278	-0.116	0.447	0.894	-0.894	-0.447
	p value	0.894	0.250	0.647	0.553	0.106	0.106	0.553
Amniotic fluid index III trimester	ρ	0.083	-0.522	0.232	-0.775	-0.775	0.258	-0.258
	p value	0.735	0.026	0.354	0.225	0.225	0.742	0.742
Umbilical artery resistance index	ρ	-0.290	-0.012	0.012	.	.	.	.
	p value	0.229	0.962	0.962	.	.	.	.
Middle cerebral artery resistance index	ρ	-0.105	0.136	0.205	-0.894	-0.447	0.007	-0.894
	p value	0.667	0.590	0.416	0.106	0.553	0.946	0.106
Biophysical profile	ρ	0.017	-0.417	0.011	-0.632	-0.316	-0.316	-0.632
	p value	0.944	0.085	0.965	0.368	0.684	0.684	0.368
Non-stress test	ρ	-0.051	0.173	0.124	0.894	0.447	0.007	0.894
	p value	0.835	0.492	0.624	0.106	0.553	0.946	0.106

TT – triple test; HCG – human chorionic gonadotropin; AFP – alpha fetoprotein; E3 – estriol; Q – quadriple test; MoM – multiple of medians; ρ – Spearman's rho correlation coefficient

rho correlation coefficient. In this study, Pearson's χ^2 was applied in order to assess the significance of the difference in the ultrasound indicators of the fetal condition. Statistically significant differences were considered below 0.05 ($p < 0.05$).

Consent was obtained from all patients for all procedures as well as the study.

RESULTS

Study included 104 pregnant women with average age of 30.54 ± 4.93 years. Majority of examined fetuses had an appropriate level of growth and development (10–90 percentiles) assessed by ultrasound during the second and third trimesters of pregnancy. In the second trimester of pregnancy, amount of amniotic fluid below 10th percentile had 18.2% of fetuses, and in the third trimester 30.7% of fetuses (Table 1).

In the third trimester, most fetuses had a biophysical profile value 8, 15 fetuses had BFP 6, two fetuses rated BFP 4 (Table 1). Besides the more frequent (21.2%) pathological RiAu, other evaluated Doppler parameters were normal in most fetuses in the third trimester of pregnancy (Table 1).

Table 2 shows the results of correlations of fetal biometry, fetoplacental circulation and oxygenation with the maternal blood biochemical markers of first trimester screening (βHCG and PAPP-A) during the Double test.

Values of βHCG in the I trimester correlated negatively with fetal growth during the II and III trimesters as well as the amount of amniotic fluid in the II trimester. In fetuses whose mothers had elevated βHCG levels in the first trimester, intrauterine FGR was more frequently registered in the second and third trimesters. A significant correlation was observed between PAPP-A values, RiCm values and NST in our study. We registered different categories of values from extremely low values below 0.5 MoMs and extremely high values above 2 MoMs. When PAPP-A was above the reference range in the first trimester, over the 2 MoMs, the RiCm was more frequently elevated, fetuses had lower biophysical profile scores, which was often followed by some kind of pathological findings on the NST.

Results in Table 3 show correlations of fetal biometry, fetoplacental circulation, and oxygenation with the biochemical markers of second trimester biochemical screening. Elevated E3 values in the second trimester correlated positively with fetal growth in the second trimester of pregnancy, i.e., lower values of unconjugated estriol correlated with intrauterine FGR. Elevated serum AFP levels in the second trimester correlated with the lower values of AFI in the third trimester of pregnancy. Regarding fetal oxygenation and circulation parameters, no correlations were observed with Triple and Q test screening parameters.

DISCUSSION

In this study we found the negative correlation of βHCG values of the I trimester with fetal growth of the II and III trimesters as well as the amount of amniotic fluid in the II trimester. In fetuses whose mothers had elevated βHCG levels in the first trimester, intrauterine FGR was more frequently registered in the second and third trimesters as well as AFI below 50th percentile in the second trimester of pregnancy. In some literature data βHCG values over 90th percentile was linked to fetal growth disturbance [17]. In other large studies βHCG values of I trimester below 5th percentile was correlated with growth restriction below 10th percentile [18]. According to some data βHCG values above 4.0 MoM were associated with low birth weight and hypertensive disorders in 22.5% of pregnant women. βHCG values, over 10 MoM were found in 92% of cases with adverse perinatal outcomes in terms of severe FGR and neonatal complications, placental abruption as well as severe hypertensive disorders [19]. Authors reported an association of elevated second-trimester HCG values with growth restriction, which we did not establish [20].

In our study we did not confirm the connection between values of PAPP-A and fetal growth and AFI. Contrary, some authors found a significant degree of association between low PAPP-A values and the risk of intrauterine FGR in as many as 73% of pregnancies that ended before 37 weeks of gestation and in 46% of term pregnancy terminations [21]. According to literature data, the value of PAPP-A below 5th percentile for gestational age is significantly correlated with premature birth and intrauterine fetal death. In studies assessing a combination and interaction of several factors, including βHCG values as well as parity, age, smoking and increased BMI it was shown that measuring values before and after the 13th week of gestation during pregnancy screening gives similar results in prediction of pregnancy outcome [22]. On the other hand, in our study when PAPP-A was above the referral range in the first trimester, the RiCm was more frequently elevated, end-diastolic block occurred, children had lower biophysical profile scores, and the NST was more often of the intermediate type. Recent research has mainly found that the first trimester biophysical markers such as uterine artery Doppler could be used in combination with biochemical markers for the prediction of perinatal outcome. On the other hand, other studies found that faulty parameters of flow through umbilical and cerebral circulation between 35th and 37th weeks may imply on FGR, preeclampsia, and fetal hypoxia, all as a consequence inadequate placentation [23]. When biochemical markers with changes in hemodynamics were analyzed, extremely decreased PAPP-A values below the third percentile were registered in pregnant women with increased systolic-diastolic ratio in the umbilical artery, end-diastolic block and diastolic flow reversal [24]. In previous investigations low values of PAPP-A around 0.45 MoM are reported in correlation with FGR, and usually in such cases elevated AFP is registered in the second trimester, which is usually explained by the presence of a placenta of smaller dimensions and its morphological damage [25]. Adequate secretion of all placental markers is affected by the invasion and structure of trophoblast while compromising trophoblast circulation causes the change in the concentration of these markers. For these reasons, in the case of placental hypo perfusion, PAPPA levels are reduced, resulting in intrauterine FGR [25].

In our study elevated E3 values in the second trimester correlated positively with fetal growth in the second trimester of pregnancy, i.e., lower values of unconjugated estriol were linked to growth restriction. According to data from the literature, E3 values are reduced in both intrauterine FGR and in pregnancies with reduced amniotic fluid [26].

Furthermore, our results show that elevated serum AFP levels in the second trimester are associated with oligohydramnios in the third trimester of pregnancy. The data of our study regarding the second trimester markers partially agree with the results of research by other authors, which is that AFP values over 2 MoM were correlated with oligohydramnios, for which we found an association in the third trimester of pregnancy, as well as the correlation of lower values of unconjugated estriol with fetal growth. In a large study of over 60,000 singleton pregnancies, where the Triple test was routinely performed, elevated AFP values above 2.5 MoM were found to be closely associated with gestational hypertension, miscarriage, preterm birth, intrauterine growth restriction, oligohydramnios and placental abruption [27]. Low AFP values below 0.25 MoM have been associated in the literature with more frequent intrauterine fetal death [28].

Regarding fetal oxygenation and circulation parameters, no correlations were observed with Triple and Q test

screening parameters in this study. Studies by other authors generally report lower first-trimester marker values in fetuses with FGR. In our study, in the overall sample, elevated marker values correlated with growth restriction, which we can conclude that fetuses with FGR also had normal marker values, i.e. and fetuses with elevated markers may have an orderly fetal growth trend by weeks of gestation. Data from a large meta-analysis that included 91 studies showed that placental function markers are isolated and insufficient to anticipate fetal and neonatal birth conditions, and that a combined antepartum approach assessing separately or jointly a number of biochemical markers should be included to get a better prediction of pregnancy outcome [29, 30].

CONCLUSION

Maternal blood biochemical markers routinely determined in the first and second trimester screening (βHCG, PAPP-A, HCG, AFP, E3) in the assessment of the risk of chromosomal abnormalities, correlate well with ultrasound parameters of fetal monitoring that are regularly used in clinical practice [biophysical parameters of fetal surveillance (biophysical profile, Doppler measures of fetoplacental circulation and oxygenation)] and, therefore, may be significant indicators of impending fetomaternal complications and good predictors of adverse outcomes in singleton pregnancies.

ACKNOWLEDGMENT

This scientific work is part of Dr Dušica Kocijančić-Belović PhD thesis titled "Fetal biochemical markers in prediction of adverse maternal and fetal pregnancy outcome".

Conflict of interest: None declared.

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Биохемијски и ултрасонографски маркери у надзору фетуса

Душица Коцијанчић-Беловић, Јелена Дотлић, Славица Акшам

Универзитетски клинички центар Србије, Клиника за гинекологију и акушерство, Београд, Србија;
Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод/Циљ Застој у расту плода је повезан са повећаним феталним и неонаталним морталитетом и морбидитетом. Циљ студије је био да се испита корелација биохемијских маркера из крви мајке који се рутински користе у скринингу првог и другог триместра трудноће и ултрасонографских параметара феталног надзора у предикцији феталног раста и стања у једноплодним трудноћама.

Методе У првом триместру мерили смо серумске нивое бета субјединице хуманог хорионског гонадотропина (*βHCG*) и протеина плазме повезаног са трудноћом (*PAPP-A*). У другом триместру мерили смо *HCG*, алфа фето-протеин (*AFP*), неконјуговани естриол (*E3*) и инхибин А и проценили ултрасонографске биометријске феталне параметре, индекс амнионске течности и доплер индексе резистенције. Застој у расту плода је дефинисан као рестрикција раста фетуса испод десетог перцентила за дату гестацијску доб. Добијени биохемијски и ултрасонографски параметри су затим корелисани.

Резултати Студија је обухватила 104 труднице са једноплодном трудноћом. Вредности *βHCG* у првом триместру су имале негативну корелацију са растом фетуса током другог и трећег триместра, као и са индексом амнионске течности у другом триместру. Повећана вредност *PAPP-A* позитивно је корелирала са повишеним индексом резистенције у медијалној церебралној артерији, нижим резултатима биофизичког профила и нон-стрес тестом интермедијарног типа. Ниже вредности E3 биле су повезане са рестрикцијом раста фетуса. Повишени нивои *AFP* у серуму били су повезани са олигоамнионом у трећем триместру трудноће. Није постојала корелација инхибина А са феталним стањем.

Закључак Биохемијски маркери првог и другог триместра трудноће (*βHCG, PAPP-A, HCG, AFP* и *E3*) у комбинацији са ултрасонографским биофизичким параметрима фетуса имају предиктивну вредност за процену раста и развоја фетуса.

Кључне речи: трудноћа; биохемијски маркери; ултразвук; интраутерусни застој раста

DOI: https://doi.org/10.2298/SARH220929024K
UDC: 617.7-001-036.22(497.11)"2018/2022"

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The epidemiology of blunt ocular trauma in a tertiary health care institution in Serbia – a four-year-long retrospective study

Igor Kovačević[1,2], Mladen Bila[1], Jelena Mirković[1], Ivan Mišić[1], Jelena Vasilijević[1,2]

[1]University Clinical Centre of Serbia, Clinic for Eye Diseases, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective Ocular trauma is a globally important cause of visual impairment. The aim of our study was to analyses demographic, epidemiological, and clinical characteristics of blunt ocular trauma.

Methods The retrospective study enrolled patients with blunt ocular trauma, hospitalized at the Eye Clinic, University Clinical Centre of Serbia in Belgrade during a four-year period (2018–2022). Demographic characteristics, mechanism of injury, best corrected visual acuity on admission and discharge and injured eye structure were analyzed.

Results Out of 283 patients, the majority (n = 233, 82%) were men. People aged 61 and over (n = 82, 29%) were at greatest risk for blunt ocular trauma. Injuries from splitting wood (n = 78, 28%) and various blunt tools and objects (n = 70, 25%) were the most common mechanism in the entire study group, both in men and in women. Visual acuity on admission was better than 0.6 in 147 (52%) patients and at discharge in 185 (65%). The most common eye structure affected are pathological findings in anterior chamber (n = 160, 56%), which are mainly related to hyphemia.

Conclusion Present study showed that blunt ocular trauma affects all age groups, but most often elderly and children. Men are injured more often than women. Splitting wood and manipulating blunt tools and objects are activities with the highest risk of blunt ocular trauma.

Keywords: blunt trauma; Serbia; epidemiology; injury

INTRODUCTION

Ocular trauma is a globally important cause of visual impairment. According to estimates, traumatic eye injury is the cause of 1.6 million cases of blindness and 19 million cases of monocular blindness worldwide [1, 2]. According to the reports of the World Health Organization, every year there are about 55 million cases of eye trauma in the world [3], therefore eye trauma is a considerable public health issue. It can seriously limit patient's social and working abilities [4]. When it comes to eye trauma in the pediatric population, it represents a specific problem, in terms of rehabilitation, greater emotional stress for the child and parents, and the possibility of amblyopia [5, 6]. Rates of ocular trauma are higher in young adults, specifically ages 5–25, and in people over the age of 70. Additionally, men are at greater risk of ocular injuries [2, 3]. However, it is estimated that around 90% of eye trauma is relatively preventable, especially in children [7].

According to widely accepted Birmingham Eye Trauma Terminology system, all eye injuries can be divided into closed and open globe injuries, depending on presence of a full thickness wound [8]. Open globe injuries refer to rupture, laceration, penetrating, intraocular foreign body and perforating injury, while closed globe injuries are lamellar laceration and contusion. In some cases, wounds are of a mixed nature. Blunt ocular trauma can cause either open (rupture) or closed globe injury (contusion and lamellar laceration). Standardized classifying of eye injuries is required for documentation and determination of the extent of injury [9].

The aim of our study was to analyses demographic, epidemiological, and clinical characteristics of blunt ocular trauma patients who were hospitalized at the Clinic for Eye Diseases of the University Clinical Centre in Belgrade. These researches are useful in recognizing risk factors and prognosis, thereby improving preventive and management strategies.

METHODS

This retrospective study was conducted at the Clinic for Eye Diseases, University Clinical Centre of Serbia in Belgrade. Analyzed patients were hospitalized at the Department of Eye Traumatology and the Department of Children's Diseases at the Clinic for Eye Diseases in the period from December 2018 to May 2022. Patients data has been obtained from medical records – medical history and the database of the Heliant software (Heliant,

Received • Примљено: September 29, 2022
Accepted • Прихваћено: January 30, 2023
Online first: March 3, 2023

Correspondence to:
Jelena B. VASILIJEVIĆ
University Clinical Centre of Serbia
Clinic for Eye Diseases
Pasterova 2
Belgrade
Serbia
bkjelena@gmail.com

Belgrade, Serbia). The collected data included sex, age, diagnosis, mechanism of injury, eye structure affected by the injury, as well as the method of treatment and the correlation of all these parameters.

Patients were divided according to sex and into groups according to age (under 18, 18–39, 40–60, and 61 and older). In correlation with these groups, a division was made according to the mechanism of injury as follows: injuries while chopping woods, injury with different blunt tools and objects, fall injury, injury by a projectile, sport injuries, assaults, explosions, traffic injury and injury resulting from an unknown cause. For each cause of injury, the affected structures of the eye (eyelid, conjunctiva, cornea, anterior chamber, iris, lens, vitreous body and retina) were analyzed. The best-corrected visual acuity (BCVA), obtained with Snellen charts, was also analyzed at admission and discharge, and then divided into three groups: below 0.1, 0.1–0.5 and 0.6–1.0. In relation to the applied therapy, all patients were divided into two groups: patients who received conservative therapy, and patients who were treated surgically.

This study was conducted according to the tenets of Helsinki Declaration and approved by the Hospital's Committee on Ethics.

Statistical analysis

The description of the categorical variables was performed by using an absolute and relative number in the form n (%). Comparisons were made using the χ^2 test and Student's t-test. Continuous variables are displayed as mean value and standard deviation and were compared using the Mann–Whitney test (with the assessment of the distribution normality). The result was considered statistically significant for the level of significance from 0.05. Statistical analysis was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) 2010 software.

RESULTS

Our retrospective study consisted of 283 patients with blunt eye trauma, including contusions, lamellar lacerations and globe ruptures. There were 233 males (82%), and 50 females (18%), with male to female ratio of 4.7:1. In all age study groups, males represented the majority.

The majority of the study population (n = 82, 29%) was older than 61 years, while 76 (27%) patients were younger than 18 years. In the group between 18 and 39 years was 75 (26%) patients, and 50 of them (18%) were between 40 and 60 years. The youngest patient was 1 year old, and the oldest was 87, with average age 40.32 ± 23.89. In the female population, injuries occurred most commonly at the age over 61 years (n = 23, 46%), followed by females younger than 18 years (n = 17, 34%). In each of the remaining groups, there were five cases (10%) of women, i.e., in the groups between 18 and 39 years old and between 40 and 60 years old. In the male population, different results were obtained compared to the female population. Seventy cases (30%) of all injured men were in the age group between

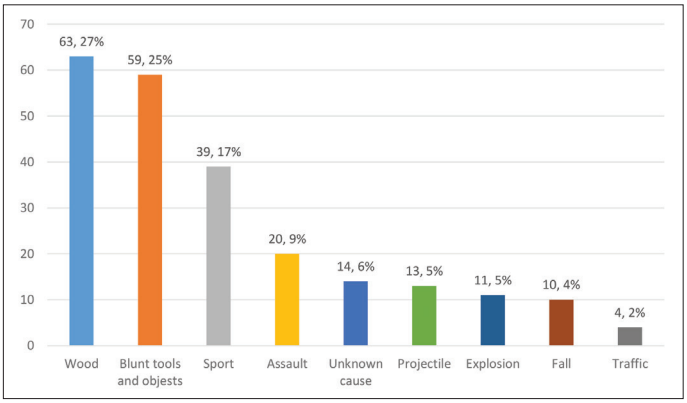

Figure 1. Mechanism of injury in males

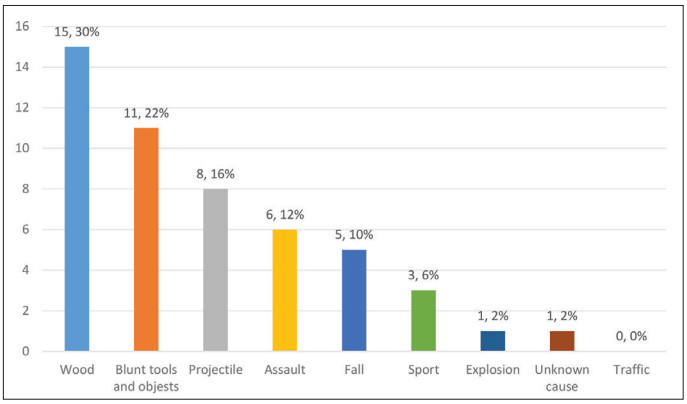

Figure 2. Mechanism of injury in females

18 and 39 years, while 59 cases (25%) were younger than 18 years. In addition, 59 (25%) of all injured men were older than 61 years, while 45 (20%) of men were in the 40–60 age group.

In our sample, patients were most often injured when splitting wood (n = 78, 28%). The second most common cause is injuries with various blunt tools and objects (n = 70, 25%), followed by sport injuries (n = 42, 15%), assaults (n = 26, 9%), projectile injuries (n = 21, 7%), fall injuries (n = 15, 5%), unknown cause of injury (n = 15, 5%), explosions (n = 12, 4%) and traffic injuries (n = 4, 2%). The first and second most common mechanism of injury in men and women were the same as in the entire examined population. Third in order are sports injuries in men (n = 39, 17%), while in women it is projectile injuries (n = 8, 16%). The fourth most common cause in both men and women was assault (n = 20, 9% and n = 6, 12%, respectively). Patients injured in traffic are all males. Detailed analysis regarding the mechanism of injury in males and females are shown in Figures 1 and 2. In the group up to 18 years of age, the most common cause of injuries was sport (n = 20, 26%), while injuries caused by various tools and objects were the most common cause in the population between 18 and 39 years (n = 24, 32%), as well as in the population aged 40–60 (n = 15, 30%). Chopping wood was the most common mechanism of injury among people over 61 years old (n = 45, 55%). Detailed analysis regarding the mechanism of injury in all age study groups are shown in Table 1.

Table 1. Mechanism of injury in all age study groups

Mechanism of injury	Age			
	Under 18	18–39	40–60	61 and older
Wood	10 (13%)	10 (13%)	13 (26%)	**45 (55%)**
Blunt tools and objects	18 (24%)	**24 (32%)**	**15 (30%)**	13 (16%)
Sport	**20 (26%)**	16 (21%)	5 (10%)	1 (1%)
Assaults	5 (7%)	11 (15%)	4 (8%)	6 (7%)
Projectile	11 (14%)	4 (5%)	1 (2%)	5 (6%)
Fall	4 (5%)	1 (2%)	3 (6%)	7 (9%)
Unknown cause	2 (3%)	4 (5%)	6 (12%)	3 (4%)
Explosions	5 (7%)	3 (4%)	2 (4%)	2 (2%)
Traffic	1 (1%)	2 (3%)	1 (2%)	0 (0%)
Total	76 (100%)	75 (100%)	50 (100%)	82 (100%)

Visual acuity on admission was better than 0.6 in 147 (52%) patients, while in 106 (37%) of them it was worse than 0.1 while 30 (11%) patients had visual acuity between 0.1 and 0.5. At discharge, BCVA was better than 0.6 in 185 (65%), worse than 0.1 in 63 (22%) and between 0.1 and 0.5 in 35 (12%) patients.

In the vast majority of the study population (n = 197, 70%) conservative treatment was the treatment method. In total, 86 cases (30%) required surgery, most of whom were older than 61 years (n = 47, 55%).

Regarding the structure of the injured eye, the most prevalent are the pathological findings in the anterior chamber (n = 160, 56%). These mostly included hyphemia, however cells, proteins and vitreous were also seen in some patients. The second most common site of injury was the conjunctiva (n = 147, 52%) involving hyperemia, suffusion and lacerations, followed by the corneal erosions, edema and lacerations (n = 123, 43%). Retinal edema, hemorrhages, tears or detachments were observed in 121 (43%) patients. Eyelids were also often injured (n = 113, 40%). Lens injuries, including traumatic cataract, subluxation and luxation were present in 85 (30%) patients. Partial or total vitreous hemorrhages were found in 64 (23%) patients, and the iris was the least injured (n = 46, 16%). Nine (3%) globe ruptures were observed.

DISCUSSION

Ocular trauma in general, is one of the leading preventable causes of monocular blindness worldwide [8]. According to many previous studies, blunt ocular trauma accounts for the majority of all ocular traumas, so the analysis of this type of trauma by itself could be very useful [3, 4, 6, 9, 10, 11]. To our knowledge, this is one of the first studies that examines the epidemiology of hospitalized blunt eye trauma in the Serbian population. Our study provides insight into the epidemiology of eye trauma in hospitalized patients in Serbia and supports findings that eye trauma is a significant cause of vision loss in our population.

Our study showed that men are at, approximately four times greater risk of blunt ocular trauma compared to women. This is consistent with most others studies [3–13] with the link believed to be due to occupational hazards, more frequent involvement in assaults, alcohol use, and high-risk driving activities [8, 11, 12, 13]. In this study, all patients injured in traffic accidents were male. Our study, as well as previous studies involving only pediatric populations, reported a male predilection for ocular trauma in children. This can be related to more aggressive games in boys than in girls [5, 6]. One study that included only patients older than 70 years, with globe rupture due to a fall, showed a predominance of women [2]. Although our study observed a male predilection in all age groups and across all mechanisms of injury, the mentioned study suggests that women may be at greater risk of ocular trauma in some specific circumstances [2].

Regarding the age distribution, the majority of our study group consisted of patients older than 61 years. These data are in contrast to the results observed in most other studies, where the highest rates of ocular trauma are usually found in children or younger adults [3, 9, 11–14]. This difference may be due to different demographic characteristics of various countries and nations. Additionally, the ranges of age groups were not the same in all studies, so they are more difficult to compare. However, one research conducted in Spain noted the highest incidence of eye trauma in people over 65 years of age, as well as a much stronger association with older age in female group, all of which is consistent with our results [15]. Most of our male patients were in the group between 18 and 39 years, followed by men younger than 18 years, which is consistent with previous studies [12, 16].

In our study, patients were most often injured when chopping woods and with various tools and objects. These two mechanisms of injury together were found in nearly half of the entire study population. Also, in men and women separately, these two were the most common causal mechanisms. In some studies, it was found that wooden objects are the most common cause of eye trauma [3, 16, 17], while in others, blunt object injuries were the most common [9, 13, 14]. This is in agreement with results obtained in this study. Additionally, another Serbian research from 2010 reported wood as the most prevalent causal mechanism in all eye injuries [18]. Therefore, over the years, this tendency remains the same in our nation, according to the present study. We found that sport is the most common cause of injury in pediatric population, which is in agreement with previous studies [19, 20]. Contrary to our results, Shah and Shah [5] as well as Choovuthayakorn et al. [17] reported that children are at the highest risk of being injured by wooden objects or stones. Still, our second most common causal mechanism in children were blunt tools and objects which includes stone objects as well. Wooden objects were the most common cause of eye trauma in people over 60 years old according to a study from Thailand, which is the same as in our research [17]. Assaults are not insignificant, considering that they were the fourth causal mechanism in entire study group, as well as in both men and women. The same, increasing trend in assaults is also found in other studies [4, 9].

Patients with BCVA greater than 0.6 at admission comprised more than half (52%) of our study group. At

discharge, an even higher percentage (65%) of patient had a visual acuity greater than 0.6. Severe visual impairment (BCVA less than 0.1) was noted in 37% of our patients at admission, while at discharge that number was 22%. Similar results were obtained in other studies [3, 5]. However, some researchers have found worse visual prognosis after eye trauma, comparing to our findings [21, 22].

Data found in the literature on the structure of the eye affected by trauma are controversial. Pathological findings in the anterior chamber, related mainly to hyphemia, were the most frequently observed in this study. One study that included only closed globe injuries also reported hyphemia as the most common anterior segment presentation [23]. However, another study involving blunt ocular trauma exclusively in pediatric population, gave different results, as hyphemia was not that common [5]. In our patients, the conjunctiva, cornea, retina, and eyelids are often damaged. Two studies, one from Oman [13] and the other from Jordan [4], described similar but not exactly the same results. They also reported frequent wound to the conjunctiva, cornea and lid, but the retina was rarely injured compared to our study. These differences can be explained by the fact that most other studies described total eye injuries and not just blunt eye trauma.

CONCLUSION

The current study showed that blunt ocular trauma affects all age groups, but most often the elderly and children. Men are injured more often than women. Splitting wood and manipulating blunt tools and objects are activities with the highest risk of blunt ocular trauma. Further studies are desired to better understand the epidemiology and nature of these injuries. Attention should also be focused on educating people about safety measures to prevent blunt ocular trauma.

Conflict of interest: None declared.

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Епидемиологија тупе трауме ока у терцијарном здравственом центру у Србији – четворогодишња ретроспективна студија

Игор Ковачевић[1,2], Младен Била[1], Јелена Мирковић[1], Иван Мишић[1], Јелена Василијевић[1,2]

[1]Универзитетски клинички центар Србије, Клиника за очне болести, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод/Циљ Повреде ока представљају важан узрок оштећења вида на глобалном нивоу.

Циљ наше студије био је да анализирамо демографске, епидемиолошке и клиничке карактеристике тупих повреда ока.

Методе Спроведена је ретроспективна студија која је укључила пацијенте са тупом повредом ока, хоспитализоване на Клиници за очне болести Универзитетског клиничког центра Србије у Београду током четворогодишњег периода (2018–2022). Анализиране су демографске карактеристике, механизам повреде, најбоље коригована видна оштрина на пријему и отпусту, као и повређене структуре ока.

Резултати Од 283 пацијента, већину су чинили мушкарци (*n* = 233, 82%). Људи стари 61 годину или више (*n* = 82, 29%) били су у највећем ризику од тупе трауме ока. Повреде током цепања дрва (*n* = 78, 28%) и различитим тупим алатима и предметима (*n* = 70, 25%) представљале су најчешћи механизам повређивања у целој студијској групи, како код мушкараца, тако и код жена. Видна оштрина при пријему била је боља од 0,6 код 147 (52%) пацијената, а на отпусту код 185 (65%) пацијената. Најчешће захваћене структуре ока били су патолошки налази у предњој комори (*n* = 160, 56%), који су се углавном односили на хифему.

Закључак Ова студија показала је да тупа траума ока погађа све старосне доби, али најчешће старију популацију и децу. Мушкарци се чешће повређују од жена. Цепање дрва и руковање тупим алатима и предметима су активности са највећим ризиком од тупе трауме ока.

Кључне речи: тупа траума; Србија; епидемиологија; повреда

DOI: https://doi.org/10.2298/SARH220207006D
UDC: 616-006.81-033.2

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Real-world treatment patterns and outcomes in patients with metastatic melanoma

Dejan Đokanović[1,2], Bojana Lazić[1,2], Zdenka Gojković[1,2], Željka Cvijetić[3], Emir Sokolović[4], Timur Cerić[4], Saša Jungić[1,2]

[1]University Clinical Centre of the Republic of Srpska, Oncology Clinic, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[2]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[3]Apeiron Pan-European University, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[4]Clinical Center University of Sarajevo, Oncology Clinic, Sarajevo, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina

SUMMARY

Introduction/Objective The purpose of this study was to assess the effectiveness of different approaches in the treatment of metastatic melanoma in daily clinical practice in a situation with limited and late availability of new drugs in a resource-limited country and to compare these parameters with those reported in clinical studies and from other real-world data.

Methods Main methods included assessment of overall survival (OS) and progression-free survival (PFS). Patients were included in the study if they were treated with first or second-line systemic therapy for radiologically/pathologically confirmed metastatic melanoma. Patients were divided into four groups based on the type of therapy they received: chemotherapy (dacarbazin), BRAF inhibitor (vemurafenib), BRAF/MEK inhibitors (vemurafenib/cobimetinib and trametinib/dabrafenib) and anti PD-1 therapy with pembrolizumab.

Results Regardless of the line of therapy, the calculated median OS in chemotherapy and vemurafenib group was nine months. The median OS in the BRAF/MEK inhibitor group was 14 months and 15 months in the pembrolizumab group. Median PFS in the chemotherapy group was four months, seven months for vemurafenib, in the BRAF/MEK inhibitor group nine months and in the pembrolizumab group six months. There was a statistically significant difference in survival between first and second-line therapy in the pembrolizumab group.

Conclusion Our results showed lower median OS and PFS in comparison to reported data from clinical trials. Compared to other real-world data from countries with similar problems related to the late reimbursement of new drugs, our research has shown similar results.

Keywords: metastatic melanoma; immunotherapy; targeted therapy; chemotherapy; survival; real-world data

INTRODUCTION

When we look at the not-so-distant history, patients with advanced melanoma had a poor prognosis and overall survival (OS). Chemotherapy had limited success in metastatic melanoma, with responses observed in 13.7% of patients, median OS ranging from 6.6 to 15.6 months and median PFS ranging from 1.5 to 5.6 months [1]. Significant progress in the treatment of metastatic melanoma has occurred in recent years with the introduction of MAP kinase inhibitors and immunotherapy which have shown an impressive effect on OS. Two-year survival rates have reached 50% in cases with either anti-PD1 immunotherapy (immune checkpoint inhibitor) or the BRAF/MEK inhibitors combination, compared with < 10% of patients treated with chemotherapy [2, 3]. Programmed cell death 1 (PD-1) blockade along with BRAF/MEK inhibitors is now a standard of first line care for all advanced and metastatic melanoma patients [4]. It is still unclear whether these remarkable results are also achieved in daily clinical practice. However, there are significant differences in the access to novel drugs across European countries, therefore differences in patient survival are possible [5]. This study aims to assess the effectiveness of different approaches in the treatment of metastatic melanoma in daily clinical practice in a situation with limited and late availability of new drugs in a resource-limited country and to compare these parameters with those reported in clinical studies and from other real-world data.

METHODS

This was a retrospective observational study evaluating real-world treatment and patient outcomes for metastatic melanoma. The main objectives included OS and PFS assessment. This study was conducted at the Oncology Clinic, University Clinical Centre of the Republic of Srpska, Bosnia and Herzegovina (BiH), in the period from January 2015 to December 2020. Patients were included in our analysis if they were treated with first or second-line systemic therapy for radiologically/pathologically confirmed metastatic melanoma.

Received • Примљено: February 7, 2022
Revised • Ревизија: October 26, 2022
Accepted • Прихваћено: January 3, 2023
Online first: January 16, 2023

Correspondence to:
Dejan ĐOKANOVIĆ
University Clinical Centre of the Republic of Srpska
Oncology Clinic
Dvanaest beba
78000 Banja Luka
Republic of Srpska
Bosnia and Herzegovina
dejan.djokanovic@kc-bl.com

Table 1. Demographic and disease characteristics of the patients

Patients' characteristic	Chemotherapy	BRAF inhibitor	BRAF/MEK inhibitors	Anti PD-1	Total population
Number of cases (%)	52 (48.60)	17 (15.90)	27 (25.20)	11 (10.30)	107 (100)
Median age in years	66.50 (35–85)	54 (31–79)	56 (33–81)	55 (28–67)	62 (28–85)
Male gender n (%)	28 (53.85)	10 (58.80)	20 (74)	8 (72.70)	66 (61.70)
The Eastern Cooperative Oncology Group performance status – n (%)					
0	27 (51.90)	8 (47.10)	19 (70.40)	7 (63.60)	61 (57)
1	15 (28.80)	6 (35.30)	6 (22.20)	1 (9.10)	28 (26.20)
2	8 (15.40)	2 (11.80)	2 (7.40)	2 (18.20)	14 (13.10)
3	2 (3.80)	1 (5.90)	0 (0)	1 (9.10)	4 (3.70)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anatomic site of primary n (%)					
Cutaneous	43(82.70)	17(100)	23(85.20)	9(82)	92(86)
Ocular	2(3.85)	0 (0)	0 (0)	0 (0)	2(2)
Mucosal	1(1.90)	0 (0)	0 (0)	1(9)	2(2)
Primary unknown	6(11.55)	0 (0)	4(16.80)	1(9)	11(10)
BRAF status (%)					
Wild type	19 (36.55)	0 (0)	0 (0)	10 (91)	29 (27.10)
V600E mutated	14 (26.90)	17 (100)	27 (100)	1 (9)	59 (55.15)
Not evaluated	19 (36.55)	0 (0)	0 (0)	0 (0)	19 (17.75)
Elevated baseline lactat dehidrogenase level (> 280 U/L) n (%)	29 (48.30)	11 (18.30)	13 (21.7)	7 (11.7)	60 (56)
Organs with metastatic involvement – n (%)					
1	24 (46.15)	0 (0)	1(3.70)	0(0)	25(29.90)
2	17 (32.70)	4 (23.50)	5(18.50)	5(45.45)	31(32.70)
3	7 (13.45)	8 (47)	11(40.75)	2(18.20)	28(23.40)
> 3	4 (7.70)	5 (29.50)	10(37.05)	4(36.35)	23(14)
First-line therapy n (%)	52 (100)	9 (53)	11 (40.70)	6 (54.55)	78 (73)

The disease stage was determined by using the eight version of the American Joint Committee on Cancer, the tumor, node, metastases classification system [6]. Patients were excluded if they were enrolled in clinical trials, had another cancer diagnosis besides basal cell carcinoma and some in situ carcinomas and patients that were in two different treatment groups. All relevant data were collected from medical files and entered into a data-base. Patients were divided into four groups according to the therapy they have received: chemotherapy (dacarbazin based chemotherapy), BRAF inhibitor (vemurafenib), BRAF/MEK inhibitors (vemurafenib/cobimetinib and trametinib/dabrafenib) and anti PD-1 therapy with pembrolizumab. Therapy was applied according to the valid recommendations for each protocol. Also, we collected other data related to the patient: age, sex, anatomic site of primary melanoma, BRAF mutation, baseline serum Lactat dehidrogenase (LDH), The Eastern Cooperative Oncology Group (ECOG) performance status and the number of organs with detected metastases. The efficacy of therapy was evaluated according to the response evaluation criteria in solid tumors (RECIST, version 1.1) by using computed tomography scan, positron emission tomography using 18F-fluorodeoxyglucose, magnetic resonance imaging, clinical examination and laboratory tests [7].

Statistical analysis

Statistical data was obtained using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to assess absolute values and percentages. The survival rate was calculated by the Kaplan–Meier method and compared using the log-rank test. A p value of ≤ 0.05 was considered statistically significant. OS was calculated from the date of the initiation of specific treatment until the date of death due to any cause. Patients who did not die were censored for OS on the last visit date available in the database. PFS is the interval from treatment initiation until the date of physician-documented assessed disease progression. Patients who did not progress and were still alive were censored for PFS on the last visit date available in the database. Last visit date available in database was December 31, 2020. The relationship of certain baseline characteristics was examined using Cox hazard proportional model. The study was approved by the Institutional Review Board Committee number 01.19-321-2/21 and was conducted in accordance with the ethical standards defined by the Helsinki Declaration.

RESULTS

Demographic and disease characteristics of 107 patients included in analysis are presented in more detail in Table 1. All patients were Caucasian. The median age was 62 years (range 28–85), the majority of patients (61.7%) were males, and in ECOG performance status 0 (57%). Among all of the patients, 92 (86%) had the cutaneous subtype of melanoma. A total of 59 patients (55.15%) had a BRAF V600E mutation, 29 (27.1%) were wild type, and

19 (17.75%) patients did not have a BRAF status evaluated. Normal baseline LDH was found in 42 (39.3%) of the patients, elevated LDH in 60 (56%) of the patients and in five (4.7%) of the patients LDH was not evaluated. In total, 31 (32.7%) of the patients – had two organs with metastatic involvement. In total, 52 (48.6%) of patients received chemotherapy. BRAF/MEK inhibitors were received by 27 patients (25.2%), BRAF inhibitors by 17 (15.9%) and 11 (10.3%) patients received pembrolizumab. All patients in the chemotherapy group received dacarbasine-based chemotherapy as a first-line treatment. In the mono BRAF inhibitor group, nine patients received the BRAF inhibitor as first-line therapy. First-line therapy with BRAF/MEK inhibitors were received by 11 out of 27 patients. Six patients in the pembrolizumab group received it as a first line treatment.

Survival analysis

We conducted a survival analysis for cutaneous metastatic melanoma. Regarding the efficacy of different therapies, at data cut-off, all patients in the chemotherapy group and in the BRAF inhibitor group progressed. In the BRAF inhibitor group all of the patients died, and in the chemotherapy group one patient is still alive. Seven (30.45%) patients in BRAF/MEK inhibitor group and three (33.35%) patients in the pembrolizumab group are still undergoing treatment. In the BRAF/MEK inhibitor group eight (34.8%) patients are alive, as are five (55.55%) of the patients in the pembrolizumab group. In all the treatment groups, regardless of the therapy line, there is a statistically significant difference in OS and PFS (Figure 1 and 2). The calculated median OS in both the chemotherapy group and in the vemurafenib group were nine months. The median OS in the BRAF/MEK inhibitor group was 14 months and in the pembrolizumab group 15 months. The calculated median PFS in the chemotherapy group was four months and in the vemurafenib group seven months. Median PFS in the BRAF/MEK inhibitor group was nine months and in the pembrolizumab group nine months (Table 2). Table 3 shows the results of the first and second-line of therapy for different treatment groups. In 15 patients (14%) with non-cutaneous melanoma, median OS was seven months, while PFS was four months. The survival rate differences were statistically significant ($p = 0.04$) in all of the patients, according to whether baseline LDH was elevated or not. The median OS for patients with normal LDH was 16 months (95% CI, 10.35–21.65), while patients with elevated baseline LDH had the median OS of nine months (95% CI, 6.35–11.65). We used the Cox proportional hazard model to evaluate the nominal explanatory variable – elevated LDH values were considered a prognostic factor of disease progression and death. Elevated LDH was a statistically significant prognostic factor of disease progression ($p = 0.037$) and patient death ($p = 0.007$). The risk of disease progression in patients with elevated LDH values was 1.57 times higher compared to patients with normal values of LDH. Also, patients with elevated LDH values were found to be in a statistically significant higher risk of death (HR 1.84) compared to patients

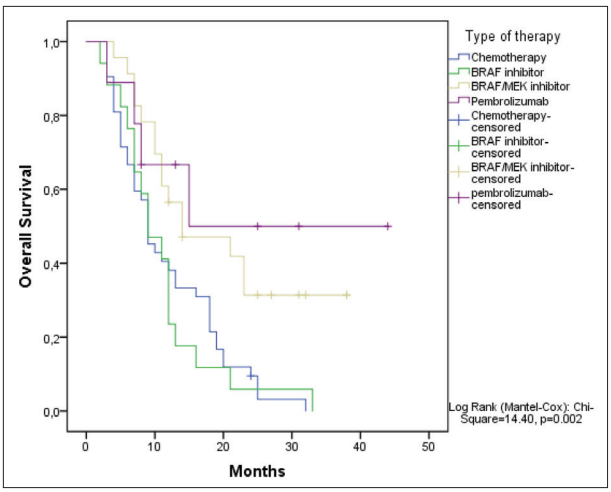

Figure 1. Caplan–Meier curve showing overall survival in different treatment groups for cutaneous melanoma

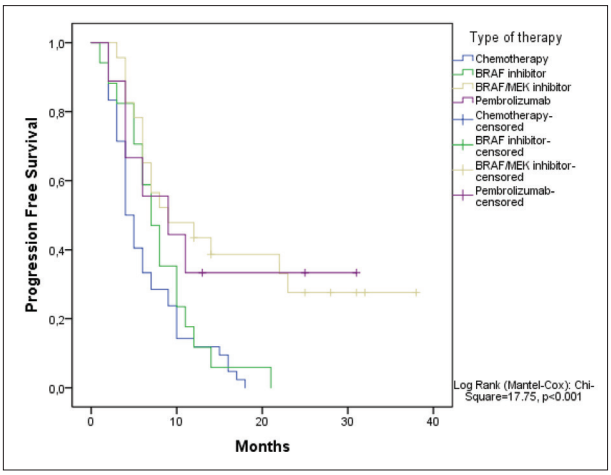

Figure 2. Caplan–Meier curve showing progression-free survival in different treatment groups for cutaneous melanoma

with normal LDH values. Similarly, the differences in survival rate according to the ECOG status were statistically significant in all patients ($p < 0.001$).

As for subsequent lines of therapy, 15 of the patients in chemotherapy group received second-line therapy. Five of them received any of the novel therapeutics available as second-line therapy. In the other three groups, only seven patients managed to receive the further line of therapy.

DISCUSSION

Public financing of new drug therapy in the Republic of Srpska and the whole BiH is usually performed within a separate financial path – the so-called "drug programmes". By a decision made by the Ministry for Health and Health Insurance Fund, a drug programme is to be performed by referent hospitals. The drug programmes provide a financing path for new drugs under strictly specified conditions. Sometimes the quantity of the new drug received is not enough for all patients, so some patients with metastatic melanoma continue to receive chemotherapy as a first-line

Table 2. Survival statistics for different treatment protocols

Type of therapy	Overall survival	95% CI	Progression-free survival	95% CI	Patients alive	Ongoing treatment
Chemotherapy (dacarbasin)	9	6.9–11.1	4	3–5	1	0
BRAF inhibitor (vemurafenib)	9	4.9–13	7	5–9	0	0
BRAF/MEK inhibitors (vemurafenib/cobimetinib, dabrafenib/trametinib)	14	3.4–26.7	9	1.2–16.8	8	7
Immunotherapy (pembrolizumab)	15	1.3–26.1	9	0.7–17.7	5	3

Table 3. Median overall survival and progression-free survival for first and second-line therapy for different protocols

Overall survival						
Type of therapy	Therapy Line	Median				p value (Log-Rank)
		Estimate	Std. Error	95% CI		
				Lower Bound	Upper Bound	
BRAF inhibitor	First-line	9	0.7	7.5	10.5	0.913
	Second-line	8	2.8	2.5	13.5	
BRAF/MEK inhibitors	First-line	23	7.7	7.8	38.2	0.294
	Second-line	12	1.8	8.4	15.6	
Pembrolizumab	First-line	Not reached	0	0	0	0.032
	Second-line	8.0	1.8	4.5	11.5	
Progression-free survival						
BRAF inhibitor	First-line	7.0	0.7	5.5	8.5	0.676
	Second-line	5.0	4.2	0	13.3	
BRAF/MEK inhibitors	First-line	12.0	7.2	0	26.1	0.084
	Second-line	8.0	2	4.1	11.9	
Pembrolizumab	First-line	Not reached	0	0	0	0.005
	Second-line	4	0.4	3.1	4.9	

therapy. This is one of the reasons why most of the patients are in the chemotherapy group. Another reason is the late reimbursement of new drugs. Results from this one-country, single-center analysis showed differences in the median OS and PFS between different groups of melanoma patients receiving these four types of therapy, compared to reported data from clinical studies. As previously mentioned, chemotherapy has limited success in metastatic melanoma [1]. Also, high dose Interleukin-2 has been used to treat metastatic melanoma with modest responses, but those who achieve complete response (< 10%) tend to have extremely durable responses and high rates of long-term survival [8]. Compared to the efficacy of different protocols of chemotherapy, our results showed similar results, with a nine-month median OS and a median PFS of four months.

Another study that was using real-world data was performed in Poland [9]. This retrospective analysis included 287 patients treated from 2013 to 2019. All enrolled patients were treated with immunotherapy (pembrolizumab/nivolumab or ipilimumab), targeted therapy (vemurafenib/cobimetinib or dabrafenib/trametinib) or chemotherapy in at least one treatment line. Brain metastases were detected in 64 (22%) patients. The first-line treatment of patients involved immunotherapy, targeted therapy, or chemotherapy, and the median OS reached 19.2, 12.6, and 15.9 months, respectively [9]. In this analysis, the unexpected finding was that the median OS for targeted therapy is lower than that in chemotherapy group. This is probably due to the high incidence of poor prognostic factors, and because the BRAF mono- and BRAF combo-therapy were analyzed as one group. Our results showed better median OS in all groups in the first line, with the exemption of the chemotherapy group.

Atkinson et al. [10] conducted a retrospective study, DESCRIBE II, consisting of a chart review of the patients with BRAF V600-mutated unresectable stage III/IV melanoma receiving dabrafenib plus trametinib as compassionate use. Treatment patterns and duration, clinical outcomes, and tolerability were evaluated. The total number of enrolled patients was 271. Stage IV melanoma had 92.6% of them, including 36.5% with brain metastases. More than half, 162 patients (59.8%) were BRAF inhibitor naive. These patients achieved an overall response rate (ORR) in 67.3% cases, median OS reached 20 months, and median PFS was 7.5 months. The number of BRAF inhibitor-naive patients with detected brain metastases was 62, ORR was 61.3%, median OS was 15.5 months, and median PFS was 6.2 months [10].

In a study evaluating real-world data efficacy of pembrolizumab in 532 patients pembrolizumab was administered to 315 (59%), 152 (29%), and 65 (12%) patients as first-, second-, and third-line/later therapy [11]. Median OS for first-line pembrolizumab was not reached, and for second-line and third-line/later was 13.9 and 12.5 months respectively, log-rank p = 0.0095 [11]. In comparison with this study, our result showed a shorter median OS in second-line therapy.

A retrospective observational multicenter study – Advanced Melanoma In Russia (Experience), evaluated a subset of patients with V600 BRAF-mutated unresectable or metastatic melanoma, who received targeted

therapy in a real-world setting. In 382 included patients, the ORR to the combined BRAF/MEK inhibitor and to the BRAF inhibitor mono-therapy were 57.4% and 39.8%, respectively. The median PFS and OS were 9.2 months and 22.6 months, respectively, for the combined first-line therapy; 9.4 months and 16.1 months, respectively, for the combined second-line therapy; and 7.4 months and 17.1 months, respectively, for the combined third or higher-line therapy [12]. The results of this study were similar to those in clinical trials and better than those in other real-world data studies. Also, it showed solid results when the drugs were applied in the second line. In the case of the mono vemurafenib group, our data of nine months median OS and seven months of median PFS, where slightly lower than results found in the BRIM-3 trial. In final overview of the BRIM-3 study, median OS, censored at crossover, was significantly longer for vemurafenib - 13.6 months, than for dacarbasine - 9.7 months [13]. Despite high initial ORR, half of the patients treated with BRAF targeted monotherapies relapsed within six months, due to the development of drug resistance and other various reasons [14, 15, 16].

Trametinib, cobimetinib, and binimetinib, targeting the MAP kinase pathway, are overcoming resistance to BRAF inhibitor therapy. They are oral small-molecule inhibitors of MEK1 and MEK2, signaling molecules downstream of BRAF in the MAP kinase pathway. When compared with either single-agent dabrafenib or single agent vemurafenib, BRAF/MEK inhibitor combination therapy with dabrafenib and trametinib, vemurafenib plus cobimetinib and encorafenib plus binimetinib showed improved ORR, duration of response, PFS, and OS [17, 18, 19]. Results are significantly better then mono BRAF inhibition, with median OS ranging from 22 to 33 months and PFS from 11 to 15 months. Our results for patients treated with BRAF/MEK inhibition with two available combinations showed inferior OS and PFS with median OS of 14 months and median PFS of nine months. Two complete responses are currently being observed, as well as three partial responses and two stable diseases in this treatment group.

In the matter of the efficacy of pembrolizumab, it showed a lower median OS of 15 months, but a similar PFS of nine months. One complete response is still ongoing, as well as two partial responses in the pembrolizumab group. A recent publication of outcomes and survival from a randomized, phase 3 trial Keynote-006 of pembrolizumab for ipilimumab naive advanced or metastatic melanoma patients, showed a median OS of 32.7 months (95% CI 24.5–41.6), median PFS of 8.4 months (95% CI 6.6–11.3) [20]. Nivolumab is another PD-1 inhibitor that is indicated for the treatment of advanced or metastatic melanoma. In a five-year outcome analysis in trial with Nivolumab CheckMate 066, the median OS was 37.3 months (95% CI, 25.4–51.6) and median PFS 5.1 months (95% CI, 3.5–12.2) [21].

There are more possible reasons for these results. Firstly, medium follow-up in our analysis was shorter in comparison to published clinical trials. Secondly, the characteristics of our patients differ from those in the mentioned clinical trials. Our patients were mainly in an ECOG performance status of 0, but there are 18 of them that were ECOG 2 or 3, which is often within the exclusion criteria in clinical trials. There were 14 (13.1%) patients with initially detected brain metastases, some of them had symptomatic brain metastases, which was an exclusion criterion in some clinical trials. We know that patients with active brain metastases not only have a poor survival rate due to their disease, but also require systemic glucocorticoids [22]. Ultimately, perhaps the most significant reason for the poor efficacy of targeted therapy and immunotherapy is that a huge number of patients did not start therapy as a first-line treatment. These patient groups received chemotherapy before starting targeted therapy or immunotherapy, which had a detrimental effect on performance status and perhaps induced drug resistance. However, at the time of initiation of the first-line treatment, the tumor burden was lower, as well as the number of metastatic sites.

The limitations of this study include a small number of patients is insufficient for definitive conclusion, as well as the retrospective design of the study results and a short follow-up time compared to recent publications. Our future perspective is to update the data, especially regarding the survival rate and the responses to immunotherapy and BRAF/MEK inhibitors. We hope to see better antitumor activity of these drugs. In October 2018, when PD-1 inhibitor pembrolizumab was available for melanoma patients in BiH, this was the only PD-1 inhibitor reimbursed by medical insurance. Even today, Nivolumab is not fully reimbursed and neither the combination of nivolumab with ipilimumab, which presents another treatment option for this group of patients, with an exceptional survival [23]. BRAF/MEK inhibitors were reimbursed in 2017, and BRAF inhibitor in 2015. Based on this, in BiH there is still a lot of space for improvement when it comes to systemic melanoma treatment. Providing faster reimbursement for new drugs, different financing options for this kind of treatment, procurement of larger quantities of these drugs so patients do not have to wait and including patients in clinical trials should be priorities. The lack of focus on these priorities is possibly reflected in the data showing an increase in the mortality-to-incidence ratios in Eastern European countries compared to Western Europe [24].

CONCLUSION

Our results show lower median OS and PFS compared to reported data from clinical studies. Compared to other real-world data in countries with similar problems, our research has shown similar results. This gives us an insight into real-life patient care and represents an important contribution to the oncology community, with the hope that it will enable a better care for our patients in the future.

Conflict of interests: None declared.

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Обрасци и исходи лечења болесника са метастатским меланомом – подаци из стварног света

Дејан Ђокановић[1,2], Бојана Лазић[1,2], Зденка Гојковић[1,2], Жељка Цвијетић[3], Емир Соколовић[4], Тимур Церић[4], Саша Лунгић[1,2]

[1]Универзитетски клинички центар Републике Српске, Клиника за онкологију, Бања Лука, Република Српска, Босна и Херцеговина;
[2]Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина;
[3]Паневропски универзитет „Апеирон", Бања Лука, Република Српска, Босна и Херцеговина;
[4]Универзитет у Сарајеву, Клинички центар, Клиника за онкологију, Сарајево, Федерација Босне и Херцеговине, Босна и Херцеговина

САЖЕТАК

Увод/Циљ Сврха овог истраживања је да се процени ефикасност различитих приступа у лечењу метастатског меланома у свакодневној клиничкој пракси у ситуацији са ограниченом и касном доступношћу нових лекова у земљи са ограниченим ресурсима и да се ови параметри упореде са оним објављеним у клиничким студијама и са другим подацима из стварног света.

Методе Главни методе су укључивале процену укупног преживљавања и преживљавања без прогресије болести. Анализирани су болесници који су били лечени првом или другом линијом системске терапије за радиолошки/патохистолошки потврђени метастатски меланом. Болесници су подељени у четири групе према терапији коју су примали: хемотерапију (дакарбазин), БРАФ инхибитор (вемурафениб), БРАФ/МЕК инхибиторе (вемурафениб/цобиметиниб и траметиниб/дабрафениб) и анти ПД-1 терапију пембролизумабом.

Резултати Без обзира на терапијску линију, израчуната медијана укупног преживљавања у групи која је примала хемиотерапију и вемурафениб била је девет месеци. Медијана укупног преживљавања у групи која је примала БРАФ/МЕК инхибитор била је 14 месеци, а у групи која је примала терапију пембролизумабом 15 месеци. Преживљавање без прогресије болести у хемиотерапијској групи било је четири месеца, у групи која је примала вемурафениб седам месеци, у групи која је примала БРАФ/МЕК инхибитор девет месеци и у групи која је имала терапију пембролизумабом шест месеци. Постоји статистички значајна разлика у преживљавању између прве и друге линије у групи која је имала терапију пембролизумабом.

Закључак Наши резултати показују нижу медијану укупног преживљавања и преживљавања без прогресије болести у поређењу са пријављеним подацима из клиничких испитивања. У поређењу са другим подацима из стварног света у земљама са сличним проблемима са касним увођењем нових лекова, наше истраживање је показало сличне резултате. Нове терапије значајно су продужиле преживљавање, али још много тога треба да се уради како би болесници постигли веће стопе преживљавања.

Кључне речи: метастатски меланом; имунотерапија; циљана терапија; хемиотерапија; преживљавање; подаци из стварног света

DOI: https://doi.org/10.2298/SARH220319121C
UDC: 616.71/.72-002-085; 606:616.71/.72-002

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Persistence on anti-TNF therapy – data from Serbian National Spondyloarthritis Registry

Jovana Cvetković[1], Tatjana Živanović-Radnić[2], Jelena Vojinović[3], Sonja Stojanović[4], Bojana Stamenković[4], Mirjana Veselinović[5], Biljana Erdeljan[6], Marija Atanasković[7], Zoran Veličković[7]

[1]Niška Banja Institute for Treatment and Rehabilitation, Niš, Serbia;
[2]University of Belgrade, Institute for Rheumatology, Belgrade, Serbia;
[3]University of Niš, Clinical Center of Niš, Niš, Serbia;
[4]University of Niš, Niška Banja Institute for Treatment and Rehabilitation, Niš, Serbia;
[5]University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine, Kragujevac, Serbia;
[6]Special Hospital for Rheumatic Diseases, Novi Sad, Serbia;
[7]Institute for Rheumatology, Belgrade, Serbia

SUMMARY

Introduction/Objective The aim of our study was to retrospectively analyze data about efficacy and persistence on different anti-TNFα treatment in spondyloarthritis (SpA).

Methods We retrospectively analyzed SpA patients whose data were entered into the Serbian national SpA registry. All patients were divided in two groups: non-switcher (patients who were treated with one anti-TNFα) and switcher group (who has switched from first to second and third anti-TNFα). Disease activity was measured by the Ankylosing Spondylitis Disease Score and the Bath Ankylosing Spondylitis Disease Activity Index and functional status was measured by the Bath Ankylosing Spondylitis Functional Index.

Results We identified 290 SpA patients – 250 patients with axial SpA (axSpA) and 40 patients with peripheral SpA (pSpA). Among 250 patients with axSpA, 192 (76.8%) did not change first anti-TNFα, while 58 (23.2%) switched to the second and 14 (5.6%) switched to the third anti-TNFα. Among 40 patients with pSpA, 29 (72.5%) did not change first anti-TNFα while 11 (27.5%) switched to the second and three (7.5%) switched to the third anti-TNFα. Survival on the first anti-TNFα was 35.16 ± 28.5 months (switchers 29.41 ± 21.89 *vs.* non-switchers 36.89 ± 30.04). At the moment of this cross-section 37 (19.3%) patients still had very high disease activity, while only 75 (39%) patients had inactive disease.

Conclusions In real-life clinical practice in our country, as well as in others, there is reluctance to anti-TNFα switch in SpA patients. Administrative limitations and national reimbursement policy could be one of the main reasons limiting treat to target implementation in SpA patients. Additionally, specific drug efficacy on extra-articular manifestations is often the reason for choosing the first line medication or switching to the next one.

Keywords: anti-TNFα drugs; anti-TNFα switch; registry; spondyloarthritis

INTRODUCTION

Spondyloarthritis (SpA) is a heterogeneous group of chronic inflammatory joint diseases. Depending on the clinical presentation and joint involvement, SpA is divided into axial (axSpA) and peripheral (pSpA) form of the disease. The clinical manifestations of SpA include arthritis, dactylitis, enthesitis, and typical extra-articular manifestations (EAM), such as psoriasis, acute anterior uveitis, and inflammatory bowel disease (IBD) [1]. In the last decades, due to the usage of biological drugs such as TNF-α inhibitors, there were great achievements in the treatment in terms of reduction of the disease activity, improvement of functional capacity and the quality of life of these patients. All TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol) are effective in treating different forms of SpA, but it is also known that some patients do not respond to treatment at the very beginning of the therapy or stop responding to the medication over time due to secondary ineffectiveness or adverse effects of the drug [2].

There are also differences in the efficacy of different anti-TNFα agents in relation to the presence of EAM and this should be included when choosing treatment option [3]. For example, in acute anterior uveitis adalimumab and infliximab showed better treatment results than treatment with etanercept [4]. Etanercept is ineffective in IBD [5] and some data suggest that it may also be less effective than adalimumab in patients with psoriasis [6]. Among the TNFα-blocking agents, only infliximab and adalimumab are effective in SpA and IBD [7, 8].

As TNF-α inhibitors are different in structure and mechanism of action, patients who fail to respond to treatment with first anti TNFα drug or receive some adverse reactions during therapy, may benefit from the application of the second anti TNFα drug [9].

The aim of our study was to retrospectively analyze everyday practice data about efficacy and persistence on different anti TNF treatment in SpA patients followed up as observational cohort within the National Biologics' Registry and in accordance with medication evaluability.

Received • Примљено: March 19, 2022
Revised • Ревизија: December 21, 2022
Accepted • Прихваћено: December 24, 2022
Online first: December 29, 2022

Correspondence to:
Jovana CVETKOVIĆ
Niška Banja Institute
for Treatment and Rehabilitation
Niš
Serbia
miljevicjovana@yahoo.com

METHODS

We have retrospectively analyzed data of SpA patients who were entered into the Serbian national SpA registry (2009–2018). The Serbian National Biologics Registry is official software application established and founded by the Serbian Rheumatology Association after obtaining IRB/EC approval. It is based on Declaration of Helsinki and other relevant regulations to protect patient privacy. Registry enables all rheumatologists across the country to enter patient data during regular periodic follow up classified in four domains: basic demographic data, disease onset and history, outcome measures (disease activity) and safety data. Data entry started in 2009 when biologics became evaluable and reimbursed by National Health Insurance Fund (NHIF). The first evaluable biologic was etanercept (in 2009) followed by adalimumab in 2011 and golimumab in 2015. Secukinumab, as IL-17 blocker, become evaluable at the end of 2019 while other biologics are yet not present.

SpA diagnosis was established using Modified New York criteria [10] for patients who started treatment from 2009 up to 2013 or using the Assessment of Spondyloarthritis International Society (ASAS) criteria for patients who started treatment after 2013 [11]. All patients fulfilled ASAS classification criteria for diagnosis of axial or peripheral SpA [11]. Patients with psoriasis and SpA disease features were classified as psoriatic arthritis and were not included in this study. Only patients who had details about the disease diagnosis, activity, treatment and follow up data at the moment of this cross-sectional analysis were eligible for inclusion into the study. Disease activity was measured by the Ankylosing Spondylitis Disease Score (ASDAS) and/or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and functional status was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). Radiographically confirmed sacroiliitis was defined as bilateral grade II/IV or unilateral grade III/IV sacroiliitis according to New York criteria [10] in patients enrolled before 2013 while magnetic resonance imaging was used for patients enrolled later on. For patients enrolled before 2013, according to data entered into the system in the past, ASDAS score was calculated retrospectively and used for analysis.

Data collected and analyzed were sex, age, disease duration before starting biologic therapy, the length of treatment with each anti-TNFα, presence of different EAM, drug persistence, reasons for drug discontinuation and switch to next anti-TNFα and side effects recorded during follow up. According to treatment used all patients were divided in two groups: non-switcher (including patients who were treated with only one anti-TNFα as a first biologic drug) and switcher group (including patients who switched from first to second and third anti-TNFα). According to the axSpa national treatment algorithm [12] and NHIF regulation, patients who had high disease activity (BASDAI ≥ 4, and ASDAS C-reactive protein values ≥ 2.1) after applying the previous treatment modality (non-steroidal anti-rheumatic drugs in axSpA and chemical disease modifying drugs and local corticosteroids in pSpA, were approved to, start treatment with biological drugs (bDMARDs).

All bDMARDs were used according to their summary of product characteristic and standard clinical practice. When patients fail to respond to treatment after six months, they should be switched from the first to the second and some of them with the same reason to the third anti-TNFα drug.

Lack of reduction in BASDAI index by 50% or ≥ 2 of pre-drug value, or no decrease in ASDAS index ≥ 1.1 in the first six months of treatment was defined as primary inefficacy, while insufficient reduction in BASDAI or ASDAS score after at least 12 months of treatment with primary good response to the drug, was defined as secondary treatment inefficacy.

Drug survival was calculated as the number of months from first to last dose of the same drug at the time of the cross-section. The efficacy of the biological drug as the first, second or third line was measured as a change of the BASDAI and/or ASDAS score from the initial dose of the specific medication.

Statistical methods

Differences in average age at diagnosis, age at initiation of therapy, duration of disease until initiation of therapy between switchers and non-switchers, were tested by t-test. Previously, the normality of the observed values was confirmed by the Kolmogorov–Smirnov test. Differences in the length of drug administration as the first drug were tested by ANOVA. Differences in the presence of EAM between switchers and non-switchers and the association between the first drug and presence of EAM were tested by χ^2 test.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008 (5), as well as the national law. All the data were retrospectively analyzed from Serbian National Registry for Spondyloarthritis formed with the approval of the Ethics Committee of the Institute of Rheumatology in Belgrade. Code availability: not applicable.

RESULTS

We have identified a total of 290 SpA patients who fulfilled inclusion criteria regarding the availability of data entered into the registry. There were 250 patients with axSpA and 40 patients with pSpA. Detailed demographic characteristics are presented in Table 1.

Patients with axial spondyloarthritis

Among 250 patients with axial SpA, 192 (76.8%) did not change first anti-TNFα (non-switcher group), while 58 (23.2%) switched to the second anti-TNFα and 14 (5.6%) switched to the third anti-TNFα (switcher group).

Patients in non-switcher group had significantly shorter disease duration before introduction of biologic therapy (Table 1). In the same group of patients there

Table 1. Demographic characteristics for axial spondyloarthritis and peripheral spondyloarthritis patients

Parameters	All	Axial spondyloarthritis			Peripheral spondyloarthritis		
	n = 250	non-switchers (n = 192)	switchers (n = 58)	t	non-switchers (n = 29)	switchers (n = 11)	t
		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age at diagnosis (years)	32.89 ± 11.32	32.81 ± 11.20	34.09 ± 11.53	2.54	32.25 ± 12.85	25.09 ± 10.87	-5.59
Disease duration (years)	10.2 ± 8.2	9.20 ± 7.48	13.48 ± 9.54	10.09**	7.18 ± 6.18	14.64 ± 9.19	7.70*
Disease duration before biologic therapy (years)	6.23 ± 7.47	5.59 ± 7.06	8.33 ± 8.40	6.71*	4.98 ± 6.29	9.27 ± 7.47	4.56
Treatment duration of biologic therapy (months)	41.3 ± 31.57	36.90 ± 30.03	55.88 ± 32.38	22.36**	26.04 ± 20.31	64.73 ± 26.94	22.48**
Clinical manifestations							
		n (%)	n (%)	χ^2	n (%)	n (%)	χ^2
Radiographically confirmed sacroiliitis	214	169 (88.02)	45 (77.59)	3.93*	19 (65.52)	3 (27.27)	5.29*
Peripheral arthritis	101	78 (40.63)	23 (29.66)	0.02	28 (96.55)	10 (90.91)	0.54
Dactylitis	10	10 (5.21)	0 (0)	3.14	5 (17.24)	1 (9.09)	0.42
Enthesitis	54	41 (21.35)	13 (22.41)	0.03	20 (68.97)	7 (63.64)	0.10
Iridocyclitis/uveitis	48	39 (20.31)	9 (15.52)	0.99	4 (13.79)	2 (18.18)	0.12
Inflammatory bowel disease (Crohn's disease / ulcerative colitis)	15	6 (3.31)	9 (15.52)	12.08**	3 (10.34)	2 (18.18)	0.45

Data shown in the upper part of the table (continuous variables) represent mean ± SD; data shown in the lower part of the table are frequencies (counts) of patients with particular articular and extra-articular manifestations
* $p < 0.05$;
** $p < 0.01$

Table 2. Articular and extra-articular manifestations of axial spondyloarthritis patients at the time of anti-TNF introduction in switchers and non-switchers group

Parameters	Non-switchers					Switchers				
Anti TNF used	Adalimumab (n = 64)	Etanercept (n = 64)	Golimumab (n = 57)	Infliximab (n = 7)	χ^2	Adalimumab (n = 15)	Etanercept (n = 27)	Golimumab (n = 9)	Infliximab (n = 7)	χ^2
Radiographically confirmed sacroiliitis	55 (85.94%)	53 (82.81%)	56 (98.25%)	5 (71.43%)	9.39*	12 (80%)	19 (70.37%)	8 (88.89%)	6 (85.71%)	1.78
Peripheral arthritis	31 (48.44%)	28 (43.75%)	17 (29.82%)	2 (28.57%)	5.06	6 (40%)	9 (33.33%)	4 (44.44%)	4 (57.14%)	1.43
Dactylitis	6 (9.38%)	1 (1.56%)	3 (5.26%)	0 (0%)	4.36	0 (0%)	0 (0%)	0 (0%)	0 (0%)	/
Enthesitis	12 (18.75%)	13 (20.31%)	14 (24.56%)	2 (28.57%)	0.87	5 (33.33%)	5 (18.52%)	2 (22.22%)	1 (14.29%)	1.53
Iridocyclitis/ uveitis	26 (40.63%)	5 (7.81%)	8 (14.04%)	1 (14.29%)	26.85**	4 (26.67%)	3 (11.11%)	0 (0%)	2 (28.57%)	4.38
Inflammatory bowel disease (Crohn's disease/ ulcerative colitis)	3 (4.69%)	1 (1.56%)	1 (1.75%)	1 (14.29%)	4.15	4 (26.67%)	2 (7.41%)	0 (0%)	3 (42.86%)	8.12*

* $p < 0.05$;
** $p < 0.01$

were significantly more patients with radiographically confirmed sacroiliitis ($p < 0.05$), and statistically less patients with IBD compared to switchers group ($p < 0.001$) (Table 1).

Median survival of the first TNF alpha inhibitors in all axSpA patients was 35.16 ± 28.5 months (switchers 29.41 ± 21.89 *vs.* non-switchers 36.89 ± 30.04). In non-switchers group etanercept was the most commonly used anti-TNFα as the first drug compared to other TNFα inhibitors ($p < 0.001$). In the non-switchers group, patients with iridocyclitis were more frequently treated with adalimumab as the first drug ($p < 0.001$), while in those without eye manifestation etanercept or golimumab were the first drug (Table 2).

Out of 192 patients with axSpA in non-switchers group at the beginning of the treatment, 135 had a very high disease activity (VHDA) according to the ASDAS score. At the moment of this cross-section, 30 (15.6%) patients were still having VHDA, seven (3.7%) had high disease activity (HAD), 80 (41.7%) minimal disease activity (MDA), and 75 (39%) patients had inactive disease (ID). The details are presented in Figure 1. The second anti-TNFα drug survival for switchers was 22.14 ± 20.29 months and for the third-time anti-TNFα switchers it was 26.57 ± 35.8 months. In the same group etanercept was the most common drug to be changed (29; 50%), while adalimumab was most commonly used as the second anti-TNFα (23; 39.7%) and golimumab as the third anti-TNF α (8; 57.1%).

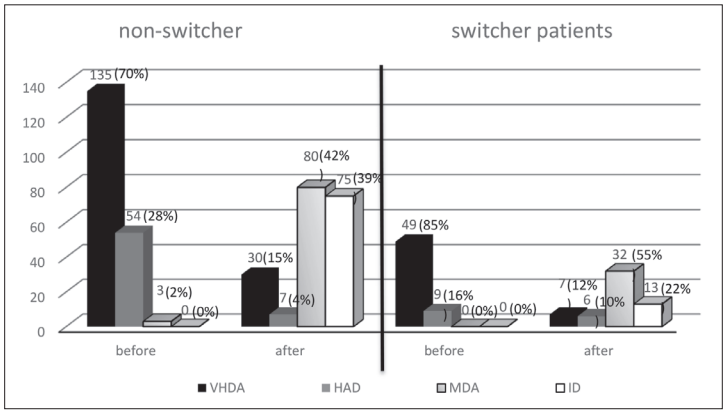

Figure 1. Disease activity at the beginning and at time of cross-section in non-switchers and switcher group patients with axial spondylarthritis; VHDA – very high disease activity; HAD – high disease activity; MDA – minimal disease activity; ID – inactive disease

After the treatment with the third TNFα inhibitor, two patients still had VHDA (both patients were receiving drug less than six months), four patients had HDA (two patients were receiving drug less than six months), while five patients had MDA and three patients ID. At the time of cross-section in whole switchers group, among 58 patients, 13 patients (22.4%) had ID, 32 (55.2%) MDA, six (10.3%) had HDA and seven (12.1%) VHDA (Figure 1).

All indices (BASDAI, BASFI, and ASDAS) were statistically significantly lower at cross-sectional time point compared to the initiation period of the treatment in patients with axSpA (Table 3).

The reasons for switching or discontinuing TNFα blockers were:

1. inadequate response to drug (insufficient reduction in ASDAS score or BASDAI index);
2. side effect of the drug;
3. development of extra-articular manifestation;
4. on patient's request (e.g., planned pregnancy, disease remission).

Reasons for switching from the first anti-TNFα include secondary inefficiency in 40 (68.97%), primary inefficiency in six patients (10.34%), recurrent uveitis and IBD each in one patient (1.72%), and elevated transaminases in one (1.72%) patient. Nine patients stopped treatment due to remission (five patients, 8.6%) and administrative reasons (four patients, 6.9%).

Reasons for switching from the second anti-TNFα were: secondary inefficiency in six (42.86%), primary inefficiency in four (28.57%), remission of Crohn's disease in one (7.14%), pregnancy in one (7.14%) and skin changes in two patients (14.29%).

In the switchers group (n = 58), at the beginning of the treatment with the second anti TNFα drug, 49 patients had VHDA and nine had HAD, while at the moment of cross-section only 10 patients had ID after treatment with the second anti TNFα drug. In the group of VHDA and HDA there were seven patients who had started biologic therapy six months or less before the cross-section moment, while 14 patients from this group switched to the third TNFα inhibitor.

Patients with peripheral SpA

Among 40 patients with pSpA, 29 (72.5%) did not change first anti-TNFα (non-switchers) while 11 (27.5%) switched to the second anti-TNFα and three (7.5%) switched to the third anti-TNFα (switchers).

Patients in non-switchers group had significantly shorter duration of the disease in general and before starting biologic therapy (Table 1).

A total of 38 patients were under concomitant therapy with DMARD – 12 patients on methotrexate at an average dose of 13.44 ± 5.5 mg, 19 patients on sulfasalazine and seven patients on methotrexate and sulfasalazine.

Survival on the first TNFα inhibitor in all pSpA patients was 27.4 ± 22.35 months (in switchers 27.4 ± 22.35, and in non-switchers 25.2 ± 21.4), on the second drug 28.64 ± 14.1 months, and on the third it was 16.33 ± 7.37 months. In pSpa non-switchers, most commonly used first anti-TNFα was adalimumab (12 patients; 41.4%), while etanercept was used in nine (31%), golimumab was in six patients (20.7%) and infliximab in two (6.9%) patients. In pSpA switchers adalimumab was most commonly used as the first drug, but it was also the most often changed drug in these patients. As in the axSpA switchers, golimumab was most commonly used as the third drug (in all three patients).

In pSpA switchers and non-switchers group there was no significant difference in the use of any of the TNFα inhibitors as the first drug, compared to the presence of articular and EAM.

Table 3. The value of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis Disease Score (ASDAS) indexes before first anti-TNF drug and at cross-sectional time in axial spondyloarthritis patients (n = 250)

Index	Before TNFα inhibitor in non-switchers	Actual in non-switchers	t	Before the first TNFα inhibitor in switchers	Before the second TNFα inhibitor in switchers	t	Before the third TNFα inhibitor in switchers	Actual in switchers	t
BASDAI	6.1 ± 1.59	2.07 ± 1.57	29.35**	6.2 ± 1.61	5.48 ± 1.68	3.68	5.65 ± 0.91	2.5 ± 1.53	7.36**
BASFI	5.6 ± 1.78	2.08 ± 1.93	22.07**	6.42 ± 1.65	5.6 ± 1.68	4.16	4.72 ± 2.25	2.38 ± 2.15	3.94**
ASDAS	4.05 ± 0.98	1.56 ± 0.98	29.48**	4.44 ± 0.96	3.87 ± 0.75	5.09	3.59 ± 0.67	2.08 ± 1.0	4.11**

Data shown in the upper part of the table represent mean ± SD; significances presented by asterisks are significances of t-test comparing means of indices of non-switchers and switchers between different stages of medical treatment;
**p < 0.001

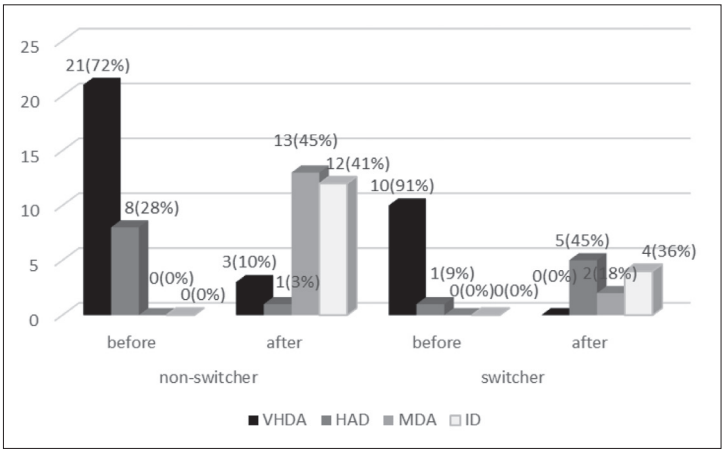

Figure 2. Disease activity at the beginning and at time of cross-section in non-switchers and switcher group patients with peripheral spondylarthritis; VHDA – very high disease activity; HAD – high disease activity; MDA – minimal disease activity; ID – inactive disease

Reasons for switching the first drug were: secondary inefficiency in six (54.55%), primary inefficiency, recurring iridocyclitis and administrative reasons, each in one patient (9.09%), and remission in two patients (18.18%). Reason for switching the second drug in all three patients was secondary inefficiency.

At the beginning of the treatment in non-switchers group 21 patients had VHDA according to the ASDAS score and 8 had HDA. At the moment of intersection three (10.4%) patients were in the group of VHAD and one patient (3.4%) in HAD, 13 had (44.8%) MDA and 12 had (41.4%) ID. In the group of VHDA and HDA there were two patients who had started biologic therapy six months or less before the moment of intersection.

After the treatment with the second TNFα inhibitor, three patients still presented VHDA and two patients had HDA (these two patients were treated by second drug less than six months at the time of intersection), two patients had MDA and four patients had ID. All three patients from the group of VHDA were switched to the third TNFα inhibitor. Out of these three patients, two patients still had HDA, and one patient had MDA. In whole switchers group at the time of intersection five (45.4%) patients had HAD, two had (18.2%) MDA and four had (36.4%) ID (Figure 2).

In the whole group of pSpA patients the value of index ASDAS was statistically significantly lower at cross-sectional time point compared to the onset of treatment in switchers (4.05 ± 0.75 *vs.* 1.71 ± 0.73) and in non-switchers (4.07 ± 0.95 *vs.* 1.58 ± 1.08, $p < 0.001$).

DISCUSSION

Our study analyzed real practice data and found out that one third of patients with axSpA (23.2%) and pSpA (27.5%) switched to second TNFα inhibitor and only a small number of them switched to the third anti TNFα drug during a follow-up period of nine years. These results are in accordance with French registries, where switching rate for the first anti TNF alpha drug was of 32% in patients with spondyloarthropathy [13, 14]. In the Norwegian-NOR-DMARD registry only 14.9% of AS patients switched the first anti TNF alpha drug during in a period of nine years [15]. Also, in the Danish-DANBIO registry 30% of patients had switched once and 10% patients had switched twice during a 10-year-long follow-up [16].

Disease duration in non-switcher group of patients with axSpA and pSpA, as might be expected, was significantly shorter compared to switcher group. Many studies have proved that initiation of anti-TNFα drug in the earlier course of the disease reduces the inflammation at earlier stage and provides better chance for favorable outcome [17]. Accordingly, non-switcher axSpA patients were younger at the time of biologic therapy commencement compared to switchers group. This is not in line with the findings of other national registers where shorter disease and symptom duration and higher disease activity and functional indices were found in switchers compared to non-switchers [15, 16].

We assume this is a direct consequence of difference in anti-TNF therapy availability in each country. Unfortunately, anti-TNFα biologics became treatment option for these patients rather late in Serbia (etanercept in 2009, adalimumab and infliximab in 2011, golimumab in 2015). This fact probably explains why etanercept was found to have the longest persistence rate in all SpA patients, compared to other anti TNFα drugs, while it was also found to be the most often changed first anti-TNFα medication, as recorded in our study.

The most common reasons for switching etanercept as first line anti-TNFα in axSpA group of patients were secondary inefficacy and the presence of extraarticular manifestations, such as IBD and recurrent uveitis. In these patients, according to its proven efficacy [18], adalimumab was the second anti-TNFα chosen. Probably due to the same reason, adalimumab was the preferable first anti-TNF for patients in the non-switcher group with a history of uveitis revealed by anamnestic data, while in the switchers axSpA group of patients the presence of IBD was the reason for switching to adalimumab or infliximab. So, similar to other registries and according to official recommendations [19], the presence of EAM influence the choice and persistence of first anti-TNF.

It is interesting that in pSpA patients the most commonly used first anti-TNFα was adalimumab, while this group of patients often had EAM. Golimumab was the most often used as the third TNFα inhibitor in axSpA and pSpA switchers, because it was the last anti-TNFα drug introduced on Serbian pharmaceutical market. It was mostly used in patients who have developed secondary inefficiency or side effects after treatment with etanercept, adalimumab, or infliximab.

Like in previous studies, the most common reason for drug switching was secondary inefficiency in our study as well [15]. Survival time on the second and third

medication was shorter compared to initial therapy both in the pSpA and in the axSpA which suggests that the risk of switching is higher over time.

The results of our study showed that two thirds of patients with axSpA (75.86%) and pSpA (72.73%) who switched the first TNFα inhibitor were responsive to the second drug which is consistent with the available data in the literature [20]. But there were still axSpA and pSpA patients who, despite switching to the third drug, could not reach the therapeutic goal. Here it is necessary to rise question of outcome measures used to assess disease outcome and activity. Until 2013 in our country BASDAI index was used to assess disease activity and after that period we started to use ASDAS index. Given that the calculation of BASDAI index is based on a subjective assessment of the patient's discomfort, we can say that this previously used measure of disease activity was less sensitive compared to the composite ASDAS index, which includes clinical and laboratory parameters. It is assumed that earlier use of the ASDAS index would provide better insight into disease activity and, if necessary, earlier and more effective changing of the biological drug [21]. At the same time, we can say that this is the main limitation of our study. Another limitation of this study is the small number of patients who are treated with biologics in this indication in our country – for economic reasons. The interleukin 17 inhibitor was approved in our country in this indication in 2019, so that is why we did not consider switching TNF alpha inhibitors to this drug.

CONCLUSIONS

In real-life clinical practice in our country, as well as in others, there is reluctance to anti-TNFα switch in SpA patients. Administrative limitations and national reimbursement policy (late initiation of treatment and late switching to another drug) could be one of the main reasons limiting treat to target implementation in SpA patients, which may explain the still high disease activity in some of our patients. Additionally, specific drug efficacy on EAM is often the reason for choosing the first line medication or switching to the next one.

Conflict of interest: None declared.

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Постојаност терапије анти-ТНФ инхибиторима – подаци из Националног регистра за спондилоартритисе у Србији

Јована Цветковић[1], Татјана Живановић-Радниħ[2], Јелена Војиновић[3], Соња Стојановић[4], Бојана Стаменковић[4], Мирјана Веселиновић[5], Биљана Ердељан[6], Марија Атанасковић[7], Зоран Величковић[7]

[1]Институт за лечење и рехабилитацију „Нишка Бања", Ниш, Србија;
[2]Универзитет у Београду, Институт за реуматологију, Београд, Србија;
[3]Универзитет у Нишу, Универзитетски клинички центар Ниш, Ниш, Србија;
[4]Универзитет у Нишу, Институт за лечење и рехабилитацију „Нишка Бања", Ниш, Србија;
[5]Универзитет у Крагујевцу, Факултет медицинских наука, Одељење интерне медицине, Крагујевац, Србија;
[6]Специјална болница за реуматске болести, Нови Сад, Србија;
[7]Институт за реуматологију, Београд, Србија

САЖЕТАК

Увод/Циљ Циљ истраживања је био да се ретроспективно анализирају подаци о ефикасности и постојаности терапије анти-ТНФα лековима код болесника са спондилоартритисом (СпА).

Методе Ретроспективно смо анализирали податке болесника са СпА уписаних у Српски национални регистар СпА. Сви болесници су подељени у две групе: они који су лечени једним анти-ТНФα леком и они који су преведени са првог на други и/или трећи анти-ТНФα лек. Активност болести је мерена скоровима *ASDAS* и *BASDAI*, а функционални статус је мерен скором *BASFI*.

Резултати Укључено је 290 болесника – 250 болесника са аксијалним СпА (ахСпА) и 40 са периферним СпА (пСпА). Од 250 болесника са аксСпА, 192 (76,8%) није променило први анти-ТНФα, док је 58 (23,2%) преведено на други, а 14 (5,6%) на трећи анти-ТНФ. Од 40 болесника са пСпА њих 29 (72,5%) остало је на првом анти-ТНФα, док је 11 (27,5%) преведено на други и три (7,5%) на трећи анти-ТНФα. Трајање лечења првим анти-ТНФα леком било је у просеку 35,16 ± 28,5 месеци (код оних који су мењали лек 29,41 ± 21,89 наспрам оних који нису 36,89 ± 30,04). У тренутку овог пресека 37 (19,3%) болесника је и даље имало веома високу активност болести, док је само 75 (39%) болесника имало неактивну болест.

Закључак У клиничкој пракси у нашој земљи, као и у другим земљама, постоји неспремност за прелазак са првог на други или трећи анти-ТНФα лек код болесника са СпА. Административна ограничења и ограничења Републичког фонда за здравствено осигурање могу бити један од главних разлога који отежавају лечење ових болесника. Поред тога, специфична ефикасност ових лекова на одређене ванзглобне манифестације болести често је разлог за избор лека прве линије или прелазак на други односно трећи лек.

Кључне речи: анти-ТНФα лекови; трајање лечења; регистар; спондилоартритис

DOI: https://doi.org/10.2298/SARH221204016J
UDC: 616.98-06:578.834; 616.72-002

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Therapeutic dilemmas in the management of a patient with long-term rheumatoid arthritis and severe clinical presentation of SARS-CoV-2 infection

Tanja Janković, Aleksandra Savić, Jelena Zvekić-Svorcan, Aleksandra Glavčić, Ksenija Bošković

University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
Special Hospital for Rheumatic Diseases, Novi Sad, Serbia

SUMMARY

Introduction The objective of this case report is to present a clinical course of SARS-CoV-2 infection in a patient with long-term rheumatoid arthritis and concomitant rituximab therapy.

Case outline A 58-year-old female patient was diagnosed with seropositive rheumatoid arthritis at the age of 35. She was primarily prescribed chloroquine and glucocorticoid, afterwards methotrexate and biological agent – etanercept. Because of a secondary loss of response, etanercept was switched to rituximab. She had 13 cycles of rituximab and the last was given in June 2020. In December 2020, she was hospitalized due to bilateral pneumonia and respiratory insufficiency. The results of the laboratory analysis revealed anemia, leukocytosis, thrombocytosis, and markedly elevated C-reactive protein, procalcitonin, D-dimer, transaminases. The findings of the chest computed tomography scan were consistent with COVID-19 pneumonia features with accompanying bilateral pleural effusion. The patient was treated with antibiotics, corticosteroids, tocilizumab, hepatoprotective, gastroprotective, oxygen therapy, and parenteral anticoagulant. Three months after recovering from pneumonia, she developed arthritis flare, hence a JAK inhibitor, baricitinib, was started. Low disease activity was achieved with baricitinib monotherapy.

Conclusion Due to risk of severe COVID-19, caution may be required when applying immunosuppressive therapy in patients with rheumatic diseases.

Keywords: inflammatory diseases; rheumatoid arthritis; immunosuppressive drug; COVID-19

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of novel coronavirus disease 2019 (COVID-19), whose complete genome sequence was identified in January 2020, after a cluster of pneumonia of unknown etiology appeared in China in December 2019 [1]. This viral disease spread across the globe, leading to the one of the largest outbreaks in recent years which resulted in COVID-19 being a major public health burden [2]. The clinical presentation of SARS-CoV-2 infection varies from asymptomatic to severe and critical illness with multiorgan involvement [3]. Growing evidence suggests that a key role in the pathogenesis and determining the severity of COVID-19 is played by the immune system of the infected host [4]. Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease with joint inflammation as a hallmark [5]. Considering the aberrant immunological pathways, COVID-19 and RA have some shared pathological features, most importantly cytokine imbalance. Due to similarities between RA and COVID-19 pathogenesis, medical professionals have questioned whether biological disease-modifying antirheumatic drugs (bDMARD) would be effective for the treatment of COVID-19. On the other hand, awareness of this group of medication being a specific risk factor for poor outcomes has drawn a lot of attention [6].

The objective of this case report is to present a clinical course of SARS-CoV-2 infection in a patient with long-term RA and concomitant rituximab therapy.

CASE REPORT

A 58-year-old female patient was diagnosed with seropositive RA at the age of 35. She was primarily treated with chloroquine and low-dose glucocorticoid. After three years of treatment, chloroquine was discontinued due to ocular side effect and methotrexate was prescribed. The weekly dose of methotrexate was gradually escalated to the maximum tolerated dose of 12.5 mg. Periodically, in phases of arthritis flare, short-term glucocorticoid was added. The treatment target was not achieved with a conventional synthetic DMARD (csDMARD), thus a bDMARD, etanercept 50 mg/mL subcutaneously once a week was initiated in combination with 12.5 mg of methotrexate and 5 mg of prednisone in 2009. Because of secondary loss of response, etanercept was switched to rituximab. In May 2010, the patient received the first course of rituximab consisting of two infusions with 1000 mg of the drug administered two weeks apart with premedication. She

Received • Примљено: December 4, 2022
Revised • Ревизија: January 28, 2023
Accepted • Прихваћено: January 29, 2023
Online first: February 6, 2023

Correspondence to:
Aleksandra SAVIĆ
Special Hospital for Rheumatic Diseases
Futoška 68
21112 Novi Sad, Serbia
aleksandra_savic@uns.ac.rs

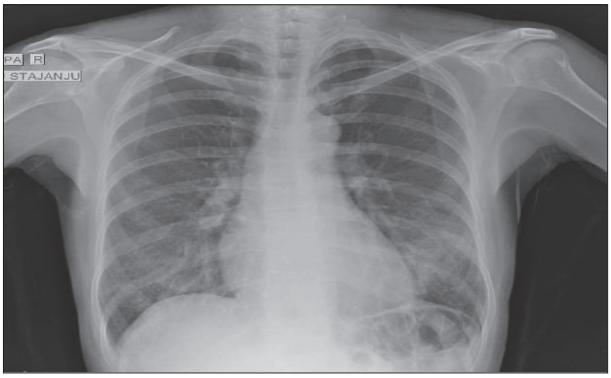

Figure 1. Chest X-ray showing signs of a bilateral pneumonia

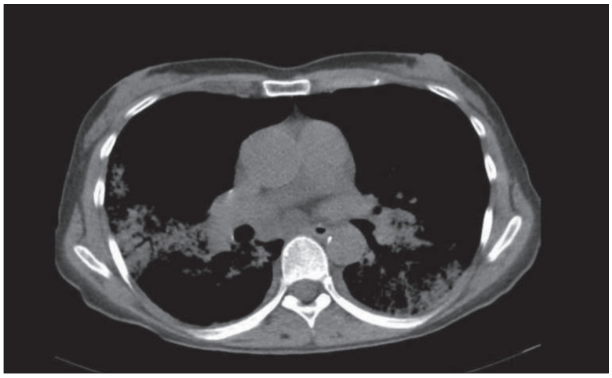

Figure 2. Computed tomography scan of the lungs showing features of COVID-19 pneumonia

had a total of 13 cycles, with the last intravenous infusion given on June 2020. The low disease activity was achieved and no adverse events regarding this biological agent occurred. Her medical history was positive for osteoporosis. In December 2020, six months after the last course, the patient developed fever, dry cough, nausea, and lower back pain, thus a nasopharyngeal swab sample was collected for the SARS-CoV-2 PCR test, which came back positive. The results of the laboratory analysis on admission to the hospital revealed mild anemia [red blood cells (RBC) = 3.7×10^{12}/L; hemoglobin (Hg) = 110 g/L), white blood cells (WBC), platelet count and the chemistry panel were within the reference range, while the C-reactive protein (CRP = 47.6 mg/L) as well as D-dimer were elevated (D-dimer = 1098 ng/mL)]. Initial radiographic work-up showed signs of a bilateral pneumonia in the lower lobes (Figure 1). Due to prolonged fever and the progression of respiratory symptoms, a chest computerized tomography (CT) was performed. The findings of the CT scan were consistent with COVID-19 pneumonia features and it detected multifocal bilateral ground-glass opacities of predominantly peripheral and peribronchial distribution, accompanied by thickening of the interlobular septa and linear opacities. Additionally, a bilateral pleural effusion with an anteroposterior diameter of up to 15 mm on the right and up to 10 mm on the left was seen (Figure 2). Echocardiographic evaluation registered a small amount of pericardial effusion as well as separation of the pericardial layers up to 3–4 mm. Repeated laboratory testing showed persistence of mild anemia (RBC = 3.4×10^{12}/L; Hb = 100 g/L), leukocytosis (WBC = 18.29×10^{9}/L) and thrombocytosis (PLT = 663×10^{9}/L), and markedly elevated inflammatory markers, CRP (203.4 mg/L) and procalcitonin (1.52 ng/mL), D-dimer (5818 ng/mL), transaminases (ALT = 347 U/L; AST = 246 U/L) and gamma-glutamyl transferase (GGT = 574 U/L). The patient was treated with broad-spectrum antibiotics, corticosteroids, hepatoprotective, gastroprotective therapy, and low-molecular-weight heparin. Due to increase in CRP concentration, high levels of interleukin-6 (154 pg/ml) and extensive pneumonic changes on chest X-ray, she received tocilizumab 400 mg in two doses 12 hours apart. Hypoxemia was corrected with conventional oxygen therapy using an oxygen mask. After four weeks of hospitalization, she was discharged home in a good general condition. She was regularly monitored by a pulmonologist, and in May 2021, a complete regression of pneumonic changes was confirmed by radiological evaluation. The patient was vaccinated with two doses of mRNA (Pfizer-BioNTech) vaccine against COVID-19 in the recommended three-week interval between the shots and was given a booster dose in December 2021. Three months after recovering from pneumonia, an exacerbation of arthritis developed, hence Janus kinase (JAK) inhibitor, baricitinib, was started in September 2021. Glucocorticoid therapy was used for the management of RA from January to September 2021. Monotherapy with JAK inhibitor has led to a clinical and laboratory improvement in two months. On the last rheumatologist visit, the patient had two tender joints without swelling, and the measured disease index was suggestive of low disease activity (Disease Activity Score 28 (CRP) = 2.9).

The paper was approved by the Ethics Board of the Novi Sad Special Hospital for Rheumatic Diseases and written consent to publish all shown material was obtained from the patient.

DISCUSSION

We report a patient with long-term inflammatory rheumatic disease (RD) treated with B-cell-depleting therapy, who presented with severe COVID-19 pneumonia. Regarding the case of our patient, a generalized conclusion cannot be drawn, but there is a reasonable possibility that the administration of rituximab affected SARS-CoV-2 infection outcome.

Patients with RA are more susceptible to infections due to the complex interactions of underlying immunological dysregulation, the use of immunosuppressive drugs and comorbidities [7]. With SARS-CoV-2 being spread globally, rheumatologists faced concern regarding an increased risk of more severe forms of COVID-19 and fatal outcome in this vulnerable group [8]. Risk factors associated with a poor prognosis in the general population are the older age, male sex and multiple comorbidities (obesity, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, cardiovascular diseases, active cancer) [9]. None of the previously mentioned predisposing factors

was present in our patient. Numerous studies have been conducted with the aim of determining predictors of the severity of COVID-19 infection along with the hospitalization and mortality rate in patients with RDs, but the results differ among each other. In one of the first comprehensive meta-analysis authors reported a higher prevalence in the group of patients with autoimmune diseases, but the severity of the infection was similar to comparators population. The interpretation of a higher prevalence should be questioned because patients with these disorders seek medical help earlier and are tested more frequently [10]. The European and American guidelines pointed out that the patients with rheumatic and musculoskeletal diseases (RMD) are not at higher risk of acquiring the SARS-CoV-2, nor when they become infected have a more severe disease course than individuals without RMD [11, 12]. The findings of an observational multicenter French cohort study on a sample of 694 participants were consistent with the conclusions stated in the previously cited guidelines. Patients with RMD compared with the general population share the same risk factors for a severe clinical presentation of COVID-19 [13]. In contrast, a team of the researchers from Boston compared 52 patients with RD and coronavirus disease to 104 participants without RD who were also infected with SARS-CoV-2 and concluded that after being matched by age, body mass index, smoking and comorbidities, these two groups differed concerning the therapeutic management. In other words, the proportion of individuals with RD treated in intensive care units was significantly higher – namely, this group had three times higher odds of requiring mechanical ventilation [14]. Ye et al. [15] conducted a study aiming to investigate the clinical characteristics and outcomes of COVID-19 infection in 21 patients with different RDs who were collected from a sample of 2326 hospitalized patients. They demonstrated that the duration of hospitalization and death rate were similar between rheumatic and non-rheumatic group, but patients with RDs were more likely to develop respiratory failure. Although these studies have several limitations, most importantly a small sample size and collider bias, they raised some concerns regarding risk factors for poor outcomes that are specific to RDs such as a disease modifying therapy. In terms of treatment, growing evidence suggests that patients using DMARD do not have an increased risk of severe COVID-19 outcomes. An Italian survey addressed whether the patients with RDs treated with biologic/targeted synthetic DMARD (b/tsDMARDs) are predisposed for a more severe clinical course when infected with SARS-CoV-2. Favalli et al. [16] found that the incidence and severity of COVID-19 were consistent with the general population. In a study conducted by Gianfrancesco et al. [17], a multivariable-adjusted models showed that patients using glucocorticosteroids in a dose greater than 10 mg daily had higher odds of hospitalization. In contrast, the use of csDMARD as monotherapy or in combination with b/tsDMARS did not lead to the higher hospitalization rate. Interestingly, patients treated with tumor necrosis factor inhibitors (TNFi) had a reduced risk of hospitalization. On the other hand, Raiker et al. [18] showed that rituximab and interleukin-6 users were more susceptible to hospitalization compared to TNFi users. Additionally, patients using JAK inhibitors or abatacept did not have and increased risk of hospitalization compared to TNFi users. Rituximab is a monoclonal antibody that binds to the CD-20 antigen on B-lymphocytes causing B-cell depletion, impaired opsonization, and reduction in antibody production [19]. Accumulated data suggest that anti-CD-20 therapy is associated with poor COVID-19 prognosis, which could be explained by a drug-induced defect in the antiviral humoral response [20]. It is essential to clarify the association between rituximab use and the risk of severe COVID-19 outcome. One should define whether rituximab has a negative effect on the coronavirus disease or whether a severity is a consequence of the confounding factors impact [21].

Through this clinical case, the authors wanted to highlight that in the context of the COVID-19 pandemic and numerous following doubts, caution may be required when applying immunosuppressive therapy in patients with RDs. Additional studies may potentially provide a better insight into individual risk stratification and determine specific factors leading to a severe COVID-19 in the RA population.

Conflict of interest: None declared.

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Терапијске дилеме у лечењу болесника са дугогодишњим реуматоидним артритисом и тешком клиничком сликом инфекције *SARS-CoV-2*

Тања Јанковић, Александра Савић, Јелена Звекић-Сворцан, Александра Главчић, Ксенија Бошковић

Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
Специјална болница за реуматске болести, Нови Сад, Србија

САЖЕТАК

Увод Циљ овог рада је да се представи клинички ток инфекције *SARS-CoV*-2 код болеснице са дугогодишњим реуматоидним артритисом и ритуксимабом у терапији.

Приказ болесника Болесници, старој 58 година, дијагноза серопозитивног реуматоидног артритиса постављена је у 35. години живота. Иницијално су за лечење прописани хлороквин и глукокортикоид, потом метотрексат и биолошки лек етанерцепт. Због развоја секундарне неефикасности, етанерцепт је замењен ритуксимабом. Укупно је примила 13 циклуса ритуксимаба, а последњи је дат јуна 2020. Због билатералне пнеумоније и респираторне инсуфицијенције примљена је на болничко лечење у децембру 2020. Резултати лабораторијских анализа су показали анемију, леукоцитозу, тромбоцитозу и изразито повишене вредности *C*-реактивног протеина, прокалцитонина, *D*-димера и трансаминаза. Компјутеризована томографија грудног коша је указала на постојање промена карактеристичних за пнеумонију изазвану ковидом 19 са пратећим билатералним плеуралним изливом. Лечење је спроведено антибиотицима, кортикостероидима, тоцилизумабом, хепатопротективном, гастропротективном, кисеоничном терапијом и парентералним антикоагулансом. Три месеца по опоравку од прележане пнеумоније јавила се акутизација артритиса; стога је у терапију уведен инхибитор Јанусове киназе, барицитиниб. Ниска активност болести је постигнута применом монотерапије барицитинибом.

Закључак Потребан је опрез приликом примене имуносупресивне терапије код болесника са реуматским обољењима због ризика за развој тешке клиничке слике ковида 19.

Кључне речи: инфламаторне болести; реуматоидни артритис; имуносупресивни лек; ковид 19

DOI: https://doi.org/10.2298/SARH220118014P
UDC: 578.834:575.22

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Postmortem detectability and viability of SARS-CoV-2 virus in various biological specimens

Tijana Petrović[1], Milenko Bogdanović[1], Tatjana Atanasijević[1], Vesna Popović[1], Milena Jovanović[2], Irina Banjanin[1], Bojana Radnić[1]

[1]University of Belgrade, Faculty of Medicine, Milovan Milovanović Institute of Forensic Medicine, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Institute of Pathology, Belgrade, Serbia

SUMMARY

Introduction Without a comprehensive postmortem investigation it is impossible to determine the cause of death among the SARS-CoV-2-suspected and -positive patients. We present two cases to discuss the postmortem detectability of SARS-CoV-2 virus and RNA stability in biological samples.

Outline of cases Case No. 1: a 40-year-old man on whom the autopsy was performed four days after death. The body was stored at 4°C. Bilateral pneumonia was confirmed grossly and histopathologicaly. Molecular testing was positive for IgM antibodies, but negative for SARS-CoV-2 RNA. Case No. 2: a 28-year-old professional basketball player who suffered from SARS-CoV-2 about a month earlier. The autopsy was performed two days after death. The body was stored at 15°C. Gross autopsy findings revealed advanced putrefactive changes and an enlarged heart, with visible fibrotic focuses. The histopathological finding corresponded to the sudden cardiovascular death due to the cardiac dysrhythmia most probably formed in one of the fibrotic focuses. Tests for SARS-CoV-2 RNA and antibodies (IgM, IgG) were positive in the analyzed samples.

Conclusion This report suggests that SARS-CoV-2 virus can be isolated in the biological samples even after a long post-mortem prolongation of molecular analyses. We emphasize the necessity of wider studies that will define the infectiveness and biological stability of the virus in postmortem tissues.

Keywords: forensic medicine; forensic pathology; COVID-19; virus detection; biological samples

INTRODUCTION

To date, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused more than 304 million cases worldwide, with more than 5.4 million deaths [1].

It is well known that, in living people, respiratory viruses like SARS-CoV-2 are highly contagious, and are mainly transmitted by respiratory droplets exchanged during immediate interpersonal physical contacts. Also, it has been shown that it persists on inanimate surfaces up to nine days, which suggests its possible postmortem transmission and detectability in different biological samples. Therefore, it is clear that the biological samples should be handled with care [2–5]. The United States Centers for Disease Control and Prevention (CDC) published official guidelines for collection of postmortem specimens of confirmed or suspected COVID-19 cases [6].

Without comprehensive postmortem investigation, it is impossible to determine the exact cause of death among the SARS-CoV-2-suspected and -positive patients, which, again, highlights the role of postmortem human COVID-19-associated deaths investigations.

In order to discuss the postmortem detectability of SARS-CoV-2 virus and its RNA stability in different biological samples, we present two case reports. One case shows that SARS-CoV-2 virus can be retrospectively detected in the biological samples of the lower respiratory tract during a relatively long postmortem period, and the other that the virus RNA is lost over time, with the prolongation of the postmortem period.

CASE REPORTS

Case 1 presentation

On April 9, 2020, a 40-year-old man was found dead in front of his house. The external exam showed no evidence of mechanical and other injuries that would suggest a violent manner of death.

The deceased had no chronic conditions, but had a history of heroin abuse. Heteroanamnestic data indicated that he was not feeling well during the previous several days. He complained of weakness and shortness of breath, which is why he went to the emergency medical center and was prescribed symptomatic therapy. According to his step-sister, he was constantly in contact with his neighbors, who were SARS-CoV-2-positive.

The autopsy was performed four days after death, according to the standard procedure. Gross autopsy findings revealed heavy, grossly firm, and rubbery, shiny "ground glass"-like lungs, with severe bilateral edema. On the cut section, the lungs were dark red without

Received • Примљено: January 18, 2022
Revised • Ревизија: June 23, 2022
Accepted • Прихваћено: January 22, 2023
Online first: February 1, 2023

Correspondence to:
Bojana RADNIĆ
Deligradska 31a
11000 Belgrade, Serbia
bojana.radnic@med.bg.ac.rs

purulent discharge, with a large number of blood clots in small-caliber blood vessels around the described pulmonary changes. The hilar lymph nodes were slightly enlarged. The liver was also slightly enlarged, while the findings in other organs were unremarkable.

Toxicological analyses indicated the presence of opioid analgesic codeine, along with its metabolites and analgesic metamizole metabolite, 4-acetilaminoantipirine in therapeutic concentrations, which were interpreted as metabolic products of analgoantipyretic drugs.

Initially, the death was attributed to pneumonia of unknown origin, but after additional diagnostic procedures conducted two months later, it was proven that death was caused by COVID- 19.

Histopathological analysis

Histopathological analysis (HP) of the lungs revealed prominent intraalveolar protein- rich edema, capillary congestion, and formation of hyaline membranes. Alveolar lumen was filled with a moderate number of multinuclear giant cells presenting with a viral cytopathogenic effect. A number of embolized thrombi were present in middle-caliber pulmonary artery branches. The HP finding corresponded to the viral etiology interstitial pneumonia. HP findings of other organs were unremarkable.

Molecular testing

Nasopharyngeal swab and lower respiratory tract specimens (trachea and both lungs), as well as the femoral vein blood, were collected during the autopsy. Before the postmortem examination, the body was kept in the refrigerator at 4°C. After the RNA isolation from the swabs, using QIAamp Viral RNA mini Kit (QIAGEN N.V., Venlo, The Netherlands) on manufacturer's instructions, the presence of RNA sequence specific for OFR1ab gene of SARS- CoV-2 was tested using Real-Time Fluorescent RT-PCR Kit for Detecting SARS-CoV-2 (BGI Genomics, Shenzhen, Guangdong, China). This kit also employs human housekeeping gene β-actin as the internal control. Reverse transcription, amplification and detection was performed in ViiA7 (Applied Biosystems, Waltham, MA, USA), using the cycling profile recommended by the manufacturer. Signals specific for the internal control were the only targets detected in all the samples. Lateral flow immunochromatographic test for IgM and IgG SARS-CoV-2-specific antibodies (Wuhan UNscience Biotechnology Co. Ltd., Wuhan, Hubei, China) showed positive results for the IgM, but not for the IgG antibodies against novel coronavirus, suggestive for the acute phase of coronavirus infection. Negative results for the viral RNA could be explained by the prolonged period from death to sampling.

Case 2 presentation

A 28-year-old professional basketball player suffered a cardiorespiratory arrest during training, which was followed by an unsuccessful cardiopulmonary resuscitation. Heteroanamnestic data indicated that he suffered from SARS-CoV-2 about one month previously. He had mild symptoms (low fever, periodic dysrhythmias, and fatigue), but was not involved in any training activities during the SARS-CoV-2 infection symptoms, nor during one month afterwards. At the time of his return to training he had no complaints about any health issues.

The autopsy was performed two days after death, according to the standard procedure. While waiting for the autopsy, the body was stored in a "cold room" at 15°C, because it could not be refrigerated due to the excessive body length (over 2 m). External examination showed advanced putrefaction and several recent injection wounds on the left forearm suggesting attempted resuscitation. Gross autopsy findings revealed an enlarged heart (dimensions 17 × 14 cm, weight 570 g), with macroscopically visible fibrotic focuses, while the findings in other organs were unremarkable.

Specimens for toxicological and histopathological analyses were taken. Samples for toxicological analysis included heart blood (peripheral blood was not available because of the advanced putrefaction), as well as kidney and liver samples, which were negative for the presence of therapeutic or any other drugs of abuse.

Histopathological analysis

Although HP analysis showed advanced putrefactive changes, basic anatomical structure was still recognizable. There was a prominent intraalveolar edema and heavy capillary congestion of lungs. The alveolar lumen in better conserved tissues was filled with a moderate number of macrophages. In the heart, large fields of perivascular and interstitial fibrosis were visible and could be attributed to old myocarditis changes and advanced atherosclerotic changes in the intramyocardial blood vessels. The HP finding corresponded to the sudden cardiovascular death due to the cardiac dysrhythmia most probably formed in one of the fibrotic focuses.

Molecular testing

Nasopharingeal swab and heart blood samples were collected immediately after the admission of the body to the Institute of Forensic Medicine. Collected biological samples were analyzed using SARS-CoV-2 One-Step RT-PCR Kit (NZYTech, Lisbon, Portugal), targeting viral RNA-dependent RNA polymerase of the virus and human RNAse P gene (internal control) in WiiA7 (Applied Biosystems), as well as with serological testing for COVID-19-specific IgM/IgG antibodies. Both tests performed were positive for SARS-CoV-2 RNA and antibodies (both IgM and IgG) in the analyzed biological samples. The high Ct value from the RT-PCR test suggested low viral load in the samples. Three days later, during which time the body was kept in a room at 15°C, the same biological samples were taken during the autopsy and analyzed immediately, but were negative for SARS-CoV-2 RNA possibly due to the postmortem degradation of the samples. The lateral flow tests for antibodies were unreadable, due to the extensive hemolysis of the blood samples.

DISCUSSION

One of the crucial roles of forensic medicine and pathology during any epidemic is to perform autopsies along with all additional analyses in order to provide new insights of the pathogens' transmission and their clinical features. In contrast, in the course of this pandemic, medical public and scientists are under the impression that there is a certain degree of modesty in the performing of autopsies. This fact can potentially be explained by the very demanding safety requirements for autopsy rooms and by tight criteria recommendations for clinical autopsy requests. Despite numerous scientific publications, there is no reliable data concerning virus pathogenicity, postmortem transmission, and its viability in cadavers.

Given the fact that virus detection is more probable in cases where the viral load is higher, nowadays nasopharyngeal swab represents the golden standard sample for SARS-CoV-2 virus detection not only in live persons, but also as a part of postmortem isolation. Following the above-mentioned principles, a positive SARS-CoV-2 nasopharyngeal swab taken during early postmortem period, according to the CDC recommendations, would mean that the person was infected and, if other clinical data suggest so, died from COVID-19 disease or its complications. On the other hand, there is not enough scientific evidence that would prove that negative nasopharyngeal swab for SARS-CoV-2 virus taken during early postmortem period will definitely exclude COVID-19 as a cause of death [7].

The first case presented in this report highlights the fact that the persistence of SARS-CoV-2 RNA in the lower respiratory tract swabs can be detected as late as two months after death regardless of the fact that the swabs were not stored according to the CDC recommendations in cases of a delayed testing (at -70°C or below). Contrary to the first, in the second presented case report, after initial SARS-CoV-2 virus isolation, only two days later, when the autopsy was performed, the virus was not detectable in the same biological samples any more, even though all samples were taken and stored according to the CDC recommendations. Thus, previously mentioned facts raise a number of questions concerning postmortem SARS-CoV-2 virus viability, especially in the light of post-mortem period prolongation, and its detectability not only in different biological samples. According to CDC information concerning novel SARS-CoV-2, there is a lack of data on the frequency of detection of SARS-CoV-2 by RT-PCR on postmortem swabs collected in different intervals after death. Generally, it is said that, based on the knowledge from previous MERS-CoV and SARS-CoV epidemics, if SARS-CoV-2 testing on postmortem swab samples is considered a suspected COVID-19 case, SARS-CoV-2 RNA in the majority of cases may still be detected up to three days postmortem. Also, some scientists have shown that the sensitivity of postmortem tests may be reduced with a longer postmortem interval or embalming [8]. On the other hand, a group of German scientists showed that SARS-CoV-2 RNA may be detectable even in decomposed corpses [9].

An Italian autopsy study did not find a correlation between the results of the swabs and either the time elapsed from their collection or the time elapsed before their acceptance in the microbiology laboratory for virus isolation [8]. Therefore, it can only be concluded that the available scientific results are limited and, at the very least, unconvincing, suggesting the necessity of more thorough studies concerning this issue.

We want to highlight the fact that there are many factors that can affect the postmortem virus survival time. Besides the previously mentioned, according to some studies, refrigeration of the corpse may also prolong survival time of the coronavirus [10]. A lack of adequate antiviral therapy during the immediate pre-mortem period may play some role in the lasting persistence of SARS-CoV-2 RNA. In the first case report, the deceased did not receive specific antiviral therapy since there were no certain clinical data confirming SARS-CoV-2 infection. Also, collection of swabs from the lower respiratory tract provides a higher probability of viral RNA detection than swabs from the nasopharynx [11]. However, special attention should be paid to the interpretation of PCR testing in postmortem specimens. Positive nasopharyngeal swabs or lower airway specimens do not always mean that the deceased had the infection, because the viral RNA may persist in clinical samples without the virus being viable [12].

Our case reports suggest that post-mortem SARS-CoV-2 virus can be isolated in the biological samples even after a considerable post-mortem delay of the molecular analyses. Regardless of the facts stated in these case reports, the authors want to highlight the necessity of wider studies in order to define the infectiveness and biological stability of the virus in postmortem tissues. It is necessary to form firm arguments, supported by strong pathohistological and molecular evidence that would be the foundation for future clinical and postmortem clinical studies. This information will also ensure reducing the risks of infection for medical staff involved in autopsy procedures by increasing their knowledge and awareness of the postmortem infective status of the body.

ACKNOWLEDGEMENT

We thank Professor Oliver Stojković (University of Belgrade, Faculty of Medicine, Institute of Human Genetics) who contributed to the preparation of this paper with his expert knowledge, particularly in the molecular analyses of biological specimens concerning SARS-CoV-2.

This work was supported by the Science Fund of the Republic of Serbia – FORACOVID project, No. 7546679

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest: None declared.

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Постмортална детектабилност и вијабилност вируса *SARS-CoV-2* у различитим биолошким узорцима

Тијана Петровић[1], Миленко Богдановић[1], Татјана Атанасијевић[1], Весна Поповић[1], Милена Јовановић[2], Ирина Бањанин[1], Бојана Раднић[1]

[1]Универзитет у Београду, Медицински факултет, Институт за судску медицину „Милован Миловановић", Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Институт за патологију, Београд, Србија

САЖЕТАК

Увод Без свеобухватних постморталних истраживања није могуће утврдити узрок смрти код преминулих особа за које се сумњало да су позитивни и код оних који су били позитивни на *SARS-CoV*-2. У циљу разматрања о могућностима постморталне детекције вируса *SARS-CoV*-2 и стабилности његове РНК, приказана су два случаја.

Приказ случајева Први случај представља четрдесетогодишњи мушкарац чије је тело обдуковано четири дана после смрти. Тело је чувано на температури од 4° *C*. Макроскопским и микроскопским прегледом уочено је обострано запаљење плућа. Молекуларне анализе показале су присуство *IgM* антитела, али је *PCR* тест на РНК *SARS-CoV*-2 био негативан. Други случај представља двадесетосмогодишњи професионални кошаркаш који је боловао од инфекције вирусом корона око месец дана пре смрти. Обдукција је извршена два дана касније. Тело је чувано на температури од 15°*C*. Макроскопски налаз је показао узнапредовале трулежне промене и увећање срца са видљивим фокусима фиброзе. Хистопатолошки налаз је одговарао напрасној срчаној смрти због поремећаја срчаног ритма генерисаног највероватније на месту неког од фокуса фиброзе. Тестирањем на РНК *SARS-CoV-2* и антитела (*IgM*, *IgG*) добијени су позитивни резултати.

Закључак Овај рад указује на то да вирус може бити изолован молекуларним методама у биолошким узорцима чак и после веома продуженог постморталног интервала. Истиче се неопходност спровођења обимнијих студија које би дефинисале период инфективности и биолошке стабилности вируса у постморталним ткивима.

Кључне речи: судска медицина; патологија; ковид 19; детекција вируса; биолошки узорци

DOI: https://doi.org/10.2298/SARH230105026I
UDC: 615.46:616.314-7

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Challenges in irradiated bone implantation

Filip Ivanjac, Vitomir Konstantinović
University of Belgrade, School of Dental Medicine, Belgrade Serbia

SUMMARY
Introduction Implantation in irradiated bone is very challenging due to many factors: implant therapy parameters, irradiated tissue, and the patient's general health. Implantologists have to consider all of these aspects when planning implant therapy and during the postsurgical recovery period.
Case outline A case presented in this paper is a 54-year-old male, who was admitted to the Clinic for Maxillofacial Surgery, School of Dental Medicine in Belgrade, Serbia, for implant-anchored orbital prosthesis. One year previously, the patient had orbital exenteration and postoperatively received radiotherapy with an overall dose of 60 Gy. After planning, three disk implants – two double and one triple disk were placed (Ihde Dental, Switzerland). Implant stability was clinically satisfactory, with the immediate implant stability quotient score of 37, 46, and 51, respectively. After osseointegration implant retained prosthesis was manufactured. After six years due to osteoradionecrosis (ORN), implant stability was compromised. The patient received conservative and hyperbaric oxygen therapy. The implants regained stability, and the patient was in remission for four years. Afterwards, due to ORN, two implants were explanted, and the third implant was stable enough to anchor the prosthesis. The prosthetic plan had to be modified for one implant anchorage; afterwards, successful prosthetic rehabilitation was achieved.
Conclusion Implantation in irradiated bone is very delicate, and careful planning of implant insertion and prosthetic rehabilitation is essential. A possible occurrence of osteoradionecrosis should also be taken into account, as a result of which the implant may be lost, which compromises the retention of the prosthesis.
Keywords: extraoral implant therapy; osteoradionecrosis (ORN); bone implantation

INTRODUCTION

Therapy of malignant tumours includes radical surgical resection, with adjunctive specific oncologic therapy such as irradiation and polychemotherapy. After tumour resection, irradiation therapy is applied to reduce the probability of relapse [1, 2, 3]. A bone that has been irradiated does not have the same qualitative characteristics as an intact bone. The negative effect of X-rays on bone tissue, skin and mucosa leads to tissue hypoxia and a decrease in the number of cellular elements [3, 4, 5]. In soft tissues, they cause wounds that are difficult to heal and compromise circulation. The success of implant therapy in such tissue depends on several factors: the quality of the bone, the blood supply to the bone tissue, as well as the number and preservation of the cellular elements of the bone [1, 2, 3]. The proliferation of bone marrow, collagen, periosteal and endosteal cells is reduced in irradiated bones. All this makes osseointegration difficult. Hyperbaric oxygen therapy (HBOT) helps significantly with osseointegration in irradiated tissue. Some authors advise implantation in an irradiated area 4–6 months after the completion of radiation therapy, although many studies show good results even after immediate implantation. Sometimes, due to the high dose and frequency of radiation, osteoradionecrosis occurs [5, 6, 7]. The bones around the orbital cavity are the most prone to radiation damage. The effect of radiation dose is expressed as the "cumulative radiation effect" (CRE). A statistically significant dose of radiation for implant failure is 50 Gy and more [8, 9].

CASE REPORT

A 54-year-old male was referred to the Clinic for Maxillofacial Surgery, School of Dental Medicine in Belgrade, Serbia, for prosthetic rehabilitation after orbital exenteration. Previously, he was operated on for recurrent squamous cell carcinoma of the left eyelid with orbital propagation. After surgery, he received radiotherapy in 30 sessions for six weeks, five times a week, with an overall dose of 60 Gy. One year after irradiation, the patient was admitted for implant therapy and prosthetic rehabilitation.

After preoperative computed tomography evaluation and planning, implantation was performed in general endotracheal anaesthesia in April 2012. Three disk implants (Dr. Ihde Dental AG, Gommiswald, Switzerland) were placed (two double disk implants, and one triple disk implant) in the standard implantation protocol for disk implants. After bone exposure, implant site preparation was done with minimal trauma using specific drills (vertical cutter and lateral cutter) using a high-speed contra-angle (1:1, up to 40,000 rpm), with constant and vigorous cooling by cold saline solution (4°C). The implants were then hammered into the prepared cortical implant bed (Figures

Received • Примљено: January 5, 2023
Accepted • Прихваћено: March 1, 2023
Online first: March 4, 2023

Correspondence to:
Filip IVANJAC
Svetogorska 18
Beograd 11000
filipivanjac@yahoo.com

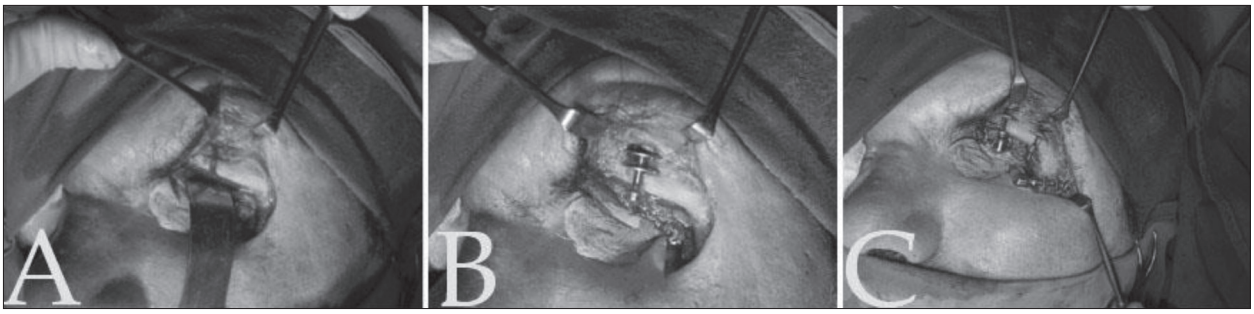

Figure 1. A: bone prepared for implant placement; B: double-disk implant placement; C: all implants placed in implant seats

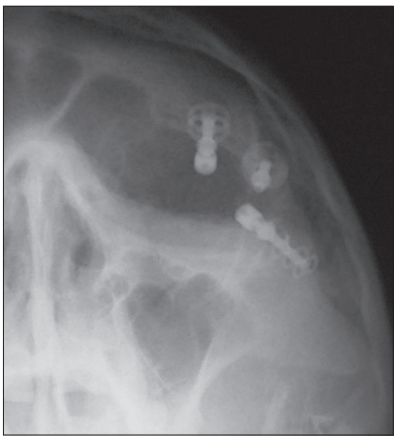

Figure 2. Waters projection radiography with placed implants

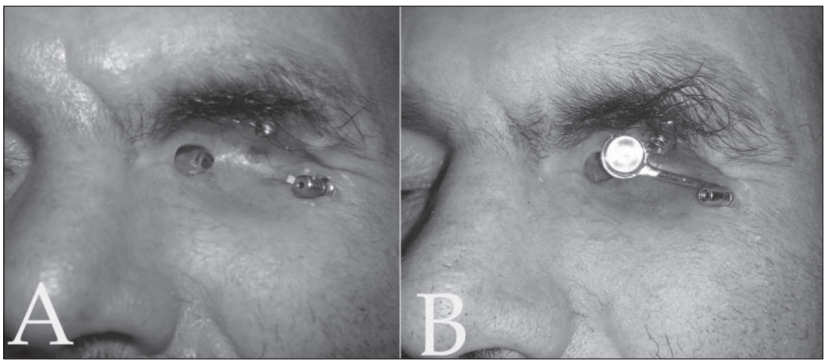

Figure 3. A: implants prepared for metal substructure placement; B: metal substructure placed for prosthesis retention

1a, 1b, and 1c). Double disk implants were inserted supraorbital in the lateral aspect of the frontal bone and triple disk in the body of the zygomatic bone. Immediately after placement, implant stability was measured using Ostell Mentor AB, (Integration Diagnostics Ltd., Gothenburg, Sweden). Implant stability quotient (ISQ) of 37 and 46 (for double disks) and 51 (for triple disk) was found. Implants were then covered under the skin for healing.

Prophylactic antibiotic therapy with amoxicillin with clavulanic acid (Amoxiclav, Sandoz, Basel, Switzerland) was prescribed – 1 g every 12 hours.

After completing osseointegration, six months later, control radiography – Waters projection – showed good implant osseointegration (Figure 2). Implants were exposed and cutaneous formers were placed onto them, to prepare for impression taking. The middle, double disk implant, was left submerged as backup retention for prosthesis anchorage.

Before the process of orbital prosthesis production, ISQ measuring for the two exposed implants was performed. Double disk showed 39 and triple disk 55. After impression taking, planning and modelling the substructure on the master model was done. The acrylic base plays the role in both magnet and silicon prosthesis holders' platform. A magnet for retention – Co-Sm magnet (Technovent, Bridgend, UK) was attached to the acrylic base by self-curing acrylic resin. The other part of the magnet was bonded to the housing at the metal substructure by composite glue. After the wax sculpting, the orbital prosthesis was converted to additional silicone with a previously selected colour. Implant-anchored metal substructure for prosthesis retention was set on the patient (Figures 3a and 3b).

Prosthesis served very well for six years with no complaints from the patient. However, in 2018, due to subsequent osteoradionecrosis, the implants were compromised. The values of ISQ for the double disk were 30 and for the triple disk it was almost the same – 53, because the implant was not in an area affected by osteoradionecrosis.

The patient was treated with local conservative treatment comprised of curettage and debris removal, as well as with 3% oxygen and betadine rinse. Afterwards, the patient underwent HBOT – 20 sessions, 70 minutes per session. Through the mask, 100% oxygen was administrated with a pressure of 2.2 atmosphere absolute. After the applied therapy, the clinical signs of osteoradionecrosis resolved and the patient used the prosthesis normally. ISQ measurements were 36 and 55, respectively (Figure 4).

Four years later (June 2022), due to osteoradionecrosis exacerbation (Figure 5), both double-disc implants had to be removed, because they were clinically unstable due to bone damage. Nevertheless, the triple-disc implant was still stable (ISQ 55), given that the zygomatic bone in which it was anchored was not affected by osteoradionecrosis. The triple-disk implant was stable enough to take over the prosthesis anchorage. In addition, the prosthesis substructure had to be readjusted due to the smaller number of retaining implants. The acrylic part of the prosthesis was somewhat reduced, which made the prosthesis lighter. Afterwards, the triple-disk implant showed good clinical stability for the orbital prosthesis retention (Figure 6).

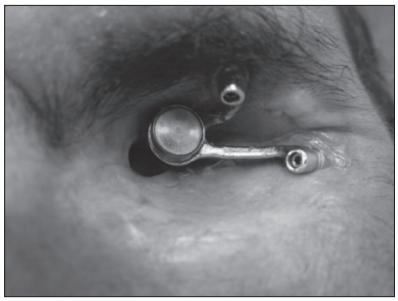

Figure 4. Patient in remission after hyperbaric and conservative therapy

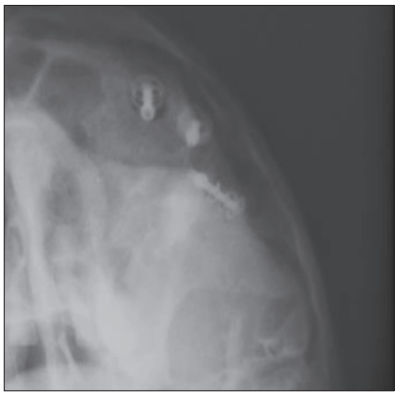

Figure 5. Waters projection radiography showing osteoradionecrosis bone damage around implant

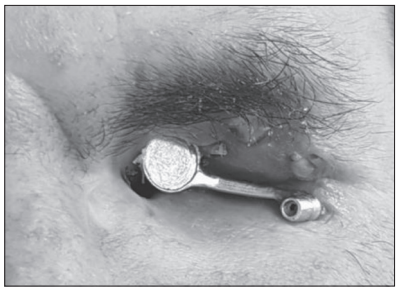

Figure 6. Prothesis substructure remodeled for one implant retention

The report has been reviewed and approved by the Ethics Committee of the School of Dental Medicine, University of Belgrade (No. 36/14).

DISCUSSION

Even for experienced surgeons it is challenging when they are faced with implantation in irradiated bone. Careful planning and implant therapy parameters (bone amount, implant type, implantation technique, and protocol) have to be taken into consideration. Also, irradiated bone issues are of great importance; some bones are more prone to osteoradionecrosis than others; if the amount of radiation dose is over 50 Gy, the risk of osteoradionecrosis (ORN) is much higher; frequency and duration of radiation therapy also play an important role in the risk of ORN [1, 2, 3].

Correspondingly, the success of implant therapy in irradiated tissue depends on the quality of the bone. The highly mineralized bone, like zygoma, is typically very resistant to infection and stable to resorption. This is why disk implants placed in compact bone are, in our opinion, the method of choice [1, 9]. Nevertheless, the blood supply to the bone tissue is one of the essential factors, as well as the number and preservation of the cellular elements of the bone. Proliferation of bone marrow, collagen, periosteal and endosteal cells is reduced in an irradiated bone. Due to these factors, bone after radiation therapy is specifically prone to osteoradionecrosis. General health factors like age or chronic illness (diabetes), risk of relapse, and nicotine consumption, are also contributing factors to the failure of implant therapy in irradiated bone [5–9].

The difference is that double-disk implants (the two explanted) generally have slightly smaller ISQ values than triple-disks implants because of a reduced number of retaining disks. Furthermore, two double-disk implants were placed in the orbital part of the frontal bone and the triple-disk one was in the body of the zygomatic bone, which made all the difference. In the orbital part of the frontal and zygomatic bone, our previous studies showed a high cortical thickness of 1.9 mm and 2.7 mm, respectively. The zygomatic bone has thicker compact bone compared to the frontal bone, it is less porous (5.7% compared to 6.7%), which gives better support for integrated implants [1, 2, 3]. Also, we assume that the zygomatic bone was not affected as much as the orbital part of the frontal bone during radiotherapy because it was not in the main focus of irradiation, hence it was not as susceptible to ORN.

Conservative treatment in combination with antibiotic therapy is helpful. HBOT involves breathing pure oxygen in a pressurized dive chamber [10–13]. This specialized chamber promotes healing by allowing more oxygen to dissolve in the blood, which results in more oxygen being delivered to tissues. HBOT is often used as the first line of treatment for ORN, but there is an ongoing debate on its effectiveness. The treatment usually consists of daily "dives" for a total of 20–40 dive sessions over several weeks [12, 13, 14].

Some implantologists insert an extra (submerged) implant as a precaution as a reserve for possible use when implant failure is expected. In the presented case, we were not able to use a submerged implant because it was also affected by osteoradionecrosis. However, the fact that the triple-disk survived allowed the patient to continue using the orbital prosthesis. In our opinion, the zygomatic bone is the ideal place for extraoral implants because of its somewhat higher compact bone thickness and lower porosity compared to the orbital part of the frontal bone, as those are the main two areas for disk implant placement.

From the prosthetic point of view in such cases, the prosthesis has to be lighter, which was accomplished by a maximum possible reduction in volume to relieve the remaining implant, but still preserve the function. Some authors resort to making hollow lightweight prostheses to decrease the load of the implants [14, 15].

To conclude this case presentation, implantation in irradiated bone is very delicate, and careful planning of implant insertion and prosthetic rehabilitation is essential. Possible occurrence of osteoradionecrosis should also be taken into account, as a result of which the implant may be lost, which compromises the retention of the prosthesis.

Conflict of interest: None declared.

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Изазови у имплантацији зрачене кости

Филип Ивањац, Витомир Константиновић

Универзитет у Београду, Стоматолошки факултет, Београд, Србија

САЖЕТАК

Увод Имплантација у зраченој кости је велики изазов због многих фактора: параметара имплантолошке терапије, зраченог ткива и општег здравственог стања пацијента. Имплантолози морају да узму у обзир све ове аспекте приликом планирања имплантолошке терапије и током постхируршког периода опоравка.

Приказ болесника У овом раду приказан је мушкарац стар 54 године, који је примљен на Клинику за максилофацијалну хирургију Стоматолошког факултета у Београду у Србији ради постављања имплантатима ретиниране орбиталне протетске надокнаде. Годину дана раније је имао егзентерацију орбите и примао је радиотерапију са укупном дозом од 60 *Gy*. После пријема на Клинику и планирања терапије постављена су три диск-имплантата (*Ihde Dental Switzerland*) (два дупла, један троструки). Опоравак пацијента био је задовољавајући, са клинички стабилним имплантатима (имедијатно *ISQ* 37, 46, 51). После осеоинтеграције направљена је протеза ретинирана имплантатима. Након шест година стабилност имплантата је била угрожена због остеорадионекрозе. Пацијент је добио конзервативни и хипербарични третман. Имплантати су повратили стабилност, пацијент је био у ремисији четири године. После тог периода, два имплантата су експлантирана због остеорадионекрозе, а трећи имплантат је био довољно стабилан да ретинира протезу. Протетски рад је морао бити модификован за сидрење помоћу једног имплантата, после чега је постигнута успешна протетска рехабилитација.

Закључак Имплантација у озраченој кости је веома деликатна, па је неопходно пажљиво планирање уградње имплантата и протетске рехабилитације. Треба узети у обзир и могућу појаву остеорадионекрозе, услед чега може доћи до губитка имплантата, што нарушава ретенцију протезе.

Кључне речи: екстраорална имплантолошка терапија; остеорадионекроза; имплантација у кости

DOI: https://doi.org/10.2298/SARH221120021V
UDC: 616.12-008.331.1-079.4; 616.12-008.315

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Right-sided heart failure as a first presentation of portopulmonary hypertension

Aleksandra Vulin[1,2], Iva Popov[2], Maja Stefanović[1,2], Dragoslava Živkov-Šaponja[3,2], Anastazija Stojšić-Milosavljević[1,2]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Institute of Cardiovascular Diseases of Vojvodina, Clinic of Cardiology, Sremska Kamenica, Serbia;
[3]University Business Academy in Novi Sad, Faculty of Pharmacy Novi Sad, Serbia

SUMMARY

Introduction Pulmonary artery hypertension and right ventricular failure are potentially fatal complications that can develop in patients with portal hypertension. The objective of this case report was to report a patient with end-stage liver disease, and portal and pulmonary artery hypertension and right heart failure.

Case outline A 57-year-old man was admitted to the Cardiology Department of a tertiary referral hospital due to signs of right-sided heart failure, ascites, pleural effusions, and pretibial edema. The patient had the history of alcohol abuse, arterial hypertension, and gout. Just prior to the admission, abdominal ultrasound revealed granular liver structure, as well as ascites. Laboratory tests showed microcytic anemia, values of transaminases below referent, hypoalbuminemia, low creatinine clearance. Echocardiography revealed pulmonary hypertension, and right ventricle failure. Right heart catheterization unraveled precapillary pulmonary hypertension, but thoracic CT scan and thoracocentesis excluded underlying pulmonary illness. Treatment continued at the Gastroenterology Department of the tertiary hospital. Abdominal CT scan diagnosed cirrhotic liver, and signs of portal hypertension. The patient was treated with symptomatic therapy, but developed acute-on-chronic renal failure and eventually died.

Conclusion Multidisciplinary approach is very important to distinguish portopulmonary hypertension early in the course of liver disease, because evolution of right sided heart failure precludes these patients from adequate lifesaving therapy.

Keywords: pulmonary arterial hypertension; right-sided heart failure; liver cirrhosis

INTRODUCTION

Right-sided heart failure (RHF) clinical syndrome is associated with increased morbidity and mortality in a variety of diseases [1]. Heart failure and liver disease often coexist, because of bidirectional cardiohepatic interactions, concomitant risk factors, or diseases affecting both organs [2]. RHF in patients with liver disease can be a consequence of cirrhotic cardiomyopathy, pulmonary vascular complications, concomitant left ventricular failure, and chronic renal failure [2, 3, 4]. Patients with portal hypertension can develop increased pulmonary vascular resistance (PVR) and pulmonary artery hypertension (PAH) condition called portopulmonary hypertension (PoPH) [3–9]. PoPH is frequently underrecognized condition for a long time, with marked diagnostics and treatment variability [3, 4, 5, 8–12]. As PVR rises, right ventricle strain is raising, function declines with ultimate signs of RHF [1, 13]. Patients with advanced stage of PoPH usually have poor prognosis, frequent hospitalizations, and high mortality from progressive RHF, acute renal failure, but the majority die of complications due to underlying decompensated liver failure [4, 11, 14].

The objective of this case report was to report a patient with end-stage liver disease, portal and pulmonary artery hypertension, and RHF.

CASE REPORT

A 57-year-old man was hospitalized for the first time at the Cardiology Department of a tertiary hospital, due to clinical signs resembling biventricular heart failure and NT-proBNP above 25,000 pg/mL, referred from a pulmonologist. The patient presented with symptoms of dyspnea on minimal effort, swellings of the abdomen, scrotum, and legs, which had been deteriorating for the previous four weeks, weight loss of 10 kg, and several black stools seven days prior to admission. The patient had a history of untreated gout and arterial hypertension for the previous seven years, without medical documentation. The patient did not smoke, but consumed alcohol almost daily over the previous 10 years. Just before admission, the patient was examined by a gastroenterologist. Abdominal ultrasound showed vast amount of ascites, enlarged spleen (156 mm), small echogenic kidneys and bilateral pleural effusion; an elective gastroscopy was indicated. The patient was referred to a pulmonologist, where chest radiography and diagnostic thoracentesis with

Received • Примљено: November 20, 2022
Revised • Ревизија: February 16, 2023
Accepted • Прихваћено: February 25, 2023
Online first: March 3, 2023

Correspondence to:
Aleksandra VULIN
Pavleka Miškine 9
21000 Novi Sad, Serbia
aleksandra.vulin@mf.uns.ac.rs

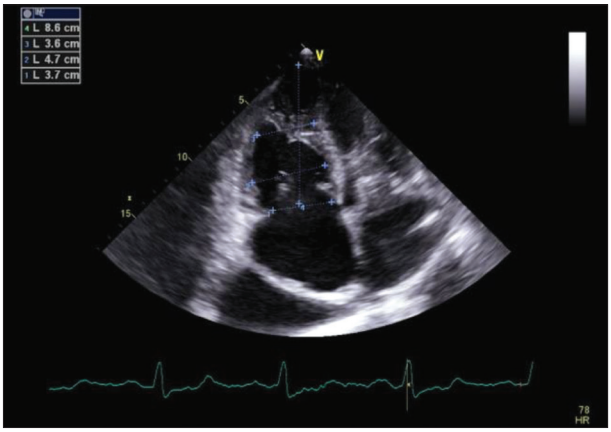

Figure 1. Dilated right atrium, the tricuspid annulus, and the right ventricle

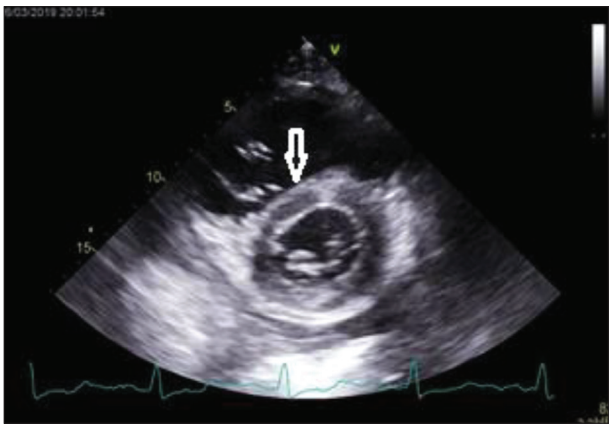

Figure 2. Flattening of the interventricular septum in systole

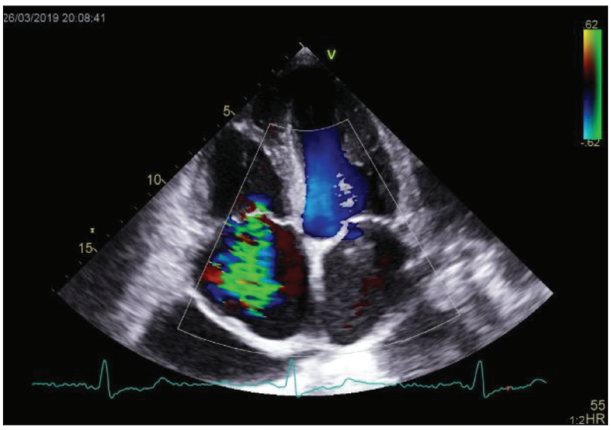

Figure 3. Severe tricuspid insufficiency

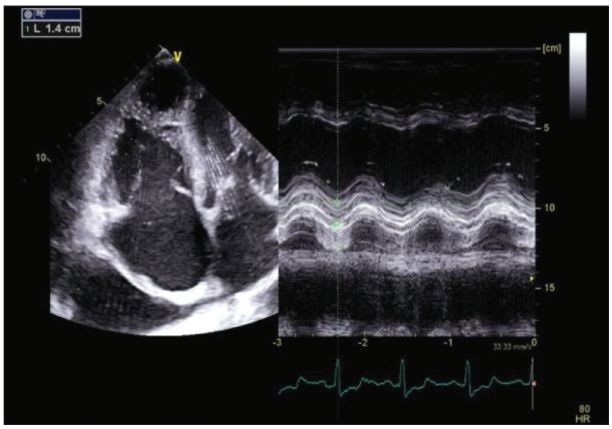

Figure 4. Low tricuspid annular plane systolic excursion (1.4 cm)

evacuation of 1000 ml of transudate was done, and the patient was referred to a cardiologist.

Physical examination on admission revealed that patient was afebrile, oxygen saturation was 93%, the skin was pale, sclera were of normal staining, hypertensive (220/120 mmHg), tachycardic (110 beats/minute), with bilateral jugular venous distention, accentuated pulmonic component of the second heart sound, tricuspid regurgitant holosystolic murmur, the right lung percussion dullness and absent breath sounds, as well as signs of ascites and pitting leg edema.

Baseline laboratory tests showed severe microcytic anemia (Hgb 73 g/l, MCV 67.9 fL), normal thrombocyte count, decreased level of liver transaminases (AST 7 U/L, ALT 13 U/L), normal bilirubin, mild direct hyperbilirubinemia (8 μmol/L), elevated gamma-glutamyl transferase (78 U/L), hypoalbuminemia (26g/L), INR value above referent (1.7), low creatinine clearance (32 mL/minute), hyperuricemia (652 μmol/L), as well as low levels of FT3 (3.73 pmol/L), normal levels of FT4 (15.04 pmol/L) and high levels of TSH (10.43 pmol/L). Serological tests for hepatitis B, hepatitis C and HIV were negative.

Transthoracic echocardiogram (TTE) revealed dilated right atrium (RAVs/BSA 43.68 mL/m^2), tricuspid annulus (3.7 cm), and right ventricle (RV1 4.7 cm, RV2 2.6 cm, RV3 8.6 cm) (Figure 1), with flattening of the interventricular septum (Figure 2), severe tricuspid regurgitation (Figure 3), high right ventricular systolic pressure (87 mmHg), peak tricuspid regurgitation velocity (4.1 m/s), low tricuspid annular plane systolic excursion (1.4 cm), and tricuspid annulus systolic velocity (0.08 m/s) (Figure 4), no mitral regurgitation, mild pulmonic regurgitation, pulmonary artery diameter (2.4 cm), and high inferior vena cava diameter (2.3 cm), without inspiratory collapsibility. Left ventricle (LV) volumes were normal, with signs of concentric hypertrophy (diameters of interventricular septum of 1.5 cm, and of posterior wall of 1.5 cm), preserved LV ejection fraction (56%). The left atrium was dilated (LAVs/BSA 38.42 mL/m^2). The ratio of peak early diastolic velocity (E) to peak velocity flow in late diastole (A) – E/A – was 1.21, tissue Doppler imaging showed low septal early diastolic velocity (es') of 0.06m/s, low lateral early diastolic velocity (el') of 0.09m/s, with normal LV feeling pressure (E/e'av = 9.3), diastolic dysfunction grade II, and minimal pericardial effusion.

The pulmonologist excluded active pulmonary disease based on the normal pulmonary parenchyma on the thorax computed tomography (CT) scan and bilateral transudative pleural effusions.

The patient was treated with red blood cells transfusion, albumin supplementation, parenteral diuretic therapy, therapeutic thoracentesis, antihypertensive therapy, and

thyroid hormone supplementation, but without improvement.

On the third day of hospitalization, right heart catheterization was performed. The values indicated severe precapillary pulmonary arterial hypertension: mean pulmonary artery pressure of 53 mmHg; PVR of 8.1 WU (703 Dynes/cm^5); pulmonary capillary wedge pressure of 15 mmHg, central venous pressure of 19 mmHg, cardiac output of 4.3 L/min, and cardiac index of 2.2 L/mL/m^2.

Given the history of untreated alcoholism in our patient, clinical signs of right heart failure, laboratory tests, TTE, abdominal ultrasound, and right heart catheterization, the diagnosis of decompensated liver cirrhosis and PoPH was suspected.

On the fourth day, the treatment was continued at the Gastroenterology Department of the tertiary hospital. Abdominal CT scan was done, revealing liver surface nodularity, portosystemic collaterals, splenomegaly, and ascites, thus confirming the diagnosis of portal hypertension and subsequent PoPH. The treatment was symptomatic, consisted of parenteral diuretics, albumins, red blood cells transfusions, several thoracenteses, and paracentesis. The patient developed acute-on-chronic renal failure, two continuous veno–venous hemofiltrations were performed, but the patient's hemodynamic status subsequently deteriorated, and he died after 35 days.

The study was approved by the Ethics Committee of the Institute for Cardiovascular Diseases of Vojvodina, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

We reported on a patient with alcohol-associated decompensated end-stage liver disease and PAH who presented with right heart failure. Almost 90% of patients with cirrhosis eventually develop portal hypertension, and this condition is crucial for the majority of complications, such as PAH [4, 10, 11, 12, 15]. PoPH is most commonly observed in the setting of cirrhosis, which is alcohol-associated in almost half of the patients, as was the case in our patient [14].

Pathophysiology of PAH in the setting of portal hypertension is not clearly elucidated yet [4]. A proposed mechanism of pulmonary arterial changes are inflammation, endothelial dysfunction, smooth muscle proliferation and *in situ* thrombosis due to hyperkinetic circulation, endotoxemia, low liver clearance, and porto-systemic shunting of vasoactive peptides [4].

PoPH is usually asymptomatic for years [11]. As the disease progress and PVR rises, patients could have nonspecific clinical findings that could be mixed with signs of liver cirrhosis and include exertional or dyspnea at rest, palpitations, syncope, followed by signs of pulmonary and portal hypertension and eventually signs of RHF [11]. In our patient, signs of RHF and portal hypertension were the first noted clinical signs. In a recent retrospective analysis of patients with PoPH, the mean age at the time of death was 56 ± 8.9 years, half of the patients were males, most of them were in New York Heart Association class III or IV, and had ascites, 25% had combined precapillary and postcapillary PH, as was in our case [14]. PAH directly caused death or contributed to death in 25% of patients with PoPH, mainly from RHF [14]. Compared to patients with portal hypertension, patients with PoPH have more cardiac structural changes, like left and right atrial and ventricular enlargement, mitral and tricuspid regurgitation, pulmonary artery widening, pericardial effusion, and aortic regurgitation than those without PoPH [12, 16]. In our patient, TTE revealed PH, normal values of estimated LV filling pressures, signs of RHF, small pericardial and pleural effusions were registered on admission, which are all associated with increased mortality [13, 17, 18].

Based on the initial echocardiographic finding, and clinical signs of liver cirrhosis, in order to diagnose PAH, right heart catheterization was done [19]. Our patient had high mean pulmonary artery pressure and PVR, but had concomitant chronic renal failure and LV diastolic dysfunction leading to further volume overload. A mild elevation of pulmonary capillary wedge pressure with high level of PVR can be observed in some PoPH patients with combined pulmonary vascular disease and a post-capillary component, due to increased left ventricular stiffness in the setting of high cardiac output and fluid overload [20]. However, transpulmonary gradient greater then 10, especially above 30, is suggestive of the presence of increased pulmonary resistance, and is a predictor of poor prognosis, as was in our patient [21].

Our patient had hypothyroidism that could have been a consequence of liver cirrhosis, especially alcoholic and/or PH, and presents a predictor of severity of liver disease and mortality [1].

Chronic kidney dysfunction is common comorbidity associated with high mortality in patients with PH, and it itself may cause pulmonary vascular remodeling [22]. According to Shao et al. [12], compared to patients with portal hypertension, patients with PoPH have lower hemoglobin and higher creatinine. Our patient had pre-existing renal impairment due to long-term hypertension. Acute worsening of renal function in patients with PH is associated with RHF and mortality [23]. It has been shown that, aside systemic arterial hypoperfusion, venous congestion is a main driver for renal function deterioration in patients with RHF [23]. Our patient developed acute-on-chronic renal failure due to advanced liver disease per se, RHF, elevated intra-abdominal pressure, hypovolemia, resulting from excessive diuretic use and large volume paracentesis and contrast agent given for the CT scan.

Treatment of patients with PoPH is usually late, complex, and requires a multidisciplinary team, as was in our patient [11, 20, 24]. Mortality rate in untreated patients with PoPH is high [25]. In a retrospective analysis conducted by Sahay et al. [14], 33% of patients with PoPH were considered unsuitable for liver transplantation because of uncontrolled PAH, as was in our patient.

Deroo et al. [26] have recently showed that in patients with PoPH, vasomodulatory therapy improves pulmonary

hemodynamics and prolongs survival, but if it is followed by liver transplantation, it could further improve prognosis.

In our case with PoPH, the first clinical presentation was RHF. Early multidisciplinary approach, including transthoracic echocardiography, is very important to distinguish PoPH early in the course of the liver disease, because evolution of RHF precludes these patients from adequate lifesaving therapy.

Conflict of interest: None declared.

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Инсуфицијенција десног срца као прва манифестација портопулмоналне хипертензије

Александра Вулин[1,2], Ива Попов[2], Маја Стефановић[1,2], Драгослава Живков-Шапоња[2,3], Анастазија Стојшић-Милосављевић[1,2]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Институт за кардиоваскуларне болести Војводине, Клиника за кардиологију, Сремска Каменица, Србија;
[3]Универзитет „Привредна академија у Новом Саду", Фармацеутски факултет, Нови Сад, Србија

САЖЕТАК

Увод Плућна артеријска хипертензија и инсуфицијенција десне коморе су потенцијално фаталне компликације које могу настати код болесника са портном хипертензијом. Циљ рада је приказати болесника са завршним стадијумом болести јетре, портном и плућном артеријском хипертензијом и инсуфицијенцијом десног срца.

Приказ болесника Мушкарац, стар 57 година, примљен је на Клинику за кардиологију терцијарне болнице због знакова инсуфицијенције десног срца, асцитеса, плеуралних излива и претибијалних едема. Имао је историју злоупотребе алкохола, артеријске хипертензије и гихта. Непосредно пре пријема ултразвуком абдомена утврђена је зрнаста структура јетре, као и асцитес. Лабораторијски тестови су показали микроцитну анемију, вредности трансаминаза испод референтних, хипоалбуминемију и низак клиренс креатинина. Ехокардиографија је указала на плућну хипертензију и инсуфицијенцију десне коморе. Катетеризација десног срца открила је прекапиларну плућну хипертензију, али компјутеризована томографија грудног коша и торакоцентеза су искључили постојање плућне болести. Лечење је настављено у Клиници за гастроентерологију терцијарне болнице. Компјутеризованом томографијом абдомена дијагностиковани су циротична јетра и знаци портне хипертензије. Болесник је лечен симптоматском терапијом, али је задобио акутизацију хроничне бубрежне инсуфицијенције са смртним исходом.

Закључак Мултидисциплинарни приступ је веома важан за разликовање портопулмоналне хипертензије у раној фази болести јетре, јер појава десностране срчане инсуфицијенције онемогућава овим болесницима адекватну терапију којом би се могао смањити морталитет.

Кључне речи: плућна артеријска хипертензија; десностране срчана инсуфицијенција; цироза јетре

DOI: https://doi.org/10.2298/SARH210420122L
UDC: 615.272.065

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Early initiation of continuous renal replacement therapy for metformin-associated lactic acidosis

Bojana Ljubičić[1,2], Violeta Knežević[1,3], Tijana Azaševac[1,3], Ana Lazarević[1,2], Bojana Radanović[1,4]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Clinical Centre of Vojvodina, Emergency Centre, Department of Emergency Internal Medicine, Novi Sad, Serbia;
[3]Clinical Centre of Vojvodina, Clinic for Nephrology and Clinical Immunology, Novi Sad, Serbia;
[4]Clinical Centre of Vojvodina, Clinic for Anesthesia, Intensive and Pain Therapy, Novi Sad, Serbia

SUMMARY

Introduction Rapid diagnosis of metformin-associated lactic acidosis (MALA) and initiation of continuous renal replacement therapy (CRRT) in diabetic patient successfully corrects a severe metabolic disorder of a patient with acute renal failure.

Case outline A 58-year-old male patient with a medical history of type 2 diabetes and alcohol abuse was admitted to the Emergency Department because of vomiting, diarrhea, and altered mental status. Initial arterial blood gas analysis revealed severe metabolic acidosis (pH: 6.8, $PaCO_2$: 12 mmHg, HCO_3: 3.2 mmol/l), but the lactate level was too high to measure. MALA was suspected based on progressive lactic acidosis and past intake of metformin. Renal replacement therapy was initiated – continuous veno–venous hemodiafiltration, and as a result a significant improvement of the clinical status, with both blood pH and lactate level showing normalization, was achieved after finishing CRRT.

Conclusion MALA carries an ominous prognosis. This case suggests early initiation of CRRT in hemodynamically unstable diabetic patients with MALA.

Keywords: MALA; acute kidney injury; dialysis; lactic acidosis

INTRODUCTION

Metformin-associated lactic acidosis (MALA) is a rare complication of metformin treatment of type 2 diabetes, which can be caused due to a large intake amount of the drug, or it can be provoked by comorbidities such as renal or hepatic insufficiency or acute infection. Clinically, MALA can be presented with gastrointestinal symptoms (nausea, vomiting, and diarrhea), altered mental status, hypotension, and hypothermia [1]. In patients with hemodynamic instability due to septic shock and MALA, continuous renal replacement therapy (CRRT) has been reported to be successful.

CASE REPORT

A 58-year-old male patient with a medical history of type 2 diabetes and alcohol abuse was admitted to the Emergency Department due to vomiting, diarrhea, and altered mental status, with a Glasgow coma score of 8, Acute Physiology and Chronic Health Evaluation II score of 29, and the Sequential Organ Failure Assessment score of 8. The patient was tachypneic (27 breaths/min.), tachycardic (118 beats/min.), hypotensive (60/30 mmHg), oliguric (diuresis 400 ml). Initial arterial blood gas (ABG) analysis revealed severe metabolic acidosis (pH: 6.8, $PaCO_2$: 12 mmHg, HCO_3: 3.2 mmol/L), but the lactate level was too high to measure. Other initial laboratory results are presented in Table 1. Due to altered mental status and hypovolemic shock, failing to respond to large volume of intravenous fluids, the patient was intubated, mechanical lung ventilation was started in combination with vasoactive support (dopamine/norepinephrine). Empirical parenteral antibiotic therapy was introduced (ceftriaxone/levofloxacin), based on the kidney function. He was given intravenous sodium bicarbonate, and ABG analysis repeated after an hour showed pH of 6.9, with bicarbonate of 4.6 mmol/L, lactate level being 24.8 mmol/L. Electrocardiogram, abdominal ultrasonography and cranial computed tomography scan showed no remarkable findings. The chest X-ray revealed bilateral paracardial areas of lung inflammation (Figure 1). MALA was suspected based on progressive lactic acidosis and past intake of metformin. Serum metformin concentration was 571 umol/L (reference range > 5 ug/ml). After intubation, a nephrologist and an anesthesiologist were consulted, the double lumen catheter was inserted in the right internal jugular vein, and renal replacement therapy (RRT) was initiated – continuous veno–venous hemodiafiltration

Table 1. Initial laboratory results

Blood glucose level (mmol/l)	18.1
Blood urea nitrogen (mmol/l)	35.2
Serum creatinine (μmol/l)	1158
Potassium (K+) (mmol/l)	6.8
C-reactive protein (mg/ml)	61
Procalcitonin (ng/ml)	6.11

Received • Примљено: April 20, 2021
Revised • Ревизија: December 23, 2022
Accepted • Прихваћено: December 26, 2022
Online first: December 30, 2022

Correspondence to:
Bojana LJUBIČIĆ
Department of Emergency Internal Medicine
Emergency Centre
Clinical Centre of Vojvodina
Hajduk Veljkova 1–9
21000 Novi Sad, Serbia
bojana.ljubicic@mf.uns.ac.rs

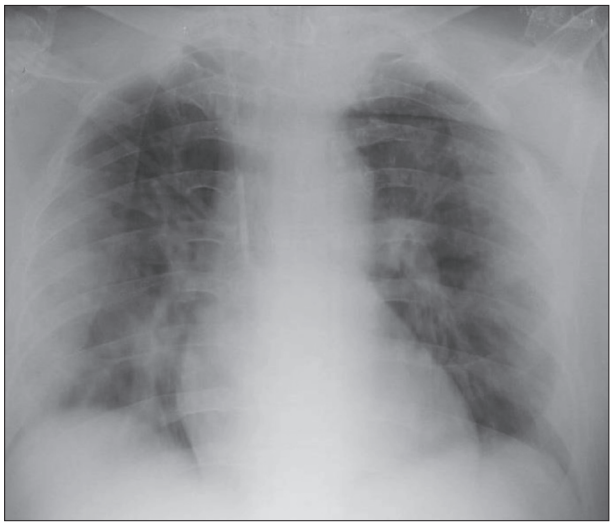

Figure 1. Chest X-ray with bilateral areas of lung inflammation

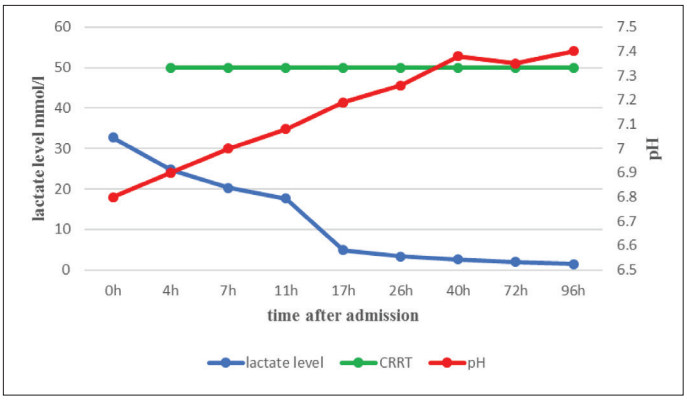

Figure 2. Improvement of blood pH and lactate level during continuous renal replacement therapy (CRRT)

with the oXiris adsorbing membrane (Baxter International Inc., Deerfield, IL, USA), through a Prismaflex CRRT set (Baxter International Inc.). Blood flow rate was 150 ml/min. The therapeutic dosage was 30 ml/kg/h. For anticoagulation, unfractionated heparin was utilized. After the first 24 hours of CRRT, pH improved to 7.179, with an ABG lactate of 21.72 mmol/L. Significant improvement of the clinical status, with both blood pH and lactate level showing normalization, was achieved after finishing one session of CRRT, which lasted 96 hours (Figure 2). Consequently, serum metformin concentration decreased to 104 umol/L. Vasoactive support was reduced on the second day after starting the CRRT, and was discontinued on the fifth day. Hourly diuresis was initially 10–15 ml/h, and during the CRRT it started increasing, so at the end of the procedure the patient had diuresis of 1700 ml/24h. The patient was extubated on day 5 and transferred to the Nephrology Clinic, where from he was discharged (blood urea nitrogen: 10.3; creatinine: 151 umol/L; pH 7.38; pCO_2: 38 mmHg; pO_2: 90 mmHg; lactate level: 0.7 mmol/l; base excess: 3.8; HCO_3 25.1, diuresis: 2200 ml/24 h).

This case report was approved by the Ethics Committee of the University Clinical Centre of Vojvodina.

DISSCUSION

Metformin is a biguanide antihyperglycemic drug, which is used as a first-line agent to treat type 2 diabetes. It inhibits the conversion of lactate to pyruvate; this results in both lactate production and its impaired metabolism. Lactic acidosis is a rare but serious adverse effect in metformin-treated patients. The incidence of MALA is mostly reported to occur in 0.03–0.1 cases per 1000 patient-years but has a high mortality rate, reported to be around 50% [2]. CRRT and sustained low-efficacy dialysis for the treatment of MALA have been documented in some case reports [3, 4].

MALA is generally treated with supportive therapy, including RRT. Applying RRT in patients with MALA, significant base deficit can be corrected; it also directly effects extracellular fluid volume and serum osmolality [5]. With regard to RRT for MALA treatment, a recent study revealed that the clearance of metformin by continuous veno–venous hemofiltration was less than that generally reported to occur with conventional hemodialysis. Thus, continuous veno–venous hemofiltration should be considered only in patients who are too hemodynamically unstable to tolerate hemodialysis. Indications for extracorporeal treatment include lactate > 20 mmol/L, pH 7.0, shock, failure of standard supportive measures, and a decreased level of consciousness [6].

In our case, CRRT was applied because the lactic acidosis was caused by metformin accumulation in the setting of acute kidney injury, gastroenteritis, and subsequent hypovolemic shock. In our patient, cardiorenal syndrome was interpreted as a prerenal deterioration of renal function due to systemic hypoperfusion with consecutive inflammatory changes in the lungs [7].

In a retrospective analysis by Mariano et al. [8], survival rate with CRRT in patients with MALA was noted to be 80%.

The clearance of drugs by CRRT may be less effective than by intermittent hemodialysis, but needs to be considered for patients who are hemodynamically unstable. In our patient, intermittent dialysis was difficult because the patient was hemodynamically unstable receiving high doses of vasopressors. After CRRT was initiated, his lactate level and pH value improved and he subsequently recovered from shock. CRRT is an effective treatment for MALA if intermittent hemodialysis cannot be performed due to hemodynamic instability. Also, one of many advantages of the CRRT is the removal of substances that can produce severe metabolic acidosis, such as alcohol, whose abuse was noted in medical history of our patient, proven by Jha and Padmaprakash [9]. In our case, the use of continuous veno–venous hemodiafiltration in the setting of hemodynamic instability led to a rapid correction of metabolic disorders and hemodynamic stabilization, and, ultimately, to recovery.

Acute MALA carries an ominous prognosis. This case suggests the application of early initiation of CRRT in hemodynamically unstable diabetic patients with MALA.

Conflict of interest: None declared.

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Рана примена континуиране терапије замене бубрежне функције код лактатне ацидозе узроковане метформином

Бојана Љубичић[1,2], Виолета Кнежевић[1,3], Тијана Азашевац[1,3], Ана Лазаревић[1,2], Бојана Радановић[1,4]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Клинички центар Војводине, Ургентни центар, Одељење ургентне интерне медицине, Нови Сад, Србија;
[3]Клинички центар Војводине, Клиника за нефрологију и клиничку имунологију, Нови Сад, Србија;
[4]Клинички центар Војводине, Клиника за анестезију, интензивну негу и терапију бола, Нови Сад, Србија

САЖЕТАК

Увод Правовремена дијагноза лактатне ацидозе узроковане метформином и започињање континуиране терапије замене бубрежне функције код дијабетесних болесника са акутном бубрежном инсуфицијенцијом успешно коригује тешки метаболички поремећај.

Приказ болесника Болесник старости 58 година, са коморбидитетима у виду дијабетесне болести типа 2 и алкохолизма, хоспитализован је у Одељењу ургентне интерне медицине због повраћања, дијареје и измењеног стања свести. Иницијалне артеријске гасне анализе крви показале су тешку метаболичку ацидозу (*pH*: 6.8, $PaCO_2$: 12 *mmHg*, HCO_3: 3.2 *mmol/l*), а ниво лактата је био превисок да би се измерио. Посумњано је да се ради о лактатној ацидози узрокованој метформином, с обзиром на тешку лактатну ацидозу и податке о узимању метформина. Започета је терапија замене бубрежне функције – континуирана вено–венска хемодијафилтрација, и као резултат постигнуто је значајно побољшање клиничког стања болесника, уз нормализацију вредности *pH* и нивоа лактата.

Закључак Акутна лактатна ацидоза узрокована метформином може имати неповољну прогнозу. Овај приказ предлаже разматрање раног започињања континуиране терапије замене бубрежне функције код хемодинамски нестабилних болесника са лактатном ацидозом узрокованом метформином.

Кључне речи: лактатна ацидоза узрокована метформином; акутно оштећење бубрега; дијализа; лактатна ацидоза

DOI: https://doi.org/10.2298/SARH211010032K
UDC: 616.617-001.3

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Rare ureteral injury in lumbar discectomy – two case reports

Emrah Keskin[1], Altuğ Tuncel[2]

[1]Bülent Ecevit University, Faculty of Medicine, Department of Neurosurgery, Zonguldak, Turkey;
[2]Bilkent University of Health Sciences, School of Medicine, Department of Urology, Ankara City Hospital, Ankara, Turkey

SUMMARY

Introduction Iatrogenic ureteral injuries are an important part of all ureteral injuries. They occur primarily during urological, gynecological, vascular, and general procedures. Urethral injury during spinal surgery is a rare complication. We wanted to emphasize that there should be limitations during the use of surgical instruments used in spine surgery.

Outlines of cases We present ureteral injury cases that occurred in two patients with lumbar disc herniation who were treated surgically at the Department of Neurosurgery. Ureteral repair was performed in both patients by the urology department. Their postoperative course was uneventful.

Conclusion This report emphasizes the importance of ureteral injury complications which are rare, but can cause medicolegal problems during lumbar disc surgery. Surgeons should consider this potential complication, which has devastating consequences, particularly in patients with abdominal pain in the early postoperative period.

Keywords: herniated intervertebral disc; iatrogenic; surgery; ureteral injury

INTRODUCTION

The conventional surgical technique for lumbar disc hernias is lumbar discectomy. The main postoperative problems that may arise related to discectomy (open or percutaneous) include severe sequelae, cerebrospinal fluid (CSF) fistula, and wound-healing problems [1, 2]. Regardless of the anatomical aspect (anterior, lateral, or posterior) in the surgical approach to the spine, injury to adjacent anatomical structures may occur at varying rates. Various organ injuries, such as those of the bowel, ureter, and vascular system, have the following approaches considered as safe and widely performed by spine surgeons [3–6]. These injuries can be seen either alone or in combination [7, 8].

Ureteral injury is a rare complication of lumbar spine surgery. Since the first case of ureteral injury due to lumbar spine surgery was reported in 1954, 47 cases have been reported to date [6, 9]. In a meta-analysis, Turgut et al. [6] found that the reporting of these 47 cases was proportional to the socioeconomic development level of the countries.

Here, we present two cases of ureteral injury that occurred following lumbar disc surgery using different approaches (posterior in one, and far-lateral in the other) and discuss the levels of injury (one L5–S1 and the other L4–L5), diagnosis time, complaints, and treatments.

CASE REPORTS

Patient 1

A 45-year-old man presented to our Neurosurgery Clinic with the complaints of back pain, right leg pain, and walking difficulties. On physical examination, the Laségue–Lazarevic sign was positive on the right side, and the dorsiflexion muscle strength of the right foot was 2/5. Right far-lateral disc herniation at L5–S1 was detected in the lumbar magnetic resonance imaging (MRI), and he was operated on at this level using the paramedian intertransverse approach (Figure 1a, b). The back and leg pain regressed, but on postoperative day 1, he began experiencing severe abdominal pain and urgency but inability to urinate; thus, a bladder catheter was inserted. However, the abdominal pain worsened, he was unable to lie on his back, and there was swelling around the navel. On physical examination, he showed signs of abdominal guarding and rebound; thus, ultrasonography and contrast-enhanced abdominal computed tomography (CT) were undertaken. These examinations detected abdominal fluid, which was then evacuated by ultrasound-guided puncture (approximately four liters). However, the patient's complaints persisted. Over the next 15 days, weight loss (10 kg), anemia (preoperative and postoperative hemoglobin levels, 13.2 g/dL and 9.6 g/dL, respectively), elevation of kidney enzymes (blood urea nitrogen, 70 mg/dL; creatinine, 2.1 mg/dL), and elevation of liver enzymes (aspartate transaminase, 78 U/L;

Received • Примљено: October 10, 2021
Revised • Ревизија: February 5, 2023
Accepted • Прихваћено: March 17, 2023
Online first: March 22, 2023

Correspondence to:
Emrah KESKIN
Bülent Ecevit University
Faculty of Medicine
Department of Neurosurgery
67600 Zonguldak
Turkey
drkeskinemrah@gmail.com

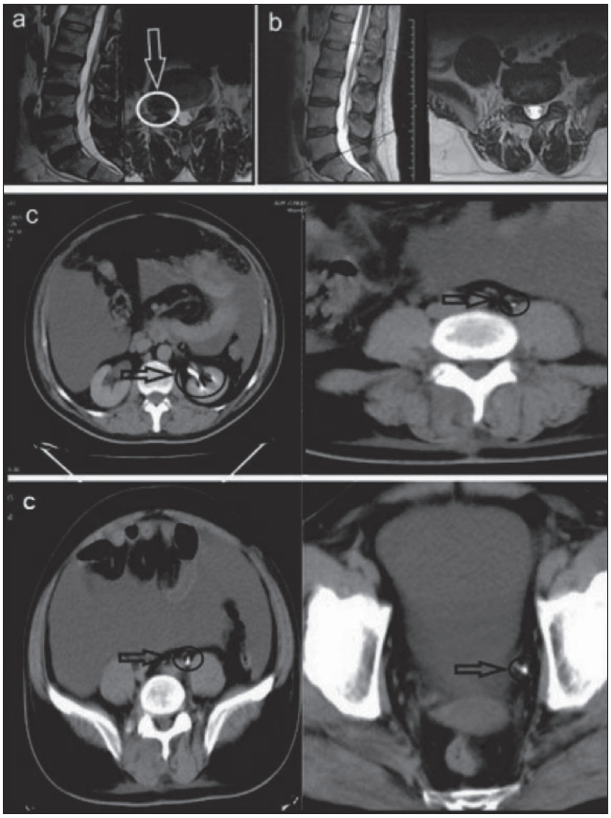

Figure 1. a – Preoperative magnetic resonance imaging showing L5–S1 right far-lateral disc herniation (white arrow and white circle); b – postoperative one-year control magnetic resonance imaging showing no disc; c – contrast-enhanced abdominal computed tomography performed on postoperative day one showing diffuse fluid in the abdomen and contrast enhancement in the left ureter at the edge of the psoas muscle (black arrow and black circle) but not on the side of the injury

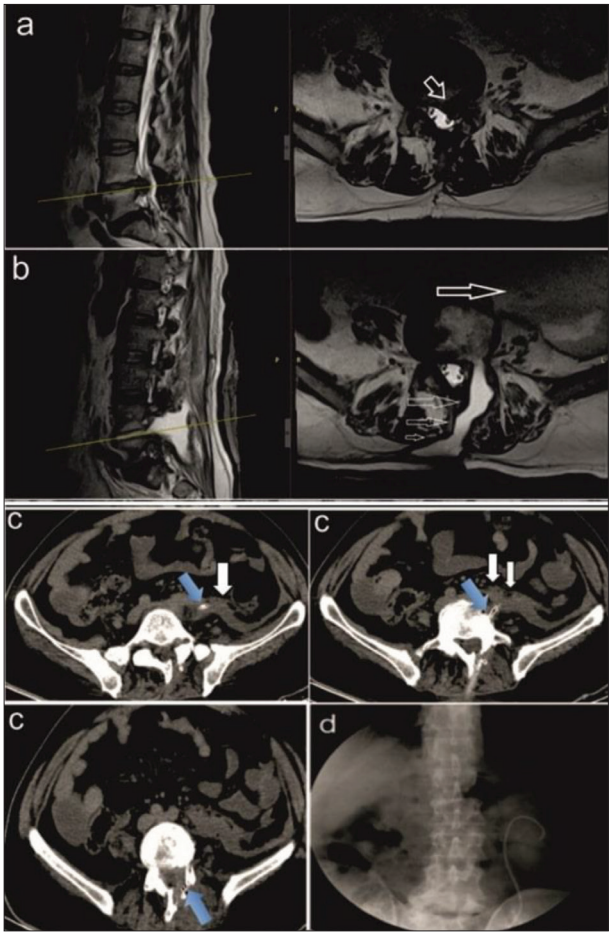

Figure 2. a – preoperative magnetic resonance imaging showing right-sided extruded disc herniation at L4–L5 (white arrow); b – postoperative magnetic resonance imaging showing a urinary fistula (thin white arrow) extending from the urinoma sac (thick white arrow) to the disc height and further to the skin; c – postoperative computed tomography showing the drainage catheter (blue arrow) extending from the urinoma sac to the skin (white arrow); d – intravenous pyelography showing that the catheter cannot go above the disc height where the injury occurred

alanine transaminase, 45 U/L) were observed. Abdominal fluid was continuously evacuated by puncture every other day (approximately one liter every time, 10 times in total). With the preliminary diagnoses of cirrhosis and stomach cancer, liver biopsy and endoscopy were performed by the gastroenterology department, which did not detect any pathologies. Following the fluid restriction, the frequency of the puncture procedure was proportionally reduced from every other day to every four days, and another contrast-enhanced CT was performed.

Contrast media extravasation was not observed on CT, but contrast enhancement was evident in the left ureter with extensive intra-abdominal fluid, whereas it was not seen in the right ureter (Figure 1c). Iatrogenic ureteral injury was considered. In addition, urine was found in the analysis of the fluid taken from the puncture. Two weeks after lumbar disc surgery, ureteral repair was performed with an end-to-end anastomosis by the urology department, which was due to the iatrogenic ureteral rupture on the right side. The patient did not have any complaints during his follow-up.

Patient 2

A 60-year-old man presented to our Neurosurgery Clinic with the complaint of lower back and left leg pain. On physical examination, left-sided Laségue–Lazarevic sign was positive, and the strengths of the tibialis anterior and extensor hallucis longus muscles of the left foot were 3/5 and 2/5, respectively. The patient was operated on for left-sided recurrent disc herniation at the L4–L5 level (Figure 2a). He recovered postoperatively and was discharged. On postoperative day 25, he presented to our clinic again with a clear color discharge from the wound site. He was operated on with the suspicion of a CSF fistula. During the operation, no dura defect was observed, but when the dura was pushed, a contralateral anterior longitudinal ligament (ALL) defect was observed. The fluid continuously flowed from the disc height where the defect was located, and approximately 1500 milliliters of clear and odorless fluid was aspirated. At this stage, a drain extending into the ALL defect was inserted (Figure 2c). After the operation, approximately 1000 milliliters of clean and odorless fluid was discharged from the drain every day for three days. Considering that the continuous amount of the drainage and amount and color were similar to the urine collected

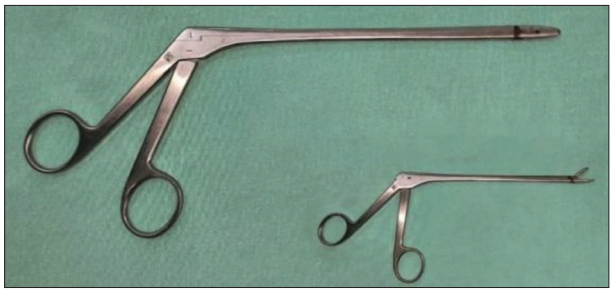

Figure 3. Red line at the tip of the mouth of the straight and reverse-angled rongeur device

in the bladder bag, the drainage fluid was analyzed and confirmed to be urine.

On preoperative reassessment by MRI, a urinoma sac was found in the anterolateral neighborhood of the disc height at the edge of the psoas muscle (Figure 2b). Intravenous pyelography was later performed by the urology department, clearly showing iatrogenic ureteral injury (Figure 2d). The patient was referred to an external center for the repair of ureteral injury with end-to-end anastomosis. He did not have any complaints during his follow-up.

All procedures performed 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 patients.

DISCUSSION

Instruments used in lumbar spine surgery may cause injury to retroperitoneal organs, such as the bowel, ureter, and vein, by damaging the prevertebral ligament [7, 8, 10]. Although the mechanism of this injury has not been explained in all cases reported in the literature, it most frequently occurs with the injury of ALL due to rongeur use [11]. Fomekong et al. [12] reported that ureteral injury occurred due to the use of Kirschner wire during the minimally invasive pedicle screw application.

Even in the most experienced hands, a rongeur can cause serious organ injuries at the stage of discectomy. In our opinion, two points should be considered while using this tool. The first and common mistake being the application of the tip of the rongeur in an open way, and more than the mouth of the instrument is inserted into the surgical field. The second is moving to inadvertently close the tool if the rongeur falls into the intertransverse space when withdrawing it. The first situation can be successfully controlled with experience. However, the second situation is extremely difficult to prevent, as it is a reflexive movement and dependent on personal skills. In this context, injuries may occur during the disc removal with a far-lateral approach, as in our first case, or they may occur when the rongeur accidentally falls into the intertransverse space while removing the tissues over the lamina before the discectomy stage [6].

During revision surgery, the risk of injury increases because of the adhesion of all tissues (such as the dura mater, vein, and ureter). Specifically, revisions of lumbar disc surgery performed with the anterior approach are more difficult than those performed with the posterior approach. In anterior revision surgery, ureteral catheterization is performed before the operation to minimize the risk of possible injury; however, despite these precautions, injuries have been reported [13]. In posterior surgery, ureter injury often occurs contralaterally [6, 11, 12]. Ipsilateral injury, as described in our second case, is usually rare. We attribute this to the use of a reverse-angled rongeur in this patient who underwent surgery due to recurrent disc herniation. It is relatively more possible to have full control over a straight rongeur. However, how far the tip can go when using a reverse-angled rongeur is entirely related to the surgeon's experience and satisfaction with disc removal. In recurrent lumbar disc surgery, the lateral of the disc is often approached due to the need for extra laminectomy and facetectomy. Accordingly, pushing the reverse-angled rongeur too far forward may result in the formation of ALL defects and ipsilateral ureteral injury. Therefore, rongeur-type tools should be manipulated in a controlled manner as much as possible.

To minimize organ injury in disc surgery after ureteral injury in both cases, we drew a straight red line at the end of the mouth part of the straight and reverse-angled rongeur device (Figure 3). We use this red line as a visual stopper. This line will provide a safer use of the rongeur device during training, especially in clinics that provide spinal surgery training. In this context, we recommend that companies manufacturing surgical hand tools place this line on the part of the rongeur, as we described above.

The duration of symptoms after ureteral injury varied (first 24 hours to one year) [6]. It may present with symptoms immediately after surgery, as in our first case, or as late as on postoperative day 25 in our second case. Among these symptoms, abdominal and flank pains are the most common, and hematuria, abdominal swelling, fever, and urinary fistula can be observed [6, 12]. These symptoms that can be encountered by spine surgeons, albeit rarely, may delay the diagnosis of an already rare ureteral injury. In our first case, a postoperative follow-up neurological examination should be a part of this routine after the patient who has undergone spine surgery recovers from anesthesia. In such cases, contrast-enhanced CT is recommended if ureteral injury is suspected.

A CSF fistula is a common complication during lumbar spine surgery [14]. Our second case presented to the Emergency Department with a discharge from the incision site, which may be because we did not focus on the urinoma sac in the lumbar MRI taken preoperatively to determine the formation of a CSF fistula. In both cases, in the presence of either fluid accumulation at a level that is more expected after lumbar disc surgery or a skin fistula, a fluid sample should be taken and urinalysis should be performed. In addition, contrast-enhanced CT is necessary to visualize the ruptured ureter. Finally, a urinoma incision

close to the surgical level can be seen on MRI, especially in late-stage cases.

Discussing the complaints, diagnosis, and treatment processes of iatrogenic urethral injury with these two cases would make it easier for spine surgeons to manage this process by considering the possibility of this complication that generally has a good prognosis.

Conflicts of interest: None declared.

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Ретка повреда мокраћног канала код лумбалне дискектомије – два приказа болесника

Емрах Кескин[1], Алтуг Тунџел[2]

[1]Универзитет Булент Еџевит, Медицински факултет, Одељење за неурохирургију, Зонгулдак, Турска;
[2]Универзитет здравствених наука Билкент, Медицински факултет, Одељење за урологију, Градска болница Анкара, Анкара, Турска

САЖЕТАК

Увод Јатрогене повреде мокраћне цеви представљају важан део свих повреда мокраћних цеви. Јављају се углавном током уролошких, гинеколошких и општих хируршких и васкуларних захвата. Повреде мокраћне цеви током операције кичме се у литератури ретко јављају као компликација. Хтели смо да нагласимо да треба да постоје ограничења током употребе хируршких инструмената који се користе приликом операције кичме.

Прикази болесника Представљамо повреду мокраћног канала која се догодила у два случаја лумбалне дискус хернije лечене хируршким путем на нашем Одељењу за неурохирургију. Уролози су у оба случаја извршили захват на мокраћном каналу. Постоперативни период је прошао без компликација код оба болесника.

Закључак У овом извештају смо нагласили важност компликација које се јављају услед повреда мокраћног канала, које су ретке и изазивају медицинске проблеме током операције лумбалног диска. Хирурзи треба да имају у виду ову могућу компликацију, која има разорне последице, посебно код болесника с боловима у абдомену у раном постоперативном периоду.

Кључне речи: дискус хернија; јатрогени; операција; повреда мокраћне цеви

DOI: https://doi.org/10.2298/SARH220926120Z
UDC: 616.62-006.04

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Metastatic malignant melanoma mimicking urinary bladder mass – a rare presentation

Mirjana Živojinov[1,2], Aleksandra Ilić[1,2], Tanja Lakić[1,2], Ivana Stanišić[2], Željka Panić[3]

[1]University of Novi Sad, Faculty of Medicine, Department of Pathology, Novi Sad, Serbia;
[2]Clinical Center of Vojvodina, Center for Pathology and Histology, Novi Sad, Serbia;
[3]University of Business Academy in Novi Sad, Faculty of Pharmacy, Novi Sad, Serbia

SUMMARY

Introduction Melanoma is a solid aggressive tumor characterized by the malignant transformation of melanocytes. To date, only about 35 primary and about 30 metastatic malignant melanomas of the bladder have been reported.

Our objective is to report a rare case of secondary tumor of urinary bladder.

Case outline A 57-year-old man presented to the Urologic Clinic due to lower urinary tract symptoms. The urologist indicated transurethral resection (TUR). His medical history was significant for cutaneous malignant melanoma resected 3 years prior, which were localized at scapular region on the left side. Microscopic examination of the TUR specimen showed several fragments of ureter mucosa with presence of tumor and focally with normal urothel. Tumor cells were markedly atypical and polygonal in a solid pattern. The nuclei were large with variation in size and prominent eosinophilic nucleoli. Also, there were present areas with abundant brown pigment. Immunohistochemical analysis of tumor cells showed positivity for Melan A and HMB45 and negativity for GATA3. Molecular analysis showed that *BRAF* was mutated.

Conclusion The incidence of malignant melanoma is high and increasing, but the urinary bladder is a rare location of metastasis. However, both primary and metastatic melanomas can occur in the bladder, so the urologist and the pathologist have to consider it when it is the primary site of onset, or when it represents the first symptomatic metastasis.

Keywords: melanoma; metastasis; urinary bladder

INTRODUCTION

Melanoma is a solid aggressive tumor characterized by the malignant transformation of melanocytes, melanin producing cells in the basal layer of the epidermis. The incidence and mortality rate are high and tend to increase [1, 2].

Overall, metastatic disease to the bladder is unusual, with only 2% of bladder cancer cases representing metastasis [3].

To date, only about 35 primary and about 30 metastatic malignant melanomas of the bladder have been reported [4, 5]. However, on autopsy series of patients with extra-regional disease, 18–37% also had metastases in the bladder [6, 7].

When it occurs, the main complaints are hematuria or lower urinary tract symptoms, urinary retention or dysuria [6, 8, 9].

Our objective is to report a rare case of secondary tumor of urinary bladder.

CASE REPORT

A 57-year-old man presented to the Urologic Clinic due to lower urinary tract symptoms. The urologist indicated transurethral resection (TUR). His medical history was significant for cutaneous malignant melanoma resected three years prior, which were localized at the scapular region on the left side. The melanoma was 2.8 cm in diameter and 2.6 cm deep (Breslow IV, Clark III). The tumor was widely resected, with negative surgical margins. Thereafter the patient underwent sentinel lymph node biopsy, which proved negative.

Microscopic examination of the TUR specimen showed several fragments of ureter mucosa with presence of tumor and focally with normal urothelium. Tumor cells were markedly atypical and polygonal in a solid pattern. The nuclei were large, with variations in size and prominent eosinophilic nucleoli. Separately, there were polypoid fragments of tumor. Also, there were present areas with abundant brown pigment (Figure 1).

Immunohistochemical analysis of tumor cells showed positivity for Melan-A and HMB-45 and negativity for GATA3 (Figure 2). The patient underwent further imaging studies. Computed tomography of the chest, abdomen and pelvis was negative for dissemination of the disease.

Molecular analysis showed that *BRAF* was mutated.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

Received • Примљено: September 26, 2022
Accepted • Прихваћено: December 20, 2022
Online first: December 29, 2022

Correspondence to:
Aleksandra ILIĆ
Hajduk Veljkova 3
21000 Novi Sad, Serbia
aleksandra.m.ilic@mf.uns.ac.rs

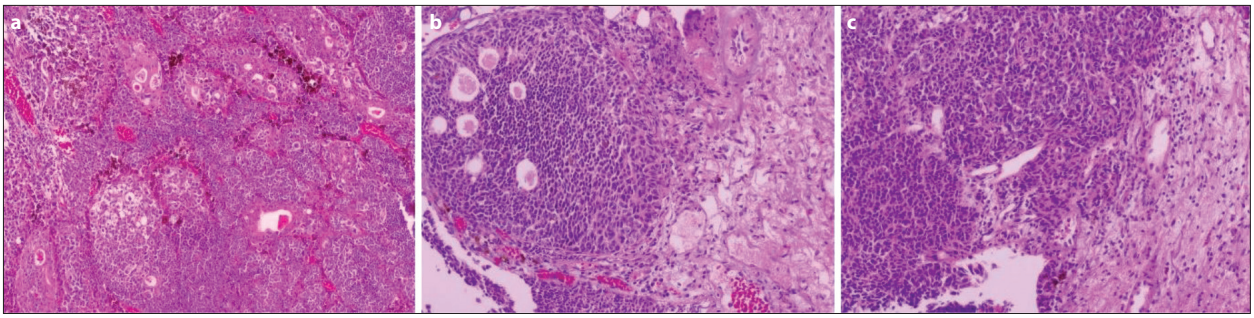

Figure 1. Metastatic malignant melanoma of the urinary bladder; a) H&E; 100 ×; b) H&E; 200 ×; c) H&E; 200 ×

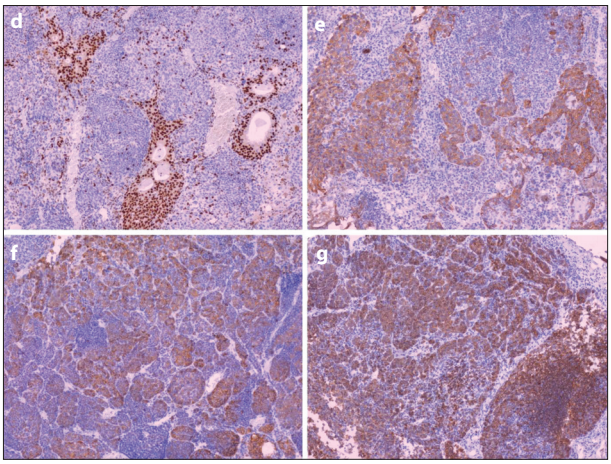

Figure 2. Metastatic malignant melanoma of the urinary bladder; d) GATA3 immunonegativity in the tumor cells; 100 ×; e) HMB-45 immunopositivity in the tumor cells, 100 ×; f) HMB-45 immunopositivity in the tumor cells, 100 ×; g) Melan-A immunopositivity in the tumor cells, 100 ×

DISCUSSION

Malignant melanoma is a highly aggressive tumor with an incidence that continued to rise in the past 30 years. It is the deadliest skin cancer, accounting for up to 60% of skin cancer-related deaths, primarily due to rapid proliferation and metastasis [10].

Melanoma can metastasize to any part of the body, but it has predilection for the skin, the lungs, the liver, and the brain, while metastases to the bladder in clinical series appear to be rare, with only about 30 reported cases in the literature [3, 4, 6]. In contrast, autopsy series indicate an 18–37% incidence of the metastatic disease in the bladder [6, 7].

Meunier et al. [11] reviewed the published data and confirmed the previously reported 23 cases of metastatic melanoma. However, some authors consider that the reason for this small number of cases is due to the fact that metastatic melanoma is often seen only at autopsy, as a result of its asymptomatic nature [3].

A study by Dasgupta and Brasfield [12] from 1964 showed that 18% of patients with melanoma had bladder metastasis on autopsy, further validating the notion that secondary melanoma of the bladder might be relatively more common than was originally thought [3].

Diagnosis of metastasis of melanoma of the urinary bladder is based on immunohistochemical confirmation of a morphological suspicion using melanoma tumor markers. Sometimes the hematoxylin and eosin appearance can be very deceptive; for example, melanotic malignant melanoma of the bladder can have many features in common with a high-grade urothelial carcinoma, leading to misdiagnosis. Also, it is important to differentiate metastatic melanoma of the bladder from primary melanoma of the bladder, for which the following criteria have been used: (1) detailed history ruling out cutaneous, regressed, or visceral melanoma; and (2) recurrence pattern consistent with the primary origin of melanoma [3, 4, 13].

On the other hand, lesions that can mimic melanoma of the bladder both clinically and cystoscopically include melanosis and pseudomelanosis (lipofuscinosis and hemosiderosis) of the bladder, which can be differentiated only by careful histological examination [4].

Several treatments for malignant melanoma metastatic to the bladder are available, considering the performance status of the patient, the anatomic location of the metastases, the existence of bladder symptoms, and the life expectancy. Radical cystectomy is an aggressive approach, while conservative options include TUR and partial cystectomy. Also, systemic chemotherapy is reported as an adjunct to endoscopic resection and should be limited to patients with good performance status [9].

According to some studies, *BRAF* mutation is present in 50% of malignant melanomas and is associated with poor prognosis. Targeted therapies, including BRAF inhibitors, have been shown to improve response rates, but not durably [5, 14, 15].

The incidence of malignant melanoma is high and increasing, but the urinary bladder is a rare location of metastasis. However, both primary and metastatic melanomas can occur in the bladder, so the urologist and the pathologist have to consider when it is the primary site of the onset and when it represents the first symptomatic metastasis.

Conflict of interest: None declared.

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Метастаза меланома као туморска маса у мокраћној бешици – редак случај

Мирјана Живојинов[1,2], Александра Илић[1,2], Тања Лакић[1,2], Ивана Станишић[2], Жељка Панић[3]

[1]Универзитет у Новом Саду, Медицински факултет, Катедра за патологију, Нови Сад, Србија;
[2]Клинички центар Војводине, Центар за патологију и хистологију, Нови Сад, Србија;
[3]Универзитет Привредна академија у Новом Саду, Фармацеутски факултет, Нови Сад, Србија

САЖЕТАК

Увод Меланом је солидан агресивни тумор који настаје малигном трансформацијом меланоцита. До данас је забележено само око 35 примарних и око 30 метастатских малигних меланома мокраћне бешике.

Циљ рада је приказати редак случај метастатског тумора мокраћне бешике.

Приказ болесника Мушкарац стар 57 година јавио се на Клинику за урологију због симптома у доњем уринарном тракту. Уролог је индиковао трансуретралну ресекцију. Из његове историје болести сазнали смо да је имао ресекцију кожног малигног меланома пре три године, који је био локализован у пределу леве скапуле. Микроскопски преглед узорка трансуретралне ресекције показао је неколико фрагмената слузнице уретера са присуством тумора и фокално са нормалним уротелом. Туморске ћелије су биле изразито атипичне и полигоналне, са великим и плеоморфним језгрима и проминентним еозинофилним нуклеолусима. Такође, постојала су подручја са обилним смеђим пигментом. Имунохистохемијска анализа туморских ћелија показала је позитивност на Мелан А и *HMB*45 и негативност на *GATA*3. Молекуларна анализа је показала да је *BRAF* мутиран.

Закључак Иако је инциденца меланома висока, са тенденцијом пораста, мокраћна бешика је веома ретка локализација метастаза. Међутим, како се и примарни и метастатски меланоми могу јавити у бешици, уролог и патолог треба да размотре да ли је примарна болест или представља први симптом метастатске болести.

Кључне речи: маланом; метастаза; мокраћна бешика

DOI: https://doi.org/10.2298/SARH200114033R
UDC: 615.357:577.175.5

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Corticosteroid treatment and growth of angiolipomas in patient with two rare diseases: Pfeifer–Weber–Christian disease and benign multiple subcutaneous angiolipomas

Goran Radunović[1], Tanja Miličić[2], Martina Bosić[3], Ivan Jeremić[4], Draško Dačić[5], Slavica Pavlov-Dolijanović[1]

[1]University of Belgrade, Faculty of Medicine, Institute of Rheumatology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, University Clinical Center of Serbia, Clinic for Endocrinology, Diabetes, and Metabolic Diseases, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Institute of Pathology, Belgrade, Serbia;
[4]Institute of Rheumatology, Belgrade, Serbia;
[5]General Hospital, Požarevac, Serbia

SUMMARY
Introduction Pfeifer–Weber–Christian disease (PWCD) is a rare inflammatory disorder of the subcutaneous fatty tissue. Angiolipoma, is a benign adipocytic soft tissue tumor composed of mature adipose tissue and small vascular proliferations. Treatment with corticosteroids could lead to proliferation of fat tissue but the stimulation of angiolipoma growth during corticosteroid therapy is extremely rare.
Case outline We describe a case of a 46-year-old female patient with histopathological confirmation two rare diseases: PWCD and benign multiple subcutaneous non-infiltrative angiolipomas. Angiolipomas were treated conservatively. Treatment for PWCD was prednisone 20 mg/day. Due to poor control of PWCD and rapid angiolipomas growth on forearms, corticosteroids were discontinued after two months of use. Administration of oral cyclosporine A led to a rapid remission of the PWCD, and with no new growth of angiolipomas.
Conclusion The successful therapy with the Cyclosporine A supports the hypothesis that PWCD is a T cell mediated autoinflammatory condition. Rapid growth of angiolipoma during corticosteroid therapy is an extremely rare condition.
Keywords: prednisone; angiolipoma; side effect; panniculitis

INTRODUCTION

Pfeifer–Weber–Christian disease (PWCD), is a rare idiopathic disease characterized by lobular panniculitis of adipose tissue with systemic symptoms and multiple organ involvement and is usually treated with corticosteroids [1]. Angiolipomas are rare, benign subcutaneous tumors, composed of adipose tissue and blood vessels and often containing fibrin thrombi, that account for approximately 10% of tumors of fat [2]. For now, the induction of growth of angiolipoma during corticosteroid treatment, was reported only in one case [3].

We described an unusual case of PWCD associated with benign multiple subcutaneous non-infiltrative angiolipomas, which gradually increased in size during corticosteroid therapy. To the best of our knowledge, there are no previous reports of this association (1944–2020).

CASE REPORT

A 46-year-old Caucasian female presented with relapsing and remitting biyearly flares of panniculitis (always masseteric space, where appear subcutaneous painful nodules with erythema in overlying skin) (Figure 1a), associated with fever, oral aphthous ulcers, arthralgia/arthritis, myalgia, and generalized weakness, for 15 years (2002–2017). Initially, the nodules spontaneously withdrew. Later, she received anti-inflammatory, local anti-edematous, and antibiotic therapy, with no improvement. In 2017, the disease recurred every month. A skin biopsy (right masseteric cheek) showed predominantly lobular panniculitis (Figure 1b–d). She also had multiple soft, well-circumscribed, round subcutaneous tumors present on lower trunk, forearms, and upper legs, distributed in a symmetric pattern, and ranged from 1 × 1 cm to 1.5 × 2 cm in size (Figure 2a). This condition started in 2013.

Her personal history revealed Raynaud's phenomenon, and dry eyes and mouth since 2002, high cholesterol and triglycerides since 2010, radical hysterectomy for chronic salpingitis and oophoritis 2015, and allergy to penicillin. There was no known tubercular contact or a family history of a similar disorder.

Her body height was 172 cm, body weight was 69.3 kg and body mass index were 23.4 kg/m^2. The percentage of fat was 34.9%, and fat mass

Received • Примљено: January 14, 2020
Revised • Ревизија: February 18, 2022
Accepted • Прихваћено: March 18, 2023
Online first: March 22, 2023

Correspondence to:
Slavica PAVLOV-DOLIJANOVIĆ
University of Belgrade
Faculty of Medicine
Institute of Rheumatology
Resavska 69
11000 Belgrade
Serbia
slavicapavlovdolijanovic@gmail.com

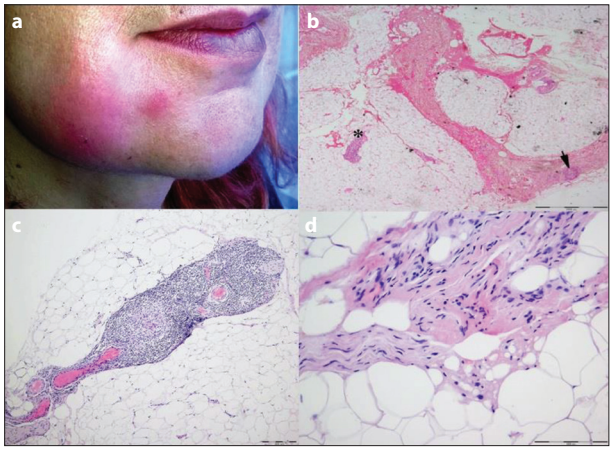

Figure 1. a – Induration of the skin in the right masseteric space; b – focal lobular lymphocytic infiltration around small blood vessels (asterisk) along with slightly widened interlobular septum with rare epithelioid granulomas (arrow), (hematoxylin and eosin staining, magnification × 40); c – granulomas were composed of epithelioid histiocytes and lymphocytes, without necrosis or giant cells (magnification × 100); d – rare small areas of fat cell necrosis and foamy histiocytes (lipophagic necrosis) were noted, unrelated to areas with granulomas (magnification × 400)

was 24.2 kg (normal range 23–34%, *vs.* 13.5–23.2 kg, respectively, Tanita analyzer). Complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, anti-neutrophilic cytoplasmic autoantibody, anticyclic citrullinated peptide, rheumatoid factor, anti-Ro/SSA, anti La/SSB antibody, anticardiolipin antibody, anti-beta 2 glycoprotein-I antibody, cryoglobulins, immunoglobulin assay, protein electrophoresis, immunoelectrophoresis, IgG 4, C1 inhibitor and $C1_{q,}$ circulating immune complexes, complement C3 and C4 levels, serum amylase, alpha 1-antitrypsin, angiotensin-converting enzyme, were all negative/normal. The renal functions and the electrolytes were also all normal. The urine was free of any sediments or protein. HLA B27 and HLA B51 was negative. Hepatitis B and hepatitis C virus, human immunodeficiency virus, IGRA test for tuberculosis, *Brucella abortus bovis* test and dirofilaria repens test were negative. The chest radiograph and the abdominal ultrasonography were normal. Ultrasound of the major salivary gland was normal. Salivary ^{99m}Tc-pertechnetate scintigraphy showed decreased accumulation an excretory function in both parotid and submandibular glands. A salivary gland biopsy showed rare dispersed lymphocytes and plasma cells without acinar atrophy, a finding consistent with nonspecific sialadenitis (grade 0). Lissamine green and Schirmer's test were negative. Capillaroscopy was normal. Dual-energy X-ray absorptiometry scanning showed osteopenia (T-score of total hip was -1.0, and spine -1.4). The endocrinology investigation revealed the following pathologic parameters: cholesterol 9.46, LDL-cholesterol 5.12 and triglycerides 2.23 mmol/l (normal range < 5.2 *vs.* < 3.4 *vs.* < 1.7 mmol/l, respectively), and autonomic neuropathy. She was absence of insulin resistance. All other endocrine parameters such as the thyroid hormones, catecholamines in 24 hours urine, cortisol, adrenocorticotropic hormone, dehydroepiandrosterone sulfate, prolactin, human growth hormone, parathyroid hormone, neuron-specific enolase and chromogranin A were normal. The luteinizing hormone and follicle-stimulating hormone showed iatrogenic menopauses. Ultrasound of the forearm showed subcutaneous masses of adipose tissue with internal vascularity suggestive of angiolipoma (Figure 2b–c).

We established the diagnosis of PWCD and benign multiple subcutaneous non-infiltrative angiolipomas, after other types of panniculitis and multiple lipomas were excluded (Table 1 and Table 2). Angiolipomas were treated conservatively, because patient had no other complaints related to the excess fat tissue. Treatment for dyslipidemia was rosuvastatin 20 mg/day, and Ezetimibe 10 mg/day, but with unsatisfactory values of total cholesterol and LDL cholesterol. Treatment for PWCD was prednisone 20 mg/day.

Due to poor control of PWCD and rapid angiolipoma growth on forearms (approximately 10 × 10 mm to 25 × 17 mm) corticosteroids were discontinued after two months of use. The patient underwent complete surgical excision of two tumors on forearms measured 25 × 15 × 10 mm and 22 × 13 × 9 mm, which were encapsulated and yellow with the appearance of adipose tissue with red areas corresponding to blood vessels (Figure 3a). Tumors were composed of the lobules of mature adipose tissue with focally grouped, branching capillaries and focal hyaline thrombi in capillaries, and were diagnosed as angiolipoma (Figure 3b–c).

Patient was treated with cyclosporine A, 6 mg/kg/day for 12 months. As she was with no disease activity reported and no new tumor growth cyclosporine A dose was reduced to 2.5 mg/kg/day. Eight months after the dose reduction, patient was readmitted due to one-month history of abdominal discomfort, weight loss, nausea, and vomiting, accompanied by arthritis, fever, and oral aphthous ulcers.

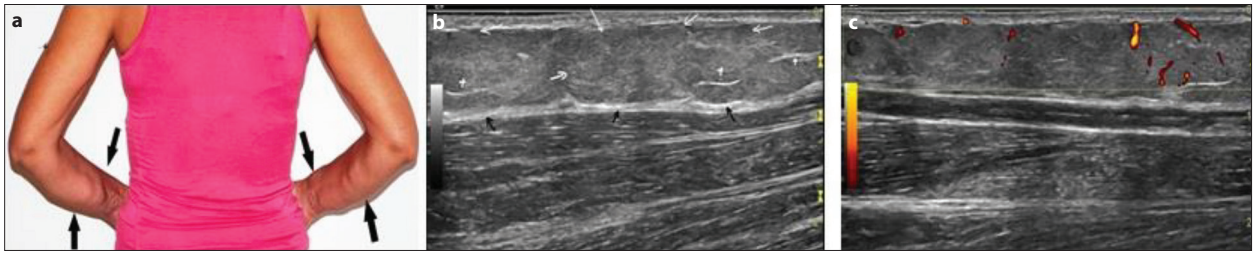

Figure 2. a – Multiple well-circumscribed, round subcutaneous tumors in the forearms of patient (black arrows); b – the grayscale sonogram of forearms tumors showed three heterogeneous hyperechoic ovoid masses in the subcutaneous layer, with internal echogenic strands (white cross), deep tumor capsules (black arrows), and no lateral and superficial capsules (white arrows); c – the color Doppler sonogram showed presence of vascularity

Table 1. Classification of panniculitis and conditions associated with panniculitis

Type of panniculitis
I. Lobular panniculitis
1. Pfeifer–Weber–Christian disease (Idiopathic relapsing febrile lobular non-suppurative panniculitis) 2. Panniculitis in systemic connective tissue diseases: (Systemic lupus erythematosus, Rheumatoid arthritis, Vasculitis, Myositis, Systemic sclerosis, Eosinophilic fasciitis, Eosinophilia-myalgia syndrome) 3. Complement deficiency 4. Lipodystrophic panniculitis 5. Enzymatic panniculitis: (pancreatitis, pancreatic carcinoma, alpha-1-antitrypsin deficiency) 6. Factitial panniculitis 7. Cytophagic histiocytic panniculitis 8. Post-steroid panniculitis (withdrawal of glucocorticoids) 9. Hodgkin's lymphoma and leukemia 10. Rothmann-Makai syndrome (Lipogranulomatosis subcutaneous)
II. Septal panniculitis
1. Erythema nodosum 2. Subacute nodular migratory panniculitis (Vilanova disease)
III. Mixed panniculitis
1. Lupus profundus panniculitis 2. Erythema nodosum-like lesions in Behcet's syndrome
IV. Panniculitis with vasculitis
1. Vasculitis of small blood vessels 2. Medium-size vessel vasculitis (small arteries or arterioles) 3. Polyarteritis nodosa 4. Erythema induratum (nodular vasculitis)

The dose of cyclosporine A was increased to 6 mg/kg/day. Appendectomy was performed and histopathological analysis revealed acute phlegmonous appendicitis. Due to pronounced peritoneal adhesions, the mesoappendix was difficult to see but seemed to be unchanged. The patient is currently disease-free with no new growth of angiolipoma.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISSCUSION

Clinically, angiolipoma are painful and relatively small tumors (< 2 cm) with a predilection for the upper extremities, and most commonly occur at an earlier age (second and third decades of life), usually in male patients [2, 4]. In our case, the patient was female and was older than most reported cases. In literature, appearance of numerous angiolipoma after corticosteroid therapy was reported only once, in a male patient after 15-year-long therapy with prednisone and azathioprine in the treatment of bilateral kidney transplantation [3]. In our case, tumors have already been present before the initiation of therapy. Their growth was induced after only two months of prednisone treatment.

Table 2. Rare syndromes associated with lipomas

Syndrome	Components
Familial angiolipomatosis	Family history of similar lesions, autosomal-recessive or autosomal-dominant fashion
Benign symmetric lipomatosis (Madelung's disease, Launois-Bensaude syndrome)	Diffuse or circumscribed symmetrical accumulation of adipose tissue, primarily around the neck, back, shoulders and upper trunk
Neurofibromatosis type I	Café au lait macules, cutaneous/subcutaneous neurofibromas, axillary or groin freckling, optic pathway glioma, nodules, bony dysplasia
Cellular angiolipoma	Histologic are composed almost entirely of small vessels (>95 % of the lesion)
Spindle cell-lipoma	Subcutaneous nodule in the head and neck region, composed of mature adipocyte and bland spindle cells
Angiomyxolipoma	Contains mature adipose tissue, extensive myxoid stroma and numerous blood vessels
Lipomatosis syndrome in patients infected with human immunodeficiency virus	Lipomas, peripheral lipodystrophy, central adiposity, dyslipidemia, insulin resistance
Bannayan–Zonana syndrome	Multiple lipomas, hemangiomas, macrocephaly
Cowden disease	Lipomas, hemangiomas, goiter, various skin and mucosal lesions (including intraoral papillomas, acral keratoses, facial trichilemmomas), colorectal hamartomatous polyps, gastric polyps with hyperplastic features
Fröhlich syndrome	Multiple lipomas, sexual infantilism, obesity
Proteus syndrome	Pelvic lipomatosis, fibroplasia of hands and feet, skeletal hypertrophy, bony exostoses, scoliosis, pigmented skin lesions

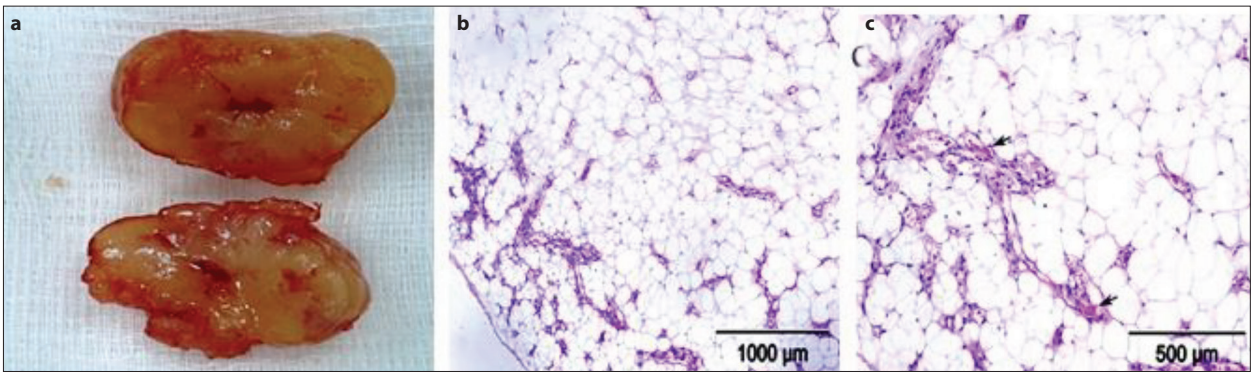

Figure 3. a – Macroscopic encapsulated yellow adipose tissue with red areas corresponding to blood vessels; b – on histopathology, in lobules of mature adipose tissue focally grouped branching capillaries were seen (Hematoxylin and Eosin staining, magnification × 100); c – some of capillaries contained hyaline thrombi (arrows) enabling diagnosis of angiolipomas (Hematoxylin and Eosin staining, magnification × 200)

Exogenous-steroids-induced angiolipoma were also described in a young male after misuse of anabolic steroids [5]. A variable length of period from initiation of steroid use till appearance of lipomatosis or angiolipoma and presence of androgen receptors expression in angiolipoma suggest anabolic effects of steroids, rather than immunosuppression, as a mechanism of fat cell proliferation [2, 3, 6]. Beside angiolipoma, there was a report of another epidural lipomatous tumor, a hibernoma in a six-year-old child with juvenile rheumatoid arthritis treated with prednisone for four years [7]. We believe this case represent spinal lipomatosis with remnants of brown fat cell rather than a true tumor.

Histopathological findings in angiolipoma, with lobules of mature adipocytes and proliferation of capillaries with focal hyaline thrombi, enable easy diagnosis. Diagnostic difficulties can occur in cases with a prominent proliferation of capillaries and small amount of fat tissue [4]. In our case, histopathological appearance was typical, and diagnosis was easily made.

However, the panniculitides are heterogenous inflammatory diseases of subcutaneous fat tissue that could bring diagnostic challenge and require thorough clinicopathological exploration [1, 8]. This is especially true in case of lobular panniculitides where a detailed clinical and histopathological evaluation led to reassessment of an entity previously known as PWCD. Because morphological findings in such biopsies pointed out to other specific diseases, it was suggested this term should be abandoned in dermatology [9]. However, in our case other types of panniculitides were excluded and diagnosis of PWCD was made.

The rarity of PWCD makes it hard to assess the response of the disease to the therapeutic strategies. Accordingly, treatment options are empiric. They are derived on the basis of individual cases. Drugs used in the treatment of PWCD include corticosteroid therapy, fibrinolytic agents, hydroxychloroquine, azathioprine, thalidomide, cyclophosphamide, tetracycline, cyclosporine A, mycophenolate mofetil, anti-TNF treatment and intravenous immune globulin therapy [1, 10, 11, 12]. Cyclosporine A and corticosteroids have been proved most effective [11, 13]. In the present case, we also showed successful response to cyclosporine A. Cyclosporine A has potent immunosuppressive properties that result from selective inhibition of T-lymphocyte activation. This suggests that the T-lymphocyte may have an important role in the pathogenesis of PWCD.

To conclude, presented case illustrated a typical problem of every patient suffering from rare disease – a too long period of time from the onset of symptoms to diagnosis and treatment. PWCD and benign multiple subcutaneous non-infiltrative angiolipomas represents diseases with a broad spectrum of symptoms and thus also a difficult differential diagnosis that require patience of the physician. This case specifically highlights the histopathological aspects of PWCD and angiolipoma as a vital clue to the diagnosis, and supports the hypothesis that PWCD is a T cell mediated autoinflammatory condition, and may represent an association between corticosteroid use and the growth of angiolipomas. We hope that our experiences will also can contribute to greater awareness of these rare disorders.

This article has been posted as a preprint on Research Square.

Conflict of interest: None declared.

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Лечење кортикостероидима и пораст ангиолипома код болеснице са две ретке болести: Фајфер–Вебер–Кристијанова болест и доброћудни вишеструки неинфилтрирајући ангиолипоми

Горан Радуновић[1], Тања Миличић[2], Мартина Босић[3], Иван Јеремић[4], Драшко Дачић[5], Славица Павлов-Долијановић[1]

[1]Универзитет у Београду, Медицински факултет, Институт за реуматологију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Клинички центар Србије, Клиника за ендокринологију, дијабетес и болести метаболизма, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Институт за патологију, Београд, Србија;
[4]Институт за реуматологију, Београд, Србија;
[5]Општа болница, Пожаревац, Србија

САЖЕТАК

Увод Фајфер–Вебер–Кристијанова болест (ФВКБ) редак је инфламаторни поремећај поткожног масног ткива. Ангиолипом је бенигни адипоцитни тумор меког ткива који се састоји од зрелог масног ткива и малих васкуларних пролиферација. Лечење кортикостероидима може да доведе до умножавања масног ткива, али је стимулација раста ангиолипома током терапије кортикостероидима изузетно ретка.

Приказ болесника Приказујемо болесницу стару 46 година која има хистолошку потврду две ретке болести: ФВКБ и доброћудне вишеструке неинфилтрирајуће ангиолипоме. Ангиолипоми су лечени конзервативно. ФВКБ је лечена преднизоном 20 *mg*/дан. Због лоше контроле ФВКБ и брзог раста ангиолипома на подлактици, кортикостероиди су прекинути после два месеца употребе. Примена оралног циклоспорина А довела је до брзе ремисије ФВКБ и није било новог пораста ангиолипома.

Закључак Успешна терапија циклоспорином А подржава хипотезу да је ФВКБ аутоинфламаторно стање посредовано Т-ћелијама. Убрзан раст ангиолипома током кортикостероидне терапије изузетно је ретко стање.

Кључне речи: преднизон; ангиолипом; нежељени ефекат; паникулитис

DOI: https://doi.org/10.2298/SARH221212008M
UDC: 618.3:616.379-008.64

CURRENT TOPIC / АКТУЕЛНА ТЕМА

Historical and statistical aspects of risk groups analysis and testing in the context of gestational diabetes mellitus

Maja Macura[1,2], Stefan Dugalić[1,2], Jovana Todorović[3], Bojana Gutić[4], Miloš Milinčić[2], Dragana Božić[1], Milica Stojiljković[2,5], Ivan Soldatović[6], Igor Pantić[7], Milan Perović[2,8], Biljana Parapid[2,9], Miroslava Gojnić[1,2]

[1]University Clinical Centre of Serbia, Clinic for Gynecology and Obstetrics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Institute of Social Medicine, Belgrade, Serbia;
[4]University of Novi Sad, Institute of Oncology of Vojvodina, Clinic for Operative Oncology; Novi Sad, Serbia;
[5]University Clinical Centre of Serbia, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia;
[6]University of Belgrade, Faculty of Medicine, Institute of Medical Statistics and Informatics, Belgrade, Serbia;
[7]University of Belgrade, Faculty of Medicine, Institute of Medical Physiology, Belgrade, Serbia;
[8]Narodni front University Clinic for Gynecology and Obstetrics, Belgrade, Serbia;
[9]University Clinical Centre of Serbia, Division of Cardiology, Belgrade, Serbia

SUMMARY
In order to enhance cost-benefit value of the gestational diabetes mellitus screening (GDM) the concept of universal screening i.e., screening of all pregnant women for gestational diabetes, has mostly been abandoned in favor of the concept of selective screening. Selective screening implies that only women with risk factors are being screened for GDM. However, some recent studies have shown that with the application of the selective screening approach, some women with GDM may not receive proper and timely diagnosis. This review addresses the pros and cons of both concepts. It will also discuss screening methods and methods of preparation and performance of oral glucose tolerance test and the interpretation of its results.
Keywords: gestational diabetes mellitus; universal screening; selective screening; oral glucose tolerance test

INTRODUCTION

In order to reduce the burden on the health system due to screening for gestational diabetes mellitus (GDM) for all pregnant women – universal screening, the concept of selective screening for GDM was developed. Selective screening, based on data from personal and family history, aims to identify a high-risk population for diabetes [1]. Some recent studies have shown the universal screening approach to be cost-effective [2]. In this review, we aim to present advantages and disadvantages of universal and selective screening for GDM.

Selective screening approach

The selective approach to screening is based on the definition of the evidence-based risk factors for the development of GDM. Age, race, and body mass index (BMI) were identified as risk factors associated with GDM, but also some other factors like polycystic ovarian syndrome [1, 3], but this association is not confirmed in all studies [4]. Adverse pregnancy outcomes (APOs) of previous pregnancies are associated with GDM and type 2 diabetes [5].

Previous studies have shown that when relying on the assessment for the GDM risk from the patient history half of the pregnant women with GDM do not provide data on the existence of the risk factors, while half of the healthy pregnant women have one or more risk factors [6].

When deciding on the recommendations for universal or selective GDM screening it is necessary to define the population that should be screened, the recommended screening methods and their timing, as well as the treatment modalities and the follow-up [7].

Adverse pregnancy outcomes

Although a systematic review of the existing studies has shown the association of the GDM according to the criteria from the World Health Organization (WHO) and according to the International Association for Diabetes in Pregnancy Study Group (IADPSG) criteria with APOs, the value of glycemia that has significant implications for pregnancy is still to be defined [8]. Preexisting diabetes is associated with the risk of having a child with congenital anomalies, and the risk is related to

Received • Примљено: December 12, 2022
Accepted • Прихваћено: January 12, 2023
Online first: January 20, 2023

Correspondence to:
Jovana TODOROVIĆ
University of Belgrade
Faculty of Medicine
Institute of Social Medicine
Dr. Subotica 15
11000 Belgrade
Serbia
jovana.todorovic@med.bg.ac.rs

hyperglycemia during embryogenesis [8]. GDM does not carry an increased risk for congenital anomalies of the fetus [9]. Pregnancy complicated by diabetes carries the risk of fetal growth disorders, birth complications, and perinatal asphyxia.

The effects of the timely treatment on the APOs also remain undefined, and although it was shown that the treatment of GDM reduces the likelihood of macrosomia, preeclampsia, and shoulder dystocia, the effects of the GDM treatment on metabolic abnormalities in newborns and APOs is still to be examined further [10].

Methods of screening and diagnosing

Oral glucose tolerance tests are cumbersome to perform, and their reproducibility is low. The determination of only glycosylated hemoglobin and fructosamine cannot identify a lesser degree of glycoregulation disorders in type 2 diabetes and GDM [11]. The study that examined the cost-effectiveness of the universal GDM screening using the IADPSG showed that, although this screening is more costly, it may be cost-effective under certain conditions [12]. More recent systematic review showed that although treatment of GDM is cost-effective, universal screening does not seem to be [13].

When deciding on the implementation of a screening program, its potential flaws, i.e., side effects, must be evaluated. One of the disadvantages of GDM screening is that pregnant women with GDM are more likely to have cesarean deliveries, even with eutrophic children [14]. This could imply that the GDM diagnosis in the pregnant women can motivate obstetricians towards easier decision-making about caesarean section [15]. The higher frequency of operative delivery in GDM, with normal newborns' weight, may also be a consequence of perinatal asphyxia.

In a population where the prevalence of type 2 diabetes and GDM is high, the number of women at low risk is small. Selective screening reduces the number of tested persons by 34.6%, without reducing GDM detection rates [16]. That is why the American Diabetes Association (ADA) changed its original position of promoting universal screening, to the current position of selective GDM screening based on risk factors [1, 3]. ADA guidelines mandate screening of high-risk populations at the first prenatal visit (pronounced obesity, if she had GDM in one of the previous pregnancies, glycosuria in pregnancy, or type 2 diabetes in the family history). Low risk is determined by age under 25 years, belonging to ethnic and racial groups with a low prevalence of diabetes, a negative history of diabetes in the immediate family, normal weight gain in the current pregnancy and an unencumbered obstetric history. If she does not meet the stated criteria of one of the two mentioned groups, the patient is classified in the group of women with a moderate risk of developing GDM. Women at high risk should be tested as soon as possible. If the initial test is negative, it should be repeated between the 24th to the 28th week of pregnancy. There are two approaches to the diagnosis of GDM in high-risk individuals, the so-called "one step approach" and "two step approach." The first one uses only one "step" in establishing the diagnosis- an oral glucose tolerance test (OGTT). The second one has two "steps." The first step is screening with an oral glucose challenge test (GCT) with 50 g of glucose, and in case of poor values, (glucose after one hour of more than 11mmol/l), a definitive, diagnostic OGTT is performed.

It was shown that screening based on risk factors will reduce the number of women tested but will result in an increase in the number of pregnant women with the missed GDM diagnosis [17]. This is in contrast to the findings of the study by Naylor et al, who did not register a reduction in GDM detection rates. Variations in the prevalence of GDM and risk factors in different populations will lead to variations in the implications of selective screening in different epidemiological settings [18]. Therefore, decisions on acceptable screening detection rates and false negative values will remain in the domain of national organizations. In a retrospective study comparing universal and selective screening (based on high risk using ADA criteria), 18,000 patients were examined [19]. If only high-risk patients were screened, 3% of women would remain with undiagnosed GDM. In this population, only 10% of women were in the low-risk category and for them screening would be waived. Failure to properly apply algorithms in a high-risk population is likely to result in a relatively large number of undiagnosed cases compared to unconfirmed cases in a low-risk population [20].

We still do not have the results from the randomized controlled trials (RCTs) that the higher detection rates of GDM lead to lower prevalence of APOs [21]. The most common GDM screening method involves an oral GCT with 50 g of glucose, the so-called O'Sullivan's test or GCT, which was promoted by O'Sullivan and Mahan [22]. It involves the oral consumption of a solution containing 50 g of glucose, regardless of the time of the previous meal. One hour later, glycemia is determined. The most common cut-off value is 7.77 mmol/l (140 mg/dl), which is usually around 15% of positive test results [23]. By reducing this value to 7.22 mmol/l (130 mg/dl), the sensitivity of the test is significantly improved [21].

GCT shows sensitivity of 80% and specificity of 90%. This means that as many as 20% of patients undergoing GCT remain undiagnosed [24, 25]. GCT has been criticized as poorly repeatable, unpleasant, impractical to perform, relatively expensive and time-consuming [26], with low specificity [27].

Pregnant women with a positive screening for GDM require the use of a diagnostic test, which is an oral glucose load test (with 75 or 100 g) – OGTT. Currently, the two-step approach is recommended by the ADA and American College of Obstetricians (ACOG) with the ADA recommending Carpenter Coustan or IADPSG criteria for diagnosis of GDM, while ACOG recommends the Carpenter Coustan or National diabetes data group criteria. IADPSG, WHO and International Federation of Gynecology and Obstetrics recommend the one-step approach [21].

Criteria for diagnosis

The different criteria define different values for the assessment of the positive test and for the establishment of the GDM diagnosis [21]. Studies have shown that if even one value is increased, the risk of macrosomic growth of the fetus and the complications that accompany it is increased [28, 29].

Glycoregulation is strongly influenced by placental hormones, so special changes are expected in twin pregnancy. In these pregnant women, a significant difference was found in fasting glycemia values. The frequency of GDM in twin pregnancies is higher.

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

CONCLUSION

Selective, unlike universal screening for GDM aims to identify a high-risk population for diabetes. In a population where the prevalence of type 2 diabetes and GDM is high, the number of women at low risk is small, so universal screening is more effective. Decisions on acceptable screening should remain in the domain of national organizations, which will adapt the decision to the characteristics of the population. The most common GDM screening method involves an oral GCT with 50 g of glucose.

Conflict of interest: None declared.

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Историјски и статистички аспект анализе ризичних група и тестирања у контексту гестацијског дијабетеса мелитуса

Маја Мацура[1,2], Стефан Дугалић[1,2], Јована Тодоровић[3], Бојана Гутић[4], Милош Милинчић[2], Драгана Божић[1], Милица Стојиљковић[2,5], Иван Солдатовић[6], Игор Пантић[7], Милан Перовић[2,8], Биљана Парапид[2,9], Мирослава Гојнић[1,2]

[1]Универзитетски клинички центар Србије, Клиника за гинекологију и акушерство, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Институт за социјалну медицину, Београд, Србија;
[4]Универзитет у Новом Саду, Клиника за оперативну онкологију, Институт за онкологију Војводине, Нови Сад, Србија;
[5]Универзитетски клинички центар Србије, Клиника за ендокринологију, дијабетес и болести метаболизма, Београд, Србија;
[6]Универзитет у Београду, Медицински факултет, Институт за медицинску статистику и информатику, Београд, Србија;
[7]Универзитет у Београду, Медицински факултет, Институт за медицинску физиологију, Београд, Србија;
[8]Универзитетска клиника за гинекологију и акушерство „Народни фронт", Београд, Србија;
[9]Универзитетски клинички центар Србије, Клиника за кардиологију, Београд, Србија

САЖЕТАК

У циљу повећања исплативости скрининга гестацијског дијабетеса мелитуса, концепт универзалног скрининга, односно скрининга свих трудница на гестацијски дијабетес, углавном је напуштен у корист концепта селективног скрининга. Селективни скрининг подразумева да само жене са факторима ризика за гестацијски дијабетес мелитус подлежу процесу скрининга. Ипак, неке скорашње студије су показале да ако се примени селективни приступ скринингу, одређени проценат жена са гестацијским дијабетесом мелитусом не добије дијагнозу или је не добије правовремено. Овај прегледни рад се бави предностима и недостацима и једног и другог концепта. Методе скрининга и методе припреме и извођења оралног теста толеранције на глукозу, као и интерпретација његових резултата биће детаљније објашњени.

Кључне речи: гестацијски дијабетес мелитус; универзални скрининг; селективни скрининг; орални тест толеранције на глукозу

DOI: https://doi.org/10.2298/SARH221128027G
UDC: 614.21(497.113)"19"; 929:61 Шосбергер А.

HISTORY OF MEDICINE / ИСТОРИЈА МЕДИЦИНЕ

Др Александар Шосбергер – први управник градске болнице у Новом Саду

Зоран Гојковић[1,2], Едита Стокић[1,3], Миа Манојловић[1,3]

[1]Универзитет у Новом Саду, Медицински факултет Нови Сад, Нови Сад, Србија;
[2]Клинички центар Војводине, Клиника за ортопедску хирургију и трауматологију, Нови Сад, Србија;
[3]Клинички центар Војводине, Клиника за ендокринологију, дијабетес и болести метаболизма, Нови Сад, Србија

САЖЕТАК
Први директор Градске болнице у Новом Саду, која је временом прерасла у савремени Клинички центар Војводине, био је др Александар-Шандор Шосбергер, рођен у Новом Саду, 13. септембра 1873. године. Медицински факултет је завршио у Будимпешти, а потом се усавршавао у болницама бројних европских градова. Жеља за учењем и даљим усавршавањем одвела га је на специјализацију из области гинекологије и акушерства, те постаје први специјалиста гинеколог-акушер у Војводини. Почетком 20. века, са наглим повећањем броја становника Новог Сада, постојеће болнице нису биле довољне за хоспитализацију болесника, те је Магистрат града априла 1907. године донео одлуку да се подигне нова Градска болница, чија је изградња завршена 1909. године, а тада подигнути објекти су јединице у којима су и данас смештене неке клинике Клиничког центра Војводине. Била је организована тако да је имала Интерно, Хируршко, Дерматовенеролошко и Гинеколошко-породајно одељење, са постељним фондом од око 300 кревета. Захваљујући свестраном образовању, искуству, високој стручности, интелигенцији и организационим способностима, др Александар Шосбергер је именован за првог управника новоизграђене Градске болнице. Први је у Градској болници применио Васерманову (*Wassermann*) реакцију, те набавио први рендгенски апарат у Новом Саду, за своју приватну ординацију. Као први специјалиста гинеколог-акушер у Војводини, велики допринос је дао увођењу и унапређењу хируршких техника. Др Александар Шосбергер показао је да се преданим професионалним радом и одговорношћу могу постићи велики резултати и унапређење области здравства, о чему говори чињеница да је Градска болница, временом, прерасла у терцијарну здравствену установу Клинички центар Војводине.
Кључне речи: историја медицине; др Александар Шосбергер; Градска болница; Нови Сад

УВОД

Настајањем и развојем Новог Сада многи народи су се доселили и ту нашли свој дом. Доносили су нова знања и искуства и тиме убрзавали и унапређивали развој града. Међу њима је било доста Јевреја, који су, доселивши се ту, схватили да су нашли кућу и дом. Међу таквима је била и породица Шосбергер, која се доселила из Моравске Словачке средином XVIII века. Један изданак те породице, Александар-Шандор Шосбергер, син лекара Георга, а и сам лекар, прихватио је да, као први управник Градске болнице у Новом Саду, организује рад у њој и унапреди здравствену службу овога града [1]. Градска болница је временом прерасла у Клинички центар Војводине.

Слика 1. Др Александар Шосбергер (1873–1944); извор: лична колекција Јосипа Шосбергера
Figure 1. Dr. Aleksandar Šosberger (1873–1944); source: personal collection of Josip Šosberger

БИОГРАФИЈА: ОБРАЗОВАЊЕ И СТРУЧНО УСАВРШАВАЊЕ

Др Александар-Шандор Шосбергер рођен је у Новом Саду, 13. септембра 1873. године, као потомак старе новосадске јеврејске породице. Шосбергери су дошли у Нови Сад из Сашвара-Шлосберга (данас Шаштинске Страже) у Моравској, у округу Нитра, данас Република Словачка. Јеврејску основну школу и гимназију завршио је у Новом Саду 1888. године, а након тога је уписао Медицински факултет у Будимпешти, на којем је дипломирао 1894. године [2, 3] (Слика 1).

Received • Примљено: November 28, 2022
Revised • Ревизија: February 5, 2023
Accepted • Прихваћено: February 11, 2023
Online first: March 7, 2023

Correspondence to:
Zoran GOJKOVIĆ
Clinical Center of Vojvodina
Clinic for Orthopedic Surgery and Traumatology
Hajduk Veljkova 1–9
21000 Novi Sad
Serbia
zoran.gojkovic@mf.uns.ac.rs

Слика 2. Детаљ уличне фасаде некадашње Управне зграде Градске болнице у Новом Саду; извор: лична колекција проф. др Дејана Иванова
Figure 2. Detail of the street facade of the former Administrative Building of the Novi Sad City Hospital; source: personal collection of Prof. Dejan Ivanov, M.D.

Средином 19. века немачки универзитети су развијали нове научне приступе у истраживању и клиничкој пракси. Др Александар Шосбергер је након завршеног факултета, са жељом даљег усавршавања, едукацију наставио у Берлину, Јени, Минхену и Хајделбергу. Имао је прилику да ради у тадашњим водећим медицинским центрима, што је подразумевало и учење медицинских доктрина од чувених лекара као што су Хохенег (*Julius Hochenegg*), Шаута (*Friedrich Schauta*), Вертхајм (*Ernst Wertheim*) и други [2, 4].

Радио је у Босанској Градишки као градски лекар, о чему сведоче именици чланова Сбора лиечника Краљевине Хрватске и Славоније издати 1895, 1896. и 1897. године [5].

Након тога, др Александар-Шандор Шосбергер се вратио у Нови Сад, који је толико волео, где је, са много амбиције, радио као лекар практичар. Био је познат и врло угледан лекар, подржаван од стране градских власти. Радио је и као лекар у Новосадском друштву за помоћ плућним болесницима, лекар социјалног осигурања, спортски лекар, лекар у Црвеном крсту, железници и пошти, као и судски вештак [2, 6].

Жеља за учењем и даљим усавршавањем одвела га је на усавршавање из области гинекологије и акушерства, те постаје први специјалиста гинеколог-акушер у Војводини [6]. Напоран рад и добро познавање клиничке праксе донело му је сигурне и довољне материјалне приходе. Био је ожењен Олгом рођ. Опенхајмер (*Oppenheimer*, 1874–1944) са којом је био у браку до краја живота. Нису имали деце, живели су повучено, без учешћа у друштвеном животу тадашњег Новог Сада. Поседовали су двоспратну кућу са великим, пространим и лепо уређеним станом у тадашњој Јеврејској улици број 11 (данас Позоришни трг у Новом Саду). Интересантно је истаћи да је Шосбергер, поред велике библиотеке, имао вредну колекцију уметничких слика. Познаваоцима аутомобилизма у Новом Саду добро је познато да је међу првима купио аутомобил. То је за Нови Сад била велика новина и посебна атракција [7]. Познато је да је рендгенске зраке (*X*-зраци) 8. новембра 1895. године открио немачки физичар Вилхелм Конрад Рендген. Имајући визију потребног унапређења дијагностике, др Александар Шосбергер је набавио први рендгенски апарат у Новом Саду, за своју приватну ординацију, 1905. године. Апарат за потребе Градске болнице у Новом Саду набавио је 1912. године. Ова опрема омогућавала је да се прегледи изводе само као скопије у мраку [8, 9, 10].

ПРВИ УПРАВНИК ГРАДСКЕ БОЛНИЦЕ У НОВОМ САДУ

Почетком 20. века, са наглим повећањем броја становника Новог Сада, постојеће болнице нису биле довољне за хоспитализацију болесника, те је, априла 1907. године, од стране Магистрата града донета одлука да се подигне нова Градска болница [11].

Њена изградња је завршена 1909. године, а тада подигнути објекти су јединице у којима су и данас смештене неке клинике, организационе јединице Клиничког центра Војводине. Градска болница сагрђена је као комплекс павиљона [7, 12, 13].

Аутор пројекта Градске болнице је будимпештански архитекта Ђерђ Копечек (*Gyorgy Kopeczek*, 1864–1920), а за извођење радова били су ангажовани новосадски градитељи Вилмош Линарић (*Vilmos Linarich*) и Бела Пекло (*Peklo Bela*, 1867–1960). Главна зграда (Павиљон

1), у којој су били смештени Управа, Пријемно одељење и Администрација, имала је сутерен, високо приземље и спрат. Уличну фасаду су красиле фигуре, израђене у техници мозаика, и између њих је година завршетка изградње: 1909 [12, 14, 15] (Слика 2). Болница је имала Интерно, Хируршко, Дерматовенеролошко и Гинеколошко-порођајно одељење, са укупним постељним фондом од око 300 кревета [11, 15]. Павиљон 2 обухватао је Одељење гинекологије и Одељење хирургије, док је у Павиљону 3 било смештено Одељење за унутрашње болести у оквиру ког су хоспитализовани болесници са заразним болестима и болестима нервног система, али и болесници са кожним и венеричним болестима. Поред споменутих одељења, болница је имала и Порођајно одељење, које је у периоду од 1909. до 1914. године било смештено у главној згради болнице, са постељним капацитетом од 20 кревета. Године 1912. изграђена је и зграда у којој је касније смештена болничка апотека, као и зграда за Антитрахомно одељење, које је имало капацитет од 96 постеља [12, 16, 17].

Као еминентан и поштован лекар, др Александар Шосбергер је именован, од стране градске управе, за првог управника новоизграђене Градске болнице. Истовремено, био је први шеф Гинеколошко-порођајног и Дерматовенеролошког одељења [2, 6, 18, 19].

Др Александар Шосбергер био је лекар великих способности и огромне енергије. Пратио је, за то време, модерне методе дијагностике и лечења, примењиване у другим земљама [2, 19]. У то време је сифилис, као хронично заразно обољење, представљао значајан медицински и социјално-економски проблем. Др Александар Шосбергер, као шеф Дерматовенеролошког одељења, први је у Градској болници применио Васерманову реакцију, тј. тест антитела на сифилис, назван по бактериологу Васерману (*August Paul von Wassermann*), заснован на фиксацији комплемента [20]. Захваљујући томе, у Градској болници је било могуће рано дијагностиковати и правовремено започети лечење тог обољења, како би се спречила његова прогресија [6].

Као први специјалиста гинеколог-акушер у Војводини, априла 1910. године у Градској болници, др Александар Шосбергер је извршио први царски рез у Новом Саду, а у односу на оперативну гинекологију, пратећи радове познатих гинеколога онога времена, новембра 1912. начинио је и прву абдоминалну хистеректомију у сарадњи са тадашњим главним хирургом болнице др Нандором Брезовским [6, 12, 17]. Интересовање према оперативној гинекологији потекло је још током његовог усавршавања након дипломирања, када је имао прилику да се упозна са радовима Ернста Вертхајма (*Ernst Wertheim*), који је још 1898. развио методу радикалне тоталне хистеректомије са уклањањем лимфних чворова и параметрија. Вертхајм је 1911. објавио резултате и искуства спроведених првих 500 операција (*Die erweiterte abdominale Operation bei Carcinoma colli uteri: auf Grund von 500 / Проширена абдоминална операција код карцинома грлића материце: на основу 500 случајева*) [21]. Године 1912. др Александар Шосбергер изводи ову операцију у Градској болници, те се сматра зачетником гинекологије у Војводини [6, 17, 18, 22].

Своја искуства у гинеколошкој пракси приказао је објављивањем рада у медицинским часописима, указујући на значај превенције и лечења пуерпералне сепсе, значајног фактора за повећан морталитет породиља [13]. Наиме, у то време, пре увођења антибиотика у медицинску праксу, пуерперална сепса је имала много већу преваленцију. Рад под насловом „*Die Serumprophylaxe der Geburt*“ („Серумска профилакса порођаја“) објављен је два пута, у часопису Минхенски медицински недељник (*Münchener Medizinische Wochenschrift*, 1931), као и у Централном часопису за гинекологију (*Zentralblatt für Gynäkologie,* 1931) [6].

После завршетка Првог светског рата и ослобађања земље, почетком 1919. године, др Шосбергер се повлачи из државне службе, те остаје само приватни лекар. У својој породичној кући, на првом спрату, 1920. године је основао приватни Санаторијум за хирургију и гинекологију, са операционом салом и осам кревета [18, 19].

ДРУГИ СВЕТСКИ РАТ – ТЕШКЕ ГОДИНЕ

Окупација града (1941–1944. године) доводи до протеривања, заробљавања и забране рада многим лекарима, па и гинеколозима-акушерима, што је отежало пружање здравствене заштите у то време [13].

Дана 19. априла 1941. године, Јеврејима у Новом Саду је од стране мађарске окупационе власти била наметнута тзв. контрибуција од пет милиона пенга. Овај износ од педесет милиона динара сакупљен је од стране свих припадника Јеврејске општине у Новом Саду. Међутим, 24. маја 1941. године, сви мушкарци Јевреји, старости од 18 до 60 година, подвргнути су обавезном присилном раду. Иако је био врло угледан човек и резервни аустроугарски санитетски официр у већ поодмаклим годинама, а такође и носилац бројних аустроугарских одликовања, Шосбергер је доживео да буде одведен на принудни рад. Прва група састојала се од преко 400 људи, а у њој је био и Александар Шосбергер (према речима Јосипа Шосбергера, који је информације добио од свог оца Павла Шосбергера). Од ове групе сачињене су радне јединице које су првобитно биле задужене за рад у бази речне флотиле, који је подразумевао чишћење рушевина, а по завршетку тог посла група је обављала сличне радове на аеродрому, обављајући тако 10–12 часова дневно, а некада и дуже, тежак физички посао. Поред исцрпљујућег посла, радници су били принуђени да се суочавају, без икаквог разлога, и са нељудским и страховитим казнама, при чему су их подофицири тукли, а неретко су морали по два сата висити обешени за руке. Доктор Шосбергер је после неколико недеља ослобођен захваљујући залагању утицајних сугрђана Мађара, након чега се повукао у свој дом. Министарство унутрашњих послова Мађарске донело је наредбу да се 7. априла

1944. године интернирају сви за окупатора „опасни“ и угледни Јевреји. У целој Бачкој, током ноћи између 25. и 26. априла 1944, излепљени су плакати са наредбом којом је Јеврејима забрањено да излазе из својих домова, а хапшење Јевреја започето је 26. априла у раним јутарњим часовима и трајало је неколико дана. Хапшење су вршиле полиција и жандармерија, као и војска, фолксдојчери и немачке безбедносне снаге, док су им неки од становника помагали [2, 19, 23, 24].

Како би избегао понижење, 26. априла 1944. године др Александар Шосбергер је убризгао смртоносну дозу морфијума својој супрузи Олги и себи, у свом стану, пре одвођења. Сахрана је обављена на новосадском Јеврејском гробљу, у породичној гробници Опенхајмер (парцела II – 106) [2, 6, 19].

ЗАКЉУЧАК

У овом раду приказан је животни пут др Александра Шосбергера, као и део његовог стручног рада у Градској болници, која је, иако првобитно скромних капацитета, после скоро више од једног века прерасла у терцијарну здравствену установу, Клинички центар Војводине. Др Александар Шосбергер је, као први гинеколог-акушер у Војводини, начинио први царски рез и абдоминалну хистеректомију у Новом Саду, а не треба занемарити ни чињеницу да је први увео Васерманову реакцију, која је била од великог значаја за дијагностику болести оног времена.

Изјава о сукобу интереса: Аутори изјављују да не постоји сукоб интереса.

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Dr. Aleksandar Šosberger – the first director of the Novi Sad City Hospital

Zoran Gojković[1,2], Edita Stokić[1,3], Mia Manojlović[1,3]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Clinical Center of Vojvodina, Clinic for Orthopedic Surgery and Traumatology, Novi Sad, Serbia;
[3]Clinical Center of Vojvodina, Clinic for Endocrinology, Diabetes and Metabolic Disorders, Novi Sad, Serbia

SUMMARY

The first director of the Novi Sad City Hospital, which eventually grew into the modern Clinical Center of Vojvodina, was Dr. Aleksandar-Šandor Šosberger, born in Novi Sad on September 13, 1873. He graduated at the Faculty of Medicine in Budapest, and then trained in hospitals in numerous European cities. The desire to learn and further hone his training led him to specialize in the field of gynecology and obstetrics – thus, he became the first gynecologist-obstetrician specialist in Vojvodina.

At the beginning of the 20th century, with the sudden increase in the number of inhabitants of Novi Sad, the existing hospital facilities were insufficient for the hospitalization of the patients; thus, the City Magistrate made a decision in April of 1907 to build a new city hospital, the construction of which was completed in 1909, and the facilities built at that time are units in which some clinics of the Clinical Center of Vojvodina are still located today. It was organized in such a way that it had Internal Medicine, Surgical, Dermatology-Venereology, and Gynecology-Obstetrics departments, with the bed capacity of about 300. With his comprehensive education, experience, high expertise, intelligence, and organizational skills recognized, Dr. Aleksandar Šosberger was appointed as the first manager of the newly built City Hospital. He was the first in the City Hospital to apply the Wasserman reaction, and he obtained the first X-ray machine in Novi Sad, for his private practice. As the first gynecologist-obstetrician specialist in Vojvodina, he made a great contribution to the introduction and improvement of surgical techniques. Dr. Aleksandar Šosberger showed that with dedicated professional work and responsibility, great results, and improvements in the field of healthcare can be achieved, as evidenced by the fact that the City Hospital, over time, grew into a tertiary healthcare institution, the Clinical Center of Vojvodina.

Keywords: history of medicine; Dr. Aleksandar Šosberger; City hospital; Novi Sad

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 СА се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се 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 објављен 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.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

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Ул. краљице Наталије 1
11000 Београд
Србија

Телефони: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Интернет адреса: *http://www.srpskiarhiv.rs*

ISSN 0370-8179
ISSN Online 2406-0895
OPEN ACCESS

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ISSN 0370-8179
ISSN Online 2406-0895
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61(497.11)

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