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GENITAL WARTS IN WOMEN – 12-YEAR INCIDENCE RATE TRENDS IN NOVI SAD

GENITALNE BRADAVICE KOD ŽENA:
DVANAESTOGODIŠNJI TREND STOPE INCIDENCIJE U NOVOM SADU

Mirjana ŠTRBAC[1], Nataša NIKOLIĆ[1, 2], Veselin BOJAT[3], Nina SMILJANIĆ[3], Vladimir PETROVIĆ[1, 2] and Mioljub RISTIĆ[1, 2]

Summary

Introduction. Data on the incidence and age distribution of women with genital warts in Serbia are limited. The aim of this study was to determine the epidemiological characteristics of genital warts in the female population aged 15 - 69 years in Novi Sad. **Material and Methods.** A descriptive epidemiological study was conducted using the data of the Primary Health Care Center "Novi Sad". The study data refer to women examined by primary care gynecologists during a 12-year period (2010 - 2021). **Results.** During the observed period, 654 out of 240,494 examined women aged 15 - 69 years, i.e. 609 out of 164,578 women aged 15 - 49 years, had newly diagnosed genital warts. The cumulative overall incidence rate of genital warts in women aged 15 - 69 was 2.7/1,000 (95% confidence interval 2.64 - 2.77), while in women aged 15 - 49 it was 3.7/1,000 (95% confidence interval 3.61 - 3.79). The trend in genital warts incidence in both observed age groups was stable. The highest annual incidence rate of genital warts was registered among women aged 15 - 19 years, and it was statistically significantly ($p < 0.0001$) higher than in all the other age groups. The annual estimated number of women with newly diagnosed genital warts in Novi Sad was 547, of which 187 (34.2%) were women aged 15 - 19 years. **Conclusion.** Our results provide essential epidemiological data that may be used as the basis for future population studies, as well as for the evaluation of the effectiveness of the human papillomavirus vaccination campaign, after its wide implementation in the vulnerable population.

Key words: Condylomata Acuminata; Women; Incidence; Papillomavirus Vaccines; Epidemiology; Diagnosis; Serbia

Sažetak

Uvod. Nema dovoljno podataka o učestalosti i uzrasnoj distribuciji genitalnih bradavica kod žena u Srbiji. Cilj ove studije bio je da se odrede epidemiološke karakteristike genitalnih bradavica u populaciji žena Novog Sada uzrasta 15–69 godina. **Materijal i metode**. Sprovedena je deskriptivna epidemiološka studija upotrebom podataka iz primarnog nivoa zdravstvene zaštite Doma zdravlja Novi Sad. Podaci studije se odnose na žene koje je pregledao ginekolog primarnog nivoa zdravstvene zaštite tokom dvanaestogodišnjeg perioda (od 2010. do 2021. godine). **Rezultati**. Tokom posmatranog perioda, 654 žene od ukupno 240.494 pregledanih, uzrasta 15–69 godina, odnosno 609 žena od pregledanih 164.578 uzrasta 15–49 je imalo novootkrivenu dijagnozu genitalnih bradavica. Kumulativna opšta stopa incidencije genitalnih bradavica za žene uzrasta 15–69 godina bila je 2,7/1000 (95% CI 2,64–2,77), dok je za žene uzrasta 15–49 godina bila 3,7/1000 (95% CI 3,61–3,79). Trend incidencije genitalnih bradavica u posmatranom periodu u obe uzrasne grupe bio je stabilan. Najviša godišnja stopa incidencije genitalnih bradavica je registrovana u uzrastu 15–19 godina i ona je bila statistički značajno ($p < 0,0001$) viša u odnosu na incidencije u svim ostalim posmatranim uzrastima. Godišnji procenjen broj novootkrivenih dijagnoza genitalnih bradavica kod žena u Novom Sadu bio je 547, a 187 (34,2%) žena je bilo uzrasta 15–19 godina. **Zaključak**. Naši rezultati daju bazične epidemiološke podatke koji se mogu koristiti kao polazište za buduća istraživanja u populaciji, kao i za procenu efikasnosti kampanje vakcinacije protiv humanog papiloma virusa, nakon njene široke primene u osetljivim grupama.

Ključne reči: genitalne bradavice; žene; incidenca; HPV vakcina; epidemiologija; dijagnoza; Srbija

Introduction

Genital warts (GWs) are the most common genital infection caused by human papillomavirus (HPV). They are one of the most common sexually transmitted viral infections worldwide, presenting as single or multiple papules on the vulva, perianal area, vagina, cervix, penis, anus, scrotum and urethra [1–3].

The prevalence of HPV infection has been steadily increasing, with an estimated 20 million people in the United States (US) being infected with the virus [2, 3]. The GWs affect both males and females,

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Abbreviations

GW – genital wart
HPV – human papillomavirus
US – United States
PHCC – Primary Health Care Center
CI – confidence interval
UK – United Kingdom

with an estimated 6.2 million new cases annually among subjects aged 14 - 44 years [4]. More than 150 HPV types have been identified, of which approximately 40 cause infections in the genital area [5, 6].

Genital HPV types are categorized according to their epidemiological association with cervical cancer. High-risk types have the potential to act as carcinogens. Types 6 and 11 can cause benign or low-grade cervical cell changes, as well as GWs, and recurrent respiratory papillomatosis [7].

Approximately 90% of all cases of GWs are caused by HPV-6 and HPV-11 types that rarely progress to cancerous lesions, whereas warts associated with HPV-16 and HPV-18 may be predisposed to oncogenic transformation [8]. The GWs caused by HPV types 6 and 11, although not fatal, require diagnosis and treatment, otherwise they may lead to a significant impairment of the quality of life [9].

So far, two vaccines have been licensed against low-oncogenic HPV types (6 and 11) [10]. According to the experiences to date, in countries where vaccination has previously been implemented, the quadrivalent vaccine has shown a significant decrease in the incidence of GWs [11].

Considering the fact that diagnosis of GWs is not subject to mandatory notification in our country [12], the estimation of their incidence and distribution can be made only based on results of specific epidemiological studies. In Vojvodina, Serbia, women with GWs are usually diagnosed and treated by gynecologists or dermatovenereologists.

According to the analysis of a representative sample in the US, approximately one in 100 sexually active adults has GWs [13]. Based on the estimate that 1% of the sexually active population aged 15 - 59 years has GWs at least once in a lifetime, and given that population of this age group in Novi Sad accounts for about 220,000 people, it may be assumed that at least 2,000 – 2,200 citizens are facing with GWs in Novi Sad.

The aim of this study was to evaluate the crude and age-specific incidence of GWs, as well as to estimate the annual number of newly diagnosed GWs in the female population of Novi Sad.

Material and Methods

We conducted a retrospective observational study covering 12 consecutive years (2010 - 2021). Six gynecologists examined a population of 25,000 women aged ≥ 15 years (corresponding to 6% of the total female population of this age in Novi Sad). Gynecologists were selected based on the number of contracts/reviews they performed annually at the Primary Health Care Center (PHCC) of Novi Sad. The data for this study were obtained from the electronic database of the PHCC, i.e. from the Gynecology Department of the PHCC in Novi Sad.

The diagnosis of GWs is based on visual inspection and no laboratory tests are required. The GWs are defined as warts in or around the genital area which include the external genitalia, perineum, and perianal region. The new case of GWs was defined as a case in a person who reported never having GWs before. The participants with recurrent episodes of GWs were excluded from the study.

The patients with the diagnosis of GWs were divided by predetermined age groups during the period from 2010 to 2021. Basic statistical indicators, general (crude) and specific incidence rates were examined. Incidence rates and 95% confidence intervals (CI) were calculated using the annual number of newly diagnosed cases of GWs in women (numerator) and the number of women visiting any of the included gynecologists annually in the study period in Novi Sad according to the Census in the Republic of Serbia (2011) (denominator) and multiplied by 100,000 women per year. The estimated number of women with GWs in Novi Sad was extrapolated from the obtained prevalence rates by age groups and the estimated population of Novi Sad according to the 2011 Census. Two tailed p-values less than 0.05 were considered statistically significant.

The personal data of the included women were not used during the analysis. Only registration forms of patients were used, and no clearance by an Ethics Committee for retrospective analysis of anonymized data is required in Serbia.

Results

During a 12-year period, 654 out of 240,494 examined women aged 15 - 69 years, i.e. 609 out of 164,578 women aged 15 - 49 years, had newly diagnosed GWs. The number of women who visited any of the six community gynecologists included in the study has significantly increased from 2010 (11,300) to 2021 (25,488) (**Table 1**).

Table 1 summarizes the crude annual incidence rate of GWs divided into two age groups during the entire study period. Namely, the cumulative crude incidence rate of GWs in the group aged 15 - 69 years was 2.7/1,000 (95% CI 2.64 - 2.77), while the age-specific incidence in the group aged 15 - 49 years was 3.7/1,000 (95% CI 3.61 - 3.79). The trend in GWs incidence during the 12-year period in both observed groups was stable.

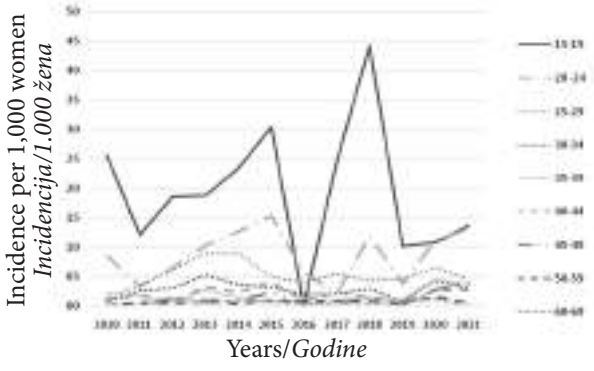
In regard to the examined age groups, the highest annual incidence rate of GWs was registered among women aged 15 - 19 years. In this age group, the incidence rates in 2015 and 2018 were 30.4/1,000 and 44.2/1,000 women, respectively, and they exceeded the incidence rates in other age groups during the study period (**Graph 1**).

The 12-year incidence rate (18.6/1,000, 95% CI 17.55 - 19.69) of GWs in women aged 15 - 19 years

Table 1. Crude incidence rates of genital warts in two observed age groups in Novi Sad, 2010 - 2021
Tabela 1*. Opšte stope incidencije genitalnih bradavica u dve posmatrane uzrasne grupe u Novom Sadu, 2010 – 2021*

Years/*Godine*	Age group/*Uzrasna grupa*					
	All ages (15 - 69)/*Sva godišta (15-69)*			Women aged 15 - 49 years/*Žene od 15 do 49 godina*		
	No of observed women/ *Broj pregledanih žena*	No of diagnosed cases of genital warts/ *Broj dijagnoza za genitalnih bradavica*	Incidence rate per 1,000 women (95% confidence interval)/ *Stopa incidencije /1.000 žena (95% granica poverenja)*	No of examined women/ *Broj pregledanih žena*	No of diagnosed cases of genital warts/ *Broj dijagnoza genitalnih bradavica*	Incidence rate per 1,000 women (95% confidence interval)/ *Stopa incidencije /1.000 žena (95% granica poverenja)*
2010	11,300	41	3.6 (3.26-3.96)	8,704	41	4.7 (4.26-5.17)
2011	13,471	31	2.3 (2.05-2.57)	10,039	30	3.0 (2.68-3.35)
2012	15,841	47	3.0 (2.74-3.28)	11,465	43	3.7 (3.36-4.06)
2013	19,153	78	4.1 (3.82-4.39)	13,427	75	5.6 (5.22-6.00)
2014	21,203	75	3.5 (3.26-3.76)	14,515	71	4.9 (4.55-5.26)
2015	22,374	73	3.3 (3.07-3.54)	15,009	67	4.5 (4.17-4.84)
2016	22,800	37	1.6 (1.44-1.77)	14,967	33	2.2 (1.97-2.45)
2017	22,829	36	1.6 (1.44-1.77)	14,619	33	2.3 (2.06-2.56)
2018	22,063	44	2.0 (1.82-2.19)	13,576	40	2.9 (2.62-3.20)
2019	22,508	24	1.1 (0.97-1.24)	13,758	18	1.3 (1.12-1.50)
2020	21,464	85	4.0 (3.74-4.27)	15,897	77	4.8 (4.47-5.14)
2021	25,488	83	3.3 (3.08-3.53)	18,602	81	4.4 (4.11-4.70)
Total/*Ukupno*	240,494	654	2.8 (2.64-2.77)	164,578	609	3.7 (3.61-3.79)

was significantly ($p < 0.0001$) higher than in all the other age groups (range 0.5 and 9.3/1000 women). There was no statistically significant ($p = 0.4708$) difference in the incidence rate between the cohorts of women aged between 15 and 19 years (20.2 95% CI 14.84 - 26.47; 21.5 95% CI 17.85 - 25.51; 23.6 95% CI 20.84 - 26.53; 20.1 95% CI 18.13 - 22.19; 14.5 95% CI 13.01 - 16.09, respectively). The estimated number of women diagnosed with GWs in Novi Sad annually was 547 (corresponding to 6,564 new GWs cases during a 12-year period), of whom 187 (34.2%) were women aged 15 - 19 years (**Table 2**). The trend of GWs incidence decreased with the increasing age ($y = -2{,}1846 x + 24{,}815$, $R^2 = 0.8714$) of women (data are not shown).



Graph 1. Incidence rates of genital warts in women by age groups in Novi Sad, 2010 - 2021
Grafikon 1*. Stope incidencije genitalnih bradavica po uzrastima žena u Novom Sadu, 2010-2021*

Discussion

To our knowledge, this is the first study to evaluate certain epidemiological characteristics of GWs in the territory of Vojvodina. Although we are aware that cases of GWs in our study were probably underreported (GWs are not subject to mandatory notification in our country and the majority of people did not seek treatment for GWs), our results are quite comparable to those reported in other various settings.

Regarding the available data, with the exception of the United Kingdom (UK), GWs is not a notifiable condition in most other countries. In line with this, there is limited epidemiological data of GWs in certain European countries, especially in Eastern Europe, and even less in other regions, such as Africa, Latin America and South Asia [1]. Direct assessment regarding the incidence and distribution of GWs depends on the type of data sources, case definitions, test methods, time periods and study designs of GWs in certain territories. Taking into account that sources of epidemiological data of GWs are usually obtained from notifications of various specialists (general practitioners, gynecologists, dermatovenereologists, urologists) for different territories, as well as from medical histories of clinically treated women or from other sources, this imposes the potential problem to gain insight into the real number of patients with GWs which complicates the possibility of comparison in different territories.

It is important to underline that our data were obtained from the period before the wide introduction of the HPV vaccine for specific age groups into the immunization calendar in Serbia [14].

Table 2. Twelve-year incidence rates and estimated annual number of women with genital warts by age groups in Novi Sad
Tabela 2. *Dvanaestogodišnje stope incidencije i godišnji procenjen broj genitalnih bradavica u određenim uzrasnim grupama u Novom Sadu*

Age *Uzrast*	Women with a diagnosis of genital warts *Žene sa dijagnozom genitalnih bradavica*		Women examined by a gynecologist *Žene koje su bile na pregledu kod ginekologa*		Incidence/1,000 women (95% confidence interval) *Incidencija/1.000 žena (95% granica poverenja)*	p value *p vrednost*	p value *p vrednost*	Estimated annual number of women with genital warts *Procenjen broj žena sa dijagnozom genitalnih bradavica (godišnje)*[a]
	No/*Br.*	%	No/*Br.*	%				
15	4	0.6	198	0.1	20.2 (14.84-26.47)			ND
16	10	1.5	466	0.2	21.5 (17.85-25.51)			ND
17	21	3.2	888	0.4	23.6 (20.84-26.53)	p=0.4708*		ND
18	31	4.7	1,543	0.6	20.1 (18.13-22.19)			ND
19	30	4.6	2,066	0.9	14.5 (13.01-16.09)			ND
Subtotal (15 - 19) *Podzbir (15-19)*	96	14.7	5,161	2.1	18.6 (17.55-19.69)	NA		187
20-24	125	19.1	13,495	5.6	9.3 (8.82-9.80)			120
25-29	142	21.7	25,966	10.8	5.5 (5.23-5.78)	p< 0.0001**		91
30-34	103	15.7	36,600	15.2	2.8 (2.63-2.97)			46
35-39	63	9.6	34,077	14.2	1.8 (1.66-1.95)		p< 0.0001****	28
40-44	48	7.3	24,396	10.1	2.0 (1.83-2.18)			27
45-49	32	4.9	24,883	10.3	1.3 (1.16-1.45)	p< 0.0001***		17
50-59	27	4.1	40,955	17.0	0.7 (0.62-0.79)			19
60-69	18	2.8	34,961	14.5	0.5 (0.43-0.58)			12
Total/*Ukupno*	654	100	240,494	100	2.7 (2.64-2.77)			547

Legend/*Legenda:*
*No statistically significant difference between each cohort in the age group of 15 - 19 years/**Bez statistički značajne razlike između svake pojedinačne kohorte u uzrastu 15-19 godina*
**Incidence rate of genital warts among women aged 20 - 24 years is statistically significantly higher than in women aged 25 - 29 and 30 - 34 years/*Stopa incidencije genitalnih bradavica kod žena uzrasta 20-24 godine je statistički značajno viša u odnosu na stope incidencije žena uzrasta 25-29 i 30-34 godine*
***Incidence rate of genital warts in the age group of 40 - 44 years is statistically significantly higher than in those aged 35 - 39, 45 - 49, 50 - 59 and 60 - 69 years/*Stopa incidencije genitalnih bradavica kod žena uzrasta 40-44 godine je statistički značajno viša u odnosu na stope incidencije žena uzrasta 35-39, 45-49, 50-59 i 60-69 godina*
****Incidence rate of genital warts in the age group of 15 - 19 years is statistically significantly higher than in all the other groups/*Stopa incidencije genitalnih bradavica kod žena uzrasta 15-19 godina je statistički značajno viša u odnosu na stope incidencije svih ostalih posmatranih uzrasta*
[a]According to the 2011 Census/*Prema Popisu stanovništva iz 2011.*
ND - not determined/*Neodređeno*; NA - not applicable/*Neprimenljivo*

During the study period, we found that the age-specific incidence of GWs in fertile women (15 - 49 years) was higher (3.7/1,000 women) than the crude incidence (2.7/1,000) in women aged 15 - 69 years) and ranged from 1.3/1,000 (2019 year) to 5.6/1,000 (2013 year). Incidence rates in women aged 15 - 69 years ranged from 1.1/1,000 (2019 year) to 4.1/1,000 (2013 year). Our results are comparable with the results of the study conducted in Italy, during 2009/2010, among women aged 15 - 64 years, where the crude incidence rate was 3.0/1,000 [15]. In addition, similar incidence rate of GWs was reported in the study conducted in England [16]. Authors from Australia analyzed the data from the nationally representative general practice cross-sectional program and from the National Hospital Morbidity Database, and determined that the annual incidence rate of GWs was 2.2/1,000 [17].

On the other hand, findings from the studies conducted in Spain [18] and Germany [19], showed lower annual incidence rates of GWs (Spain 1.6/1,000, and Germany 1.1/1,000) in comparison with our results. A possible explanation for this may lie in the fact that the study period in two listed studies was shorter than in our study.

The studies conducted in Mexico [20] and Italy [21], where the denominator was the number of women examined by physicians, reported a higher incidence rate of GWs (4.3/1,000 in both studies) than in our study. The study performed in Mexico [20] presented data from the pre-vaccination period, similar to our study, and higher GWs incidence rates compared to ours can be explained by different cultural habits and different methodological approach during the investigation. A study conducted in Italy [21] in-

volved 78 gynecologists from different regions of Italy, reported a higher incidence than in our study. It is can be explained primarily by inclusion of higher number of gynecologists and participation of women from entire Italian population in comparison with women selected in our study. Bearing this in mind, our annual estimated number (547) of newly diagnosed cases of GWs during the entire study period (6,564 new GWs cases) is probably underestimated (only medically attended cases of GWs were observed), but inclusion of a larger number of community gynecologists, dermatovenereologists, as well as general practitioners in a surveillance network during the future investigation may substantially improve the recognition of GWs in a wider population.

In the US, due to younger age of first sexual intercourse among young people and the increasing trend in the total number of sexual partners, nearly half of new cases of sexually transmitted infections are found in young adults aged 15 - 24 years [22]. In terms of age, epidemiological data from the US National Health and Nutrition Examination Survey showed that the prevalence of HPV infection in a representative sample of women was the highest (45%) among those aged 20 - 24 year [23].

The authors of the study conducted in Italy, after selecting a wider range of age participants, reported the highest incidence rate and prevalence of GWs among women aged 15 - 24 in comparison with other age groups [15]. In addition, the study conducted in Germany revealed the highest incidence of GWs among women aged 14 - 25 years [19]. Interestingly, similar to our results, the results of aforementioned Italian study [15] showed that prevalence and incidence rate of GWs significantly decreased with the increasing age of women. Finally, a published systematic review also confirmed that the highest incidence of GWs worldwide is found among women under the age of 24 years [1], which is consistent with our results.

However, if we compared the incidence and age distribution of GWs widely, it is very important to take into account different study populations, cultural differences, lifestyle of participants and other reasons specific for youth behavior. For example, contrary to most abovementioned results, the highest prevalence of GWs among observed women aged 18 - 60 years in India was in 25 - 29 year age group [24].

As we said, GWs may lead to a significant impairment of the quality of life [9]. This was confirmed by a study conducted in the UK that evaluated a measure of health-related quality of life. Authors of this study underlined that young women aged from 15 - 19 years had the highest prevalence of GWs, and therefore had the greatest loss of quality of life [25]. Considering the mentioned estimation and our findings, we can assume that girls of this age in Novi Sad had similar consequences regarding the loss of quality of life.

Recommendations of the Center for Disease Control and Prevention for reducing the risk of GWs include proper and regular use of condoms, reduction in the number of sexual partners, but the main specific measure for reduction of GWs is wide implementation of vaccination against HPV [26]. Until 2010, 50% of European countries introduced HPV vaccination within the first three years after the European Commission granted a license for human use of the first HPV vaccines. By 2019, most European Union/European Economic Area countries had introduced HPV vaccination in their national immunization programs [27]. Although HPV infection is a significant public health problem in Serbia, it is regulated, for the time being, through the recommended immunization policy [14].

Conclusion

Our results provide essential epidemiological data that may be used as the basis for future more comprehensive investigations, as well as for evaluation of the effectiveness of the human papillomavirus vaccination campaign, after its wide implementation in the vulnerable population. Although our findings should be taken with caution (we may have underestimated the incidence rates by including only medically attended cases of genital warts), it is expected that the introduction of human papillomavirus vaccination can significantly reduce the incidence of genital warts, primarily in the young population (15 - 19 years of age), similar to the experience in other developed regions.

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ADJUNCTIVE USE OF METFORMIN IN THE TREATMENT OF ATYPICAL ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

ADJUVANTNA PRIMENA METFORMINA ZA TRETMAN POVEĆANJA TELESNE TEŽINE NASTAO ZBOG KORIŠĆENJA ATIPIČNIH ANTIPSIHOTIKA

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Summary

Introduction. Atypical antipsychotics are the gold standard in the treatment of psychotic and other mental disorders due to their efficacy and tolerability. However, the relatively frequent occurrence of antipsychotic-induced metabolic syndrome has encouraged research into possible solutions to this problem, including the adjunctive use of metformin. The aim of this review article is to present a concise, comprehensive and critical overview of the aforementioned issue based on the analysis of available experimental research. **Material and Methods.** PubMed and Google Scholar databases were searched for relevant literature published in a fifteen-year period between 2008 and 2022. The following terms were used in the search: atypical antipsychotics, metformin, and weight gain. Only double-blind, placebo-controlled, randomized, and cohort studies were taken into consideration. **Results.** A total of 145 papers were analyzed, of which 10 papers with 852 subjects met the inclusion criteria. All the reviewed studies concluded that the adjunctive administration of metformin at a daily dose of 500 mg to 2,000 mg has significantly reduced atypical antipsychotic-induced weight gain, with a favorable effect on other metabolic parameters that were examined in the analyzed papers. **Conclusion.** Taking into account the increased cardiovascular morbidity and the consequent mortality among those who have been using atypical antipsychotics in the long term, it is necessary to assess the risks and benefits of introducing adjunctive metformin in every patient who is at risk of developing metabolic syndrome. In order to recommend the routine use of metformin in such indications, studies that would include a larger sample and a longer period of treatment are needed.

Key words: Antipsychotic Agents; Schizophrenia; Metformin; Body Weight; Metabolic Syndrome; Metabolic Side Effects of Drugs and Substances; Olanzapine

Sažetak

Uvod. Atipični antipsihotici predstavljaju zlatni standard u lečenju psihotičnih i drugih mentalnih poremećaja zbog svoje efikasnosti i podnošljivosti. Međutim, relativno česta pojava metaboličkog sindroma indukovanog antipsihoticima je podstakla istraživanja o mogućim rešenjima ovog problema, uključujući i adjuvantnu primenu metformina. Cilj ovog preglednog članka je da predstavi koncizan, sveobuhvatan i kritički prikaz navedene problematike na osnovu analize dostupnih eksperimentalnih istraživanja. **Materijal i metode.** Za pretragu literature su korišćene *Pubmed* i *Google scholar* baze podataka za petnaestogodišnji period od 2008. do 2022. godine. Termini koji su korišćeni prilikom pretrage su: atipični antipsihotici, metformin i povećanje telesne težine. Razmatrane su isključivo dvostruko slepe, placebo kontrolisane, randomizovane i kohortne studije. **Rezultati.** Analizirano je ukupno 145 radova od kojih je 10 radova sa 852 ispitanika odgovaralo kriterijumima za uključivanje. Utvrđeno je da je adjuvantna primena metformina u dnevnoj dozi od 500 mg do 2.000 mg kod osoba kod kojih je zbog korišćenja atipičnih antipsihotika došlo do povećanja telesne mase u svim istraživanjima dovela do redukcije telesne mase, uz povoljan uticaj i na druge metaboličke parametre koji su ispitivani u pojedinim istraživanjima. **Zaključak.** Uzimajući u obzir povećan morbiditet od kardiovaskularnih oboljenja i konsekventni morbiditet u populaciji osoba koje dugoročno koriste atipične antipsihotike potrebno je kod svakog pacijenta koji je pod rizikom od pojave metaboličkog sindroma proceniti potrebu za uvođenjem adjuvantnog metformina. Za preporuku rutinske upotrebe metformina za navedenu indikaciju potrebne su studije koje bi obuhvatile veći uzorak i duži vremenski period lečenja.

Ključne reči: antipsihotički agensi; šizofrenija; metformin; telesna težina; metabolički sindrom; metabolički poremećaji izazvani lekovima; olanzapin

Introduction

Atypical antipsychotics are medications primarily used in the treatment of psychotic disorders, but they are also widely used in other indications, such as bipolar disorder, depression, anxiety disorders, sleep disorders, personality disorders, Parkinson's and Alzheimer's disease, in line with the demands

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Abbreviations

BWG – body weight gain
BMI – body mass index
HOMA-IR – homeostasis model assessment of insulin resistance
HbA1c – hemoglobin A1c

and safety concerns of the modern emergency psychiatry [1, 2]. One of the most common side-effects of these medications is metabolic syndrome, which includes: body weight gain (BWG), insulin resistance, high blood lipids, as well as the consequently increased risk of type 2 diabetes and cardiovascular diseases [3]. This is also confirmed by the data indicating that the prevalence of type 2 diabetes in younger patients with schizophrenia is higher than in the general population [4] and that a myocardial infarction is the leading cause of death among patients suffering from major mental disorders [5]. Clozapine and olanzapine are two atypical antipsychotics with the greatest potential for cardiometabolic side-effects, risperidone and quetiapine pose a moderate risk, while ziprasidone, aripiprazole, brexpiprazole, cariprazine and lurasidone carry the lowest risk [6, 7]. The BWG rate is the highest during the first six months of treatment, and remains high even later [8]. Apart from health risks, obesity induced by psychiatric drugs also has a great impact on the patient's self-confidence [9], as well as negative effect on their compliance. A precise mechanism of body weight increase caused by the use of atypical antipsychotics has not been completely described yet, but it is believed that an important role is played by the central histamine H1 antagonism and increased appetite [10]. An important reason for the necessary intervention regarding this problem is the fact that polypharmacy, which leads to even more pronounced side-effects, is widespread in psychiatric practice [11, 12]. Potential therapeutic interventions directed towards the prevention of the antipsychotic-induced metabolic syndrome include a change of drug, which carries a risk of relapse, and a change of lifestyle, including a controlled diet and physical activities, which is a great challenge in this population. Professional literature offers some considerations on the adjuvant use of medications such as topimarate, sibutramine, aripiprazole, and reboxetine in the context of having potentially favorable effects on the reduction of cardiometabolic risk induced by atypical antipsychotics [13]. However, apart from the aforementioned interventions, the literature has recently been mentioning adjuvant use of metformin, as a highly effective method of controlling body weight increase induced by antipsychotic therapy. This medication is a derivative of biguanide and it is used in treating diabetes mellitus type 2. It reduces hepatic gluconeogenesis and impacts insulin resistance by boosting peripheral glucose utilisation, while reducing resorption of glucose from the gastrointestinal tract [14]. Recommendations for the use of metformin for this indication are also present in clinical practice guidelines, so the Clinical Practice Guidelines of the Canadian Medical Association for adult obesity also recommend the use of metformin for treating obesity induced by antipsychotics [15]. Furthermore, the Practice Guidelines of the American Psychiatric Association for the treatment of patients with schizophrenia claim that the use of metformin is justified in patients receiving atypical antipsychotics who have not been diagnosed with hyperglycemia. It is concluded that its use is safe, while the desired effects on body weight and other metabolic abnormalities are easily achieved [16].

The objective of this research is to analyze the available literature data on the use of metformin in the treatment of atypical antipsychotics side-effects, primarily increased body weight.

Material and Methods

PubMed and Google Scholar databases were searched for relevant literature published in a fifteen-year period, between 2008 and 2022. The following terms were used in the search: atypical antipsychotics, metformin, and weight gain. A total of 145 papers matched previously mentioned criteria, but only double-blind, placebo-controlled, randomised and cohort studies were analyzed. Systematic reviews, literature searches, meta-analyses and research including children and animals were excluded. It was determined that only 10 papers met inclusion criteria. We examined the titles, abstracts, and full texts of relevant papers. The collected data were then summarized and presented.

Results

This research systematically presents data obtained from ten experimental studies including 852 subjects related to adjunctive use of metformin in the treatment of atypical antipsychotic-induced metabolic syndrome.

The research conducted by De Silva et al. [17] is a double-blind, placebo-controlled, randomised study which lasted 24 weeks and evaluated the effects of metformin in patients with antipsychotic-induced weight gain. The study included 66 patients older than 18 years who met the diagnostic criteria for schizophrenia or schizoaffective disorder and whose body weight had increased by more than 10% in comparison to the period before the introduction of atypical antipsychotics. The subjects were treated with olanzapine, clozapine, risperidone, aripiprazole and amisulpride, while the patients receiving other psychotropic medications which are associated with BWG (lithium, carbamazepine, valproate and antidepressants) were excluded from the research. Metformin was given at a dose of 500 mg twice a day, while the control group received placebo. The patients with poorer tolerance to metformin received 500 mg a day. The subjects were advised to include high-fibre foods, fruits and vegetables in their diet, to reduce the intake of simple sugars and products with high concentration of fats, and to introduce 30 minutes of moderate exercise a day; however, these parameters were not monitored. The change in the group that was using metformin was -1.56 kg, while in the placebo group the change of weight was +1.0

kg, which was interpreted as a statistically significant difference (p = .03). No statistically significant difference was noted regarding the waist/hip ratio or the sugar blood level between the two groups.

Wang et al. [18] examined the efficacy of metformin in patients with the first episode of schizophrenia whose body weight had increased by more than 7% in comparison to the period before they started receiving antipsychotic therapy. This randomized, placebo-controlled 12-week study included 72 patients, 66 of whom managed to complete the study. Metformin was given at a dose of 1,000 mg/day, while the primary outcome was related to the changes in body weight, and the secondary related to the changes in the body mass index (BMI), fasting glucose and insulin, as well as in the insulin resistance index. In the group treated with metformin a decrease in body weight by 5.1% was observed, while an increase of weight by 3.9% was observed in the placebo group. The BMI decreased by 1.3 in the group treated with metformin, while it increased by 0.9 in the placebo group. The values of insulin and insulin resistance index (HOMA-IR) showed statistically significant decreases in the study group after 4, 8 and 12 weeks of the study, while they increased in the placebo group. More patients in the study group (N = 13; 40.6%) lost weight by more than 7% in comparison to the placebo group (N = 3; 8.8%), which was noted as statistically significant (p = .003).

Chen et al. [19] published a randomized, double-blind, placebo-controlled, 24-week study, in which they studied the effects of metformin on the metabolic syndrome in patients with schizophrenia who were using clozapine for more than three months. Out of 55 subjects, 28 were receiving 1,500 mg of metformin a day, while 27 were receiving placebo. The metabolic parameters were monitored during weeks 2, 4, 8, 16 and 24 and body weight was measured each time. After 24 weeks, body weight (p < .0001), BMI (p < .0001), fasting glucose (p < .0001), high-density lipoprotein cholesterol (p = .03), insulin level (p0.01) and HOMA-IR (p = .02) showed significant changes in the group treated with metformin. At the end of the metformin therapy, 8 patients lost more than 7% of weight, but they regained the weight after they stopped using metformin. Based on this research, the authors concluded that adjuvant use of metformin is efficient in treating metabolic syndrome.

Agarwal et al. [20] conducted a double-blind, randomised clinical trial to examine the effects of metformin on early comorbid glucose dysregulation in people with the schizophrenic spectrum disorders. In this study, 30 subjects who were overweight or obese (BMI > 25) under the age of 40 with a diagnosis of schizophrenia spectrum and prediabetes/diabetes were divided into two groups. The first group (N = 21) received metformin (1,500 mg/day), while the other (N = 9) was using placebo for 4 months. A total of 22 patients finished the trial (n = 14 metformin and N = 8 placebo), and the group that used metformin showed a significant decrease of the HOMA-IR index (p = .043) and fasting glucose levels (p = .007) in comparison with the placebo group, while no differences were noted between the groups in relation to the hemoglobin A1c (HbA1c) level. The weight loss in the metformin group was in significant correlation with the decrease in subcutaneous, but not in visceral or hepatic fatty tissue. The results of this trial indicate that metformin had positive effects on dysglycemia and insulin sensitivity, regardless of the weight loss in younger population with diagnosed psychotic disorder and prediabetes/diabetes.

The study conducted by Wu et al. [21] was a double-blind study assessing the efficacy of metformin in treating olanzapine-induced BWG. A total of 40 subjects diagnosed with schizophrenia were using olanzapine (15 mg/day) along with metformin (750 mg/day) (N = 20) or olanzapine (15 mg/day) with placebo (N = 20). During the trial, the parameters such as body weight, BMI, waist circumference, waist/hips ratio showed a smaller increase in the group that was receiving metformin. Furthermore, it was noticed that the values of insulin significantly increased in the eighth and twelfth week in the placebo group, while they remained unchanged in the metformin group. Less patients from the metformin group (N = 3, 16.7%) than in the placebo group (N = 12, 63.16%) presented with BWG in regard to their baseline weight by more than 7%, which was statistically significant p < .001.

Rado J. et al. [22] published a 24-week placebo-controlled pilot study during which they examined the efficacy, tolerability and safety of adjuvant metformin therapy in the treatment of olanzapine-induced BWG in adults diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, or depression with psychotic symptoms. The research included 25 patients using olanzapine, while other antipsychotics were not allowed. Metformin was administered in the study group at doses up to 2,000 mg/day. Olanzapine-metformin group showed the average weight gain of 2.5 kg, which was less than in the placebo group, where the average weight gain was 5.8 kg (p < .05). The average BMI increase in the study group was 0.85, while the control group showed an increase of 2.02 (p < .045).

A double-blind study conducted by Jarskog et al. [23] monitored the effects of metformin on weight reduction of obese patients diagnosed with schizophrenia or schizoaffective disorder. A total of 148 clinically stable, obese patients participated in this 16-week study. The study group included 58 patients who were receiving their regular psychiatric therapy along with 2,000 mg metformine a day. The results showed a significant weight reduction in the study group of - 3.0 kg, while weight reduction in the control group was - 1.0 kg. Metformin group also showed significant changes in BMI (p = .006), triglyceride levels (p = .037) and HbA1c (p = .04). The tolerance of metformin was satisfactory.

Tang C. et al. [24] published a randomized, double-blind, placebo-controlled study aiming to estimate the effects of metformin on the antipsychotic-induced weight gain, its safety and tolerability. The study lasted

24 weeks and included 17 patients between the age of 16 and 40, diagnosed with the first psychotic episode. The inclusion criterion was a weight increase of more than 5% in comparison to the period before atypical antipsychotics were introduced. The study group included 8 patients and the average dose of metformin was 1,200 mg/day, while the tolerability was good. In the metformin group, five patients completed the study, four of them lost weight (average - 1.9 kg), while one patient gained weight (1.0 kg). In the placebo group, out of eight patients who completed the study, seven gained weight (average + 3.8 kg), while only one lost weight (- 1.9 kg). During the phase of discontinuation, between 24 and 36 weeks, three out of five patients from the metformin group gained weight (average + 3.4kg) and two lost weight (average - 1.8 kg), while seven out of eight patients from the placebo group gained weight (average 1.8 kg) and in one patient the weight remained the same. The results showed that patients in the metformin group gained less weight that those in the placebo group, but there was no statistically significant difference between the two groups during the phase of discontinuation.

Spokes et al. [25] published a retrospective cohort study on the effects of metformin in patients receiving clozapine. The digital medical records of patients with

Table 1. A short presentation of the analyzed studies
Tabela 1. *Sažete karakteristike razmatranih istraživanja*

	Authors *Autori*	Type of study *Vrsta istraživanja*	Study duration (weeks) *Trajanje istraživanja (nedelje)*	Number of subjects *Broj ispitanika*	Antipsychotics *Antipsihotici*	Dose of metformin (mg/day)/*Doza metformina (mg/dan)*	Outcome measures *Mere ishoda*
1.	De Silva et al. *De Silva et al.*	Randomized double-blind, placebo-controlled/*Randomizovano duplo-slepo, placebo kontrolisano*	24	66	Several different atypical *Više različitih atipičnih*	1,000	Body weight *Telesna težina*
2.	Wang et al. *Wang et al.*	Randomized placebo-controlled/*Randomizovano placebo kontrolisano*	12	72	Several different atypical *Više različitih atipičnih*	1,000	Body weight, Insulin, HOMA-IR *Telesna težina, Insulin, HOMA-IR*
3.	Chen et al. *Chen et al.*	Randomized double-blind placebo-controlled/*Randomizovano duplo-slepo, placebo kontrolisano*	24	55	Clozapine *Klozapin*	1,500	Body weight, BMI, glucose, lipids, insulin, HOMA-IR/*Telesna težina, BMI, glukoza, lipidi, insulin, HOMA-IR*
4.	Agarwal et al. *Agarwal et al.*	Randomized double-blind/*Randomizovano duplo-slepo*	17	30	Several different atypical/*Više različitih atipičnih*	1,500	Glucose, HOMA-IR *Glukoza, HOMA-IR*
5.	Spokes et al. *Spokes et al.*	Retrospective cohort/*Retrospektivno kohortno*	108	90	Clozapine *Klozapin*	1,000 - 2,000	Body weight *Telesna težina*
6.	Wu et al. *Wu et al.*	Double-blind, placebo-controlled/*Duplo-slepo, placebo kontrolisano*	12	40	Olanzapine *Olanzapin*	750	Body weight *Telesna težina*
7.	Rado et al. *Rado et al.*	Randomized placebo-controlled *Randomizovano, placebo kontrolisano*	24	25	Olanzapine *Olanzapin*	2,000	Body weight, BMI *Telesna težina, BMI*
8.	Frederic et al. *Frederic et al.*	Double-blind *Duplo-slepo*	16	148	Several different atypical/*Više različitih atipičnih*	2,000	Body weight, BMI, lipids, HbA1c/*Telesna težina, BMI, lipidi, HbA1c*
9.	Tang et al. *Tang et al.*	Randomized double-blind placebo-controlled/*Randomizovano duplo-slepo, placebo kontrolisano*	24	17	Several different atypical/*Više različitih atipičnih*	1,200	Body weight *Telesna težina*
10.	Hakami et al. *Hakami et al.*	Retrospective cohort/*Retrospektivno kohortno*	273	309	Several different atypical/*Više različitih atipičnih*	1,000	Body weight *Telesna težina*

Legenda: BMI – indeks telesne mase, HOMA-IR – indeks insulinske rezistencije, HbA1c – glikolizirani hemoglobin

therapy-resistant schizophrenia who received clozapine in the period between 2017 and 2019 were analyzed retrospectively. In 90 of the analyzed subjects, the use of metformin was related to the overall weight gain (1.32% vs. 5.95%, p = .031), as well as a weight gain by more than 7% (37.8% vs. 63.0%, p = .025) in comparison to the placebo group.

The latest study, conducted by Hakami et al. [26] in 2022, examined the effects of antipsychotics on body weight and the effects of adjuvant use of metformin on the antipsychotic-induced weight gain. A total of 395 patients participated in the study, with 309 of them in the placebo group and 86 in the group treated with adjunctive metformin. In the placebo group, only 67 patients (21.68%) lost weight, 43 (13.92%) showed no change in body weight and 199 (64.4%) gained weight. In the metformin group, 35 (40.7%) lost weight, 18 (20.93%) showed no change in body weight and 33 (38.37%) gained weight. The first group presented a significant change in body weight of + 2.5 kg, while in the metformin group the weight change was - 0.04, p < .0001. The statistical analysis showed that a simultaneous use of metformin and antipsychotics was associated with a decrease in the trend of weight gain, while the use of antipsychotics alone was associated with an increase in body weight.

Although it did not meet the criteria for inclusion in our study, for the sake of scientific fairness, we would like to mention one research with negative results that was published in 2006. In this research, Baptista et al. [27] studied whether metformin prevents BWG and metabolic dysfunction in patients with schizophrenia who were treated with olanzapine during a 14-week double-blind study. Forty patients taking olanzapine (10 mg daily) were randomly allocated to metformin (n = 20; 850 to 1,700 mg daily) or placebo (n = 20). At week 14, BWG (kg) was similar in the metformin group (5.5 kg) and the placebo group (6.3 kg), p = .4. There were no differences in BMI, waist size, glucose, insulin, HOMA-IR, and plasma lipid levels in the study group and the placebo group. The authors concluded that metformin did not prevent olanzapine-induced BWG.

A short presentation of the analyzed studies is shown in **Table 1**.

Discussion

This review article included 10 experimental clinical trials with 852 patients in whom effects of adjuvant use of metformin on reduction of atypical antipsychotic-induced weight gain and other disturbed metabolic parameters were analyzed. All reviewed studies showed statistically significant favourable effects of metformin on increased body weight in comparison with placebo. The administered doses of metformin ranged from 500 to 2,000 mg/day and its tolerability was satisfactory. In general, in the groups receiving metformin only, mild side-effects such as nausea and vomiting were observed, which was not statistically relevant in comparison with the placebo group, while more serious side-effects such as lactic acidosis were extremely rare. Apart from body weight, the presented studies analyzed other parameters of metabolic syndrome as well. Even though De Silva et al. found statistically significant effects of metformin on body weight, no statistically significant difference related to the waist/hip ratio and fasting blood sugar level between the two groups was established [17]. However, Wang et al, Chen et al. and Agarwal et al. concluded that the levels of insulin and HOMA-IR decreased significantly in the metformin group [18–20]. Furthermore, the study conducted by Jarski et al, apart from effects on body weight and BMI, showed positive effects of metformin on the levels of triglycerides and HbA1c [23]. It is particularly important to mention the study conducted by Chen et al., which proved that the use of metformin is efficient, but the benefits disappear once the therapy is discontinued [19]. Although all studies included in this review showed statistically significant effects of metformin in regulation of body weight, it is necessary to mention that there is a research with negative results, such as the one conducted by Baptista et al. [27], which failed to prove positive effects of metformin on the olanzapine-induced weight gain. This result could perhaps be explained by the hypothesis that olanzapine-induced weight gain is mainly associated with direct appetite stimulation, a mechanism that is not primarily influenced by metformin, as pointed out by the authors [28].

The limitations of this study are a very small sample of participants who used metformin (fewer than 400), the relatively short period of monitoring, and the fact that the groups included mainly patients diagnosed with schizophrenia, even though it is known that atypical antipsychotics are also used for many other indications in psychiatry. Another limitation of this research is that metformin in the reviewed studies was not used to treat diabetes, but to reduce weight gain and other parameters of the metabolic syndrome.

Our results indicate a need to consider the introduction of adjuvant metformin in the early phase of treatment of every patient prone to weight gain using atypical antipsychotics in order to prevent morbidity caused by cardiovascular diseases and subsequent mortality, which is confirmed by the published data [29–31]. The goal of this study is consistent with one of the principal precepts of bioethics: “first, do no harm” and points to the fact that the patient, not the disease, must remain the focus of medical science [32].

Conclusion

Even though the use of metformin in treating atypical antipsychotic-induced weight gain and other metabolic abnormalities is still sporadic in our region, the available data confirm its efficiency and safety. This leads to a conclusion that it is justified to use metformin in order to prevent and reduce atypical antipsychotic-induced cardiometabolic side-effects. We believe that further research is needed in order to determine long-term efficiency and tolerability of metformin for this particular indication.

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THE MOST COMMON CRIMINAL OFFENCES AMONG PSYCHOACTIVE DRUG ADDICTS

NAJČEŠĆA KRIVIČNA DELA ZAVISNIKA OD PSIHOAKTIVNIH SUPSTANCIJA

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Summary

Introduction. Psychoactive drug addiction causes serious consequences in many countries, not only for the health of the nation, but also for the emergence of various social problems, such as high crime rates, delinquency and unemployment. **Material and Methods.** A retrospective-prospective study included data of 100 criminal offenders, drug addicts, gathered from forensic psychiatric records in the context of criminal offences committed by those persons. **Results.** Out of all the drug addicts who committed criminal offences, 98% were males and the average age was 30.44. Most of the offenders were unemployed and had a lower level of education. A total of 56% were previously convicted. The majority of them previously committed one felony. Compared to previous offences, new criminal offenses were against life and body in 70%. Comorbid mental disorders were diagnosed among 84% of examinees at the moment of committing a crime, and 60% had personality disorders. The largest number of subjects with alcohol addiction primarily make offenses against life and body, while those with substance addiction usually commit offenses against human health. **Conclusion.** In drug addicts who have committed criminal offences, it has been confirmed that gender, age, employment, history of committing criminal acts and comorbid mental disorders are criminogenic factors that are significant for the prediction of general criminality. The continuity in researching predictive factors, as well as crime prevention within the population with mental disorders is and needs to remain a priority.

Key words: Drug Users; Criminal Behavior; Substance-Related Disorders; Crime; Mental Disorders; Personality Disorders; Risk Factors; Forensic Sciences

Sažetak

Uvod. Zavisnost od psihoaktivnih supstanci u mnogim zemljama ima ozbiljne posledice, ne samo po zdravlje nacije, nego i pojavi različitih društvenih problema, koji se ispoljavaju u vidu kriminaliteta, delinkvencije i nezaposlenosti. **Materijal i metode.** Retrospektivno-prospektivna studija koja je razmatrala podatke dobijene kroz sudsko-psihijatrijska veštačenja 100 učinilaca koji su zavisnici od psihoaktivnih supstancija, a u kontekstu krivičnih dela koja su ta lica počinila. **Rezultati.** U populaciji zavisnika kao učinioca krivičnih dela muški pol je zastupljen sa čak 98% i prosečnom starošću od 30,44 godina. Učinioci su najčešće nižeg obrazovnog nivoa i nezaposleni. Ranija osuđivanost u ispitivanoj populaciji iznosi 56%. Za razliku od ranijih, sadašnja krivična dela u 70% bila su krivična dela protiv života i tela. Kod 84% ispitanika dijagnostikovano je postojanje komorbidnih mentalnih poremećaja u vreme izvršenja dela i to u 60% poremećaja ličnosti. Najveći broj onih koji su zavisnici od alkohola izvršavaju prevashodno dela protiv života i tela, dok zavisnici od opioida češće čine dela protiv zdravlja ljudi. **Zaključak.** Kod zavisnika koji su učinili krivična dela potvrđeno je da pol, starost, zaposlenost, istorija činjenja krivičnih dela i komorbidna dijagnoza mentalnog poremećaja predstavljaju kriminogene faktore kao značajne činioce za predikciju opšteg kriminaliteta. Kontinuitet u istraživanju faktora koji mogu doprineti adekvatnijoj predikciji, kao i prevenciji kriminaliteta u populaciji osoba sa mentalnim poremećajima, jeste i mora ostati stručni minimum.

Ključne reči: zavisnici od psihoaktivnih supstanci; krivična dela; bolesti zavisnosti; kriminal; mentalni poremećaji; poremećaji ličnosti; faktori rizika; forenzika

Introduction

Criminal offenses

Criminal offence is defined by Article 14 of the Criminal Code of the Republic of Serbia:

1. A criminal offence is an offence set forth by the law as a criminal offence, which is unlawful and committed with a guilty mind/mens rea.

2. There is no criminal offence without an unlawful act or culpability, notwithstanding the exist-

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ence of all essential elements of a criminal offence stipulated by law [1].

Criminal offences include criminal offences against life and body (Article 113 – Article 127) – murder, aggravated murder, heat of passion manslaughter, offences against property (Article 203 – Article 222) – theft, aggravated/compound larceny, grand larceny, robbery, as well as criminal offences against human health (Article 246 – Article 259) – unlawful production and circulation of narcotics, unauthorized possession of narcotics, etc.

Drug addiction

By definition, psychoactive substances are chemicals that alter mental functions when consumed, i.e. they affect human consciousness, cognition, behavior, and mood [2]. Substance abuse leads to addiction disease, jeopardizing mental and physical health, as well as deterioration in the quality of family, professional, and social relationships [3]. Drug addiction causes serious consequences across many countries, not only when it comes to national health, but also in the context of social issues (e.g. crime rates, delinquency, unemployment, prostitution, homelessness, poverty, severe dysfunctions in family relationships) [4].

Today, there is no unique definition of drug addiction, but there are diagnostic criteria. According to the Tenth International Classification of Diseases, definite diagnosis of dependence should be made only if three or more of the following criteria have been present together at some time during the previous year: a strong desire or sense of compulsion to take the substance; difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use; a physiological withdrawal state when substance use has ceased or been reduced as evidenced by the characteristic withdrawal syndrome for the substance, or use of the same substance with the intention of relieving or avoiding withdrawal symptoms; evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses; progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects; persisting with substance use despite clear evidence of overtly harmful consequences [5].

Forensic significance of alcohol addiction

Examination of persons under the influence of alcohol does not differ from other examinations of individuals with temporary mental disorders. Clinical presentation of alcohol intoxication is used for the analysis of psychopathological and pathophysiological effects and their impact on judgment and decision making. When examining criminal cases, experts mostly focus on assessing cognitive impairments and affective disorders caused by alcohol. Examination of persons under the influence of alcohol who also have personality disorders is a particular challenge because it requires knowledge of socio-dynamic and psychodynamic events. From the forensic-psychiatric viewpoint, alcohol stimulates immature defense mechanisms. Among psychopaths, immature defense mechanisms are already present and can be intensified by alcohol. Alcohol disrupts immature defense mechanisms and regresses them to the most primitive levels of reacting such as autoaggression, heteroaggression, splitting, primitive projection and identification, acting-out [6].

Forensic significance of opioid addiction

Opioid drugs quickly cause character deviations, loss of ethical standards and ability to live and behave normally, leading to sexual disinhibition and antisocial behavior [7]. Because of the strong desire to take the substance, people commit crimes and felonies. Evaluation of sanity is a specific task. At the beginning of examination, it is necessary to establish whether the person is an addict. If he or she is an addict, the next question is what type of drugs he or she consumes, and how; if the crime was committed under the influence of a certain psychoactive substance, and if yes – which one. If the offence is typical for addicts (e.g. theft in a pharmacy, falsification of medical prescriptions, selling drugs), it is important to confirm whether the offence was made during the withdrawal crisis or due to the fear of experiencing it. Addicts commonly think ahead and resort to thefts to gather resources for buying drugs. They do so to relieve or avoid withdrawal symptoms. Personality disorders are common among addicts. The primary personality pathology is followed by a secondary development of substance use disorders [8].

Material and Methods

A retrospective-prospective study was conducted at the Department of Forensic Psychiatry, Psychiatry Clinic, Clinical Center of Vojvodina, Novi Sad. The sample included data of 100 criminal offenders, drug addicts, gathered from forensic psychiatric records. The data were gathered over a time period of 10 years. Sociodemographic data were analyzed for all subjects, as well as the presence and type of the comorbid mental disorders and recidivism into criminal behavior.

Statistical Package for Social Sciences 22 was used for the statistical data analysis. The results were processed by using the methods of descriptive statistics. Pearson correlation coefficient (χ^2) was used for testing the frequency differences. The contingency coefficient (C) was used in situations when the criteria for Pearson correlation coefficient χ^2 were not fulfilled.

The study did not require Ethics Committee approval, considering that it does not contain any personal data of the subjects and that it was conducted according to the local court demand.

The main limitation of this research is related to the fact that only the most serious criminal acts were considered, for which the local court demand-

Table 1. Correlation coefficient between previous and new criminal offences
Tabela 1. *Koeficijent korelacije između ranije učinjenih i sadašnjih krivičnih dela*

		New criminal offences/*Sadašnja krivična dela*				Total *Ukupno*
		Against life and body *Protiv života i tela*	Against property *Protiv imovine*	Against human health *Protiv zdravlja*	Against traffic safety/*Protiv bezb. saob.*	
Previous criminal offences *Ranije učinjena krivična dela*	None/*Nema*	36	0	2	2	40
	Offences against life and body *Dela protiv živa i tela*	18	0	0	0	18
	Offences against property *Dela protiv imovine*	10	6	0	0	16
	Offences against human health *Dela protiv zdravlja ljudi*	6	0	20	0	26
Total/*Ukupno*		70	6	22	2	100

Legend: C = .699, p < .01 there is a correlation between the type of previously committed offences and new criminal offences. Those who did not commit felonies in the past were more likely to commit an offence against life and body. Those who have previously committed offences against human health (unlawful production and circulation of narcotics) were more likely to become repeat offenders for the same type of crime. Similar patterns were identified among the subjects who have previously committed offences against life and body. This is the contingency coefficient C which shows the correlation between two variables, it is strong and indicates a positive relationship.

Legenda: C=,699, p<,01 postoji povezanost između vrste ranijih krivičnih dela i sadašnjih. Oni koji nisu ranije činili krivična delaznačajno češće su bili izvršioci dela protiv života i tela. Oni koji su ranije izvršili dela protiv zdravlja ljudi (neovlašćene proizvodnje i stavljanja u promet opojnih droga) češće isto delo ponavljaju (sadašnje) u odnosu na ostala dela. Slično je i sa onima koji su i ranije imali krivična dela protiv života i tela, češće ga ponavljaju u odnosu na ostala. Ovo je C koeficijent (koeficijent kontingencije) pokazuje korelaciju između dve varijable, visok je i pozitivnog smera.

ed psychiatric assessment of offenders, while taking into account that all offences could lead to similar but not the same conclusions.

Results

Our sample included 98% of male subjects. The average age was 30.44 years; the youngest offender was 18 and the oldest 56 years of age. The majority of subjects (48%) had only primary education, followed by 28% of those with a bachelor's degree. A total of 18% had secondary education, while 6% had no formal education. When it comes to the employment status, 90% of subject were unemployed at the time when they committed the crime. A total of 56% were formerly convicted. The majority of them previously committed one offence (64.3%) compared to others who committed two or more. We also established the type of previously committed crimes, where 16 of the subjects committed offences against life and body, 16 committed offences against property, and 24 committed offences against human health. In contrast to the type of previously committed crimes, we examined offences against life and body (70%), offences against human health (22%), offences against property (6%), and criminal offences against traffic safety (2%). Despite the fact that there is no statistically significant correlation between subjects who were previously convicted and those who were not, a correlation between the type of previously committed crimes and the new ones, that we have examined, has been established. Those who did not previously commit any offences were more likely to commit an offence against life and body, while those who have previously committed offences against human health (unlawful production and circulation of narcotics) were more likely to become repeat offenders for the same type of crime. Similar patterns were identified among the subjects who have previously committed offences against life and body **(Table 1)**.

Based on the analysis of court records, available medical documentation, and psychiatric records, the expert committee of forensic psychiatrists has identified the presence of comorbid mental disorder at the moment of committing the crime in 84% of addicts. Thus, there is a statistically significant difference within the group, given the fact that the majority of the subjects had a comorbid mental disorder. Beside the 16% of addicts without a comorbid disorder and the ones with a personality disorder (60%), the most common comorbid mental disorders included organic disorders, psychotic disorders, affective disorders, or mental retardation in 4% to 6% of cases. In our research, personality disorder was found in 70% of the offenders who had some type of comorbid mental disorder. There is a significant frequency difference concerning the type of personality disorder. Emotionally unstable personality disorder (F 60.3) is significantly more frequent compared to other personality disorders. Within the sample, 44% of subjects were alcohol addicts, 30% were opioid addicts, 18% had polysubstance addiction, 4% were cannabinoid addicts, and 2% were addicted to sedatives. At the moment of committing a crime, 70% of all subjects were intoxicated with psychoactive substances, which is a statistically significant difference compared to subjects who

Table 2. Contingency coefficient between the type of offence and addiction tempore criminis
Tabela 2. *Koeficijent kontingencije između vrste dela i zavisnosti tempore criminis*

	None *Nema*	Alcohol *Alkohol*	Opioids *Opioidi*	Sedatives *Sedativi*	Cannabinoids *Kanabinoidi*	Polysubstance addiction *Više psihoaktivnih supstancija*
Offences against life and body *Dela protiv života i tela*	2	38	10	2	0	18
Offences against property *Dela protiv imovine*	0	2	4	0	0	0
Offences against human health *Dela protiv zdravlja ljudi*	0	2	16	0	4	0
Offences against traffic safety *Dela protiv bezbednosti javnog saobraćaja*	0	2	0	0	0	0
Total/*Ukupno*	2	44	30	2	4	18

Legend: C = .597, p < .05 Contingency coefficient is significant at level .05. We identified a mid-level correlation between the type of crime and type of addiction to psychoactive substances tempore criminis. The majority of alcoholic addicts committed offences against life and body, while opioid addicts most commonly committed offences against human health, i.e. unlawful production and circulation of narcotics.
Legenda: C=,597, p<,05 Koeficijent kontingencije je značajan na nivou ,05. Postoji povezanost srednjeg stepena između vrste dela i zavisnosti od psihoaktivnih supstancija tempore criminis. Najveći broj onih koji su zavisnici od alkohola izvršili su u najvećem broju dela protiv života i tela, u odnosu na druge zavisnike od opioida koji češće čine dela protiv zdavlja ljudi (neovlašćene proizvodnje i stavljanja u promet opojnih droga), u odnosu na druge vrste dela.

were not intoxicated. There were significantly more subjects who were intoxicated tempore criminis: 50% of them were under the influence of alcohol and the remaining 50% were under the influence of other psychoactive substances. We identified a mid-level correlation between the type of crime and type of addiction to psychoactive substances tempore criminis. The majority of alcoholic addicts committed offences against life and body, while opioid addicts most commonly committed offences against human health, i.e. unlawful production and circulation of narcotics **(Table 2)**.

Discussion

Research results predominantly match the demographic data of subjects from other contemporary studies. A well-known predominance of males in the population of offenders has been confirmed in our research sample [9]. Furthermore, regarding the subjects' age, offenders are mostly young adults or middle-aged person as in up-to-date studies [10]. In regard to the above-mentioned results and data from available literature, we can conclude that gender and age are probably the two best predictors of criminogenic behavior. Prison population statistics confirm these numbers. Concerning the gender statistics of the offenders, it is interesting that 93% of the American prisoners in 2014 were men. More than half of committed crimes were murders, i.e. offences against life and body. The age statistics shows that those were vastly young offenders between 15 and 29 years of age, a demographic that made up 20% of the United States population at the time. Young men are also significantly more present as crime victims compared to other demographic groups [11–13]. The ratio of adult men and women prisoners was relatively stable in 19 jurisdictions within the European Union between 2008 and 2013, where male prisoners made up 95% of the prison population [14]. An increasing number of research document the neurobiochemical basis of violence, which is more present among men. In this type of research, among men that continuously made violent offences, six criteria were noted as indicators of neurodevelopmental disorder. These criteria were defined based on the analysis of chronic violence, genetic, anatomical, and functional neuroimaging, and neuropsychology. Labor complications, minor physical anomalies, prenatal exposure to tobacco and alcohol, malnutrition, exposure to lead, and brain trauma are identified as early risk factors for violent behavior. Aberrant personality from early childhood, inadequate education, and social and professional functioning are believed to lead to persistent adult violence, which typically has a stable direction, with a negative connotation. Generally, it is argued that chronic adult violence meets the criterion for being conceptualized as having neurodevelopmental origins and that an important, but not sole, source of neural maldevelopment lies in prenatal and early postnatal risk factors [15]. At the same time, the neurodevelopmental origin of psychopathy is emphasized [16]. A dissocial personality disorder is conceptualized as neurodevelopmental at its core [17]. We should also mention that social processes are not excluded from the neurodevelopmental perspective given the fact that they do influence early brain development [18]. High unemployment rates among offenders at the moment of committing a crime, support the significant correlation prevalence between crimes and unemployment [19, 20]. The economist, Jeffrey Grogger claims that high crime rates among young men can

be explained partially by the unfavorable situation in the job market, meaning that jobs for this specific demographic group are typically low-paid. This increases the probability that they will commit crimes. Grogger's analysis shows that decreasing minimum wages leads to layoffs and an increased frequency of crimes committed by young men [21]. However, other studies (e.g. Chamlin and Cochran) claim that the correlation between unemployment and committing cromes is not significant, i.e. that the existing research are not consistent but rather complex and ambiguous [22]. The latest studies provide new theoretical arguments for the correlation between the two. The correlation reflects in the length of unemployment: the longer the person is unemployed, the bigger the chance that they will commit a crime [23]. In addition, the research mentions the need to improve the educational system to lower crime rates and secure more jobs. Simulations based on these models show that elimination of long-term unemployment among men between 15 and 24 years of age by opening new job positions, would result in decreasing crime rates by 7% per year. It is believed that, if these individuals finished higher education, crime rates would decrease by almost 15% per year [24, 25].

A research that discusses recidivism in repeat offenders [26–28] indicates that it could serve as a predictor for future offences [29]. Even though our research does not contain a statistically relevant piece of evidence to support the aforementioned indications, we think it is wise to bear them in mind. However, our research sample includes offenders who committed serious crimes and fit the profile of younger men which, according to studies, may mean that they will become repeat offenders. One of the previously published findings supports this claim. According to it, five out of six prisoners (83%) in the sample of 67.966 who were released in 2005 in 30 United States, were arrested at least once in the same year, looking at the period of nine years after being released [30]. Generally speaking, repeating the offence, as stated in review studies, was found between 50% and 99% of cases [31, 32]. Results of our research match the results of similar ones, according to which a previously committed murder is in correlation with a 1,467 increased probability that the offender will be prosecuted for the same type of felony in the future. A similar correlation has been confirmed between former and current participation in theft (249% increased probability), physical violence (200%), and unlawful production and distribution of narcotics (736%). These data enable prediction of the probability of repeat offences, while previous involvement in a certain type of crime dramatically increases the probability of participating in the same type of crime in the future [33].

The literature data are inconsistent when it comes to the type and incidence of certain mental disorders among the offenders, so this percentage varies between 10% and 91% [34–36]. In addition, review articles that discuss mental illness among adults, minors, men, women, and prisoners, claim that psychiatric disorders are generally more common among the offenders compared to the general population [37] and that the presence of comorbid mental disorder increases the chance of becoming an offender [38]. High rates of personality disorders in the sample match the data found in other studies claiming that these disorders are present in 13% to 24% of offenders and that emotionally unstable and dissocial personality disorders are the most common ones [39, 40]. This is also supported by the fact that people who start developing addiction usually have a personality disorder, which is typically treated as the premorbid personality of addicts [41]. It is estimated that prisoners are 20 times more likely to have personality disorders than the general population, which certainly points to personality disorders as risk factors for committing crimes [42]. According to some research, 85% of prisoners are addicted to psychoactive substances [43]. This distribution of addiction to psychoactive substances in offenders has been confirmed in similar research, i.e. the connection between crimes and alcohol, which can be explained by the influence of alcohol on cognitive and conative abilities [44]. Both our research and similar ones show that 34 - 59% of men commit crimes under the influence of psychoactive substances, and that most offenders were under the influence of alcohol while committing a crime [45]. Some authors report that a high number (between 50% and 90%) of felonies which include aggression (e.g. murder, grievous bodily harm, violent behavior) were committed by alcohol addicts under the influence of alcohol [46]. If we compare addiction and substance abuse, addiction increases the likelihood of committing a felony and recidivism [47, 48]. Heroin addicts commit 15 times more robberies, 20 times more burglaries, and 10 times more common thefts (all of which are offences against property) compared to other criminals [49]. However, the results of our research do not support this, but provide insights into offences against human health, i.e. unlawful production and circulation of narcotics. There are several interpretations of the nature of the relationship between drugs and crime, namely that the drug use precedes crime, then that crime precedes the drug use, and the third interpretation is that both behaviors are the result of the same risk factors [50]. There is extensive empirical material for all three models, so it is likely that there are all three variations of the common occurrence of addictive behavior and crime.

Conclusion

The results of this research indicate that in the criminal offenders from the territory of the Republic of Serbia, there is a significant connection between addiction to psychoactive substances and committing a crime, which is in agreement with the findings of current research studies. It was found that alcohol addicts, compared to persons addicted to other psychoactive substances, commit crimes significantly

more often, as well as that they most often commit offences against life and body, while opioid addicts more often commit offences against property.

By analyzing the connection between sociodemographic and psychopathological characteristics of the examined group of addicts who committed crimes, we confirmed that gender, age, employment, history of committing crimes, and comorbid diagnosis of mental disorders, are important predictors of future aggressive behavior.

The continuity in the research of factors that can contribute to more adequate prediction, as well as primary and secondary crime prevention in the population of persons with mental disorders, is and must remain the professional minimum in socially responsible postulates of psychiatry as a profession and science.

In that respect, it is necessary to construct modalities of not only transversal, but also dynamic professional monitoring of persons with increased risk of committing crimes in the future, all with the aim of interventions that would reduce crime rates in the population with a diagnosed addiction.

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FEBRILE AND AFEBRILE SEIZURES ASSOCIATED WITH MILD ACUTE GASTROENTERITIS IN CHILDHOOD

FEBRILNI I AFEBRILNI NAPADI UDRUŽENI SA BLAGIM AKUTNIM GASTROENTERITISOM U DETINJSTVU

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Summary

Introduction. Seizures associated with mild acute gastroenteritis are very common in early childhood. The aim of this study is to provide basic information about seizures associated with acute gastroenteritis in order to distinguish these two entities and contribute to proper diagnosis and treatment. **Material and Methods.** Data were collected retrospectively from the medical records of consecutive children admitted to the Pediatric Clinic due to seizures associated with mild acute gastroenteritis in the period from October 2021 to April 2022. Patients were divided into two groups: febrile and afebrile. We compared the demographic and clinical characteristics of these two groups, as well as the microbiological, neurophysiological and neuroradiological characteristics. **Results.** Of the children with acute gastroenteritis and seizures, 11 were afebrile and 20 were febrile, with male predominance. The most frequently identified enteropathogen was rotavirus. Most patients presented with generalized seizures. The comparison of febrile and afebrile patients showed that cluster seizures were more common in the afebrile group ($p < 0.05$). Seven patients had a seizure that lasted longer than 5 minutes and all of them were from the febrile group ($p < 0.01$). All patients presented with normal neuroimaging findings. **Conclusion.** In clinical settings, making a distinction between febrile and afebrile gastroenteritis-related seizures as separate entities can be very difficult. It is still unclear what effect fever has on the onset of gastroenteritis-associated seizures, and whether febrile and afebrile seizures have a distinctly different pathophysiological mechanism, which is why further research is needed.

Key words: Seizures, Febrile; Seizures; Gastroenteritis; Child; Diagnosis; Rotavirus; Fever; Signs and Symptoms

Sažetak

Uvod. Konvulzije udružene sa akutnim gastroenteritisom su veoma česta pojava u ranom detinjstvu. Cilj ove studije je da pruži osnovne informacije o konvulzijama koje su udružene sa akutnim gastroenteritisom, od čega zavisi dalja dijagnostika i lečenje. **Materijal i metode.** Retrospektivno su prikupljeni podaci iz medicinskih kartona dece koja su bila hospitalizovana na Klinici za pedijatriju zbog konvulzija udruženih sa akutnim gastroenteritisom u periodu od oktobra 2021. do aprila 2022. Pacijenti su podeljeni u dve grupe: febrilni i afebrilni. Poredili smo demografske i kliničke karakteristike ove dve grupe, kao i mikrobiološke, neurofiziološke i neuroradiološke karakteristike. **Rezultati.** Od dece koja su imala akutni gastroenteritis i konvulzije, 11 dece je bilo afebrilno a njih 20 je bilo febrilno, sa predominacijom muškog pola. Najčešće izolovani enteropatogen je bio *Rota* virus. Najviše pacijenata je imalo generalizovani napad. Poređenjem febrilne i afebrilne grupe uočeno je da su ponavljane napade češće imala deca iz afebrilne grupe ($p < 0,05$). Sedam pacijenata je imalo napad koji je trajao duže od 5 minuta, od kojih su svi bili iz febrilne grupe ($p < 0,01$). Kod svih pacijenata su dobijeni uredni neuroradiološki nalazi. **Zaključak.** U kliničkim uslovima razlikovanje febrilnog i afebrilnog napada udruženog sa akutnim gastroenteritisom može biti veoma teško. Još uvek je nepoznato kakav uticaj ima temperatura na nastanak konvulzija udruženih sa gastroenteritisom, kao i da li febrilni i afebrilni napadi imaju drugačiji patofiziološki mehanizam, zbog čega su potrebna dalja istraživanja.

Ključne reči: febrilne konvulzije; napadi; gastroenteritis; dete; dijagnoza; rotavirus; visoka temperatura; znaci i simptomi

Introduction

Acute gastroenteritis (AGE) is the leading cause of global morbidity in young children. The clinical manifestations of AGE include abdominal pain, vomiting, diarrhea and fever. Some patients with AGE may develop convulsions that may be febrile or afebrile. Specific enteric pathogens have been linked to convulsions in children, such as rotavirus, norovirus, adenovirus, Campylobacter and Shigella [1].

When seizures occur concomitantly with AGE, it is usually referred to as benign convulsions associated with mild gastroenteritis (CwG). The CwG are benign seizures that occur in infants and children aged from 6 months to 6 years and they were first described by Morooka et al. in 1982 [2, 3]. Komori et al. defined benign convulsions with gas-

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Abbreviations
AGE – acute gastroenteritis
CwG – convulsions associated with mild gastroenteritis

troenteritis as afebrile tonic-clonic convulsions in healthy children, which occur between the first and fifth sick day of viral gastroenteritis and are typically associated with normal electrolyte and glucose levels with low risk of recurrence. They are short-lasting seizures (≤ 5 minutes) that can occur in clusters within 24 hours. Additionally, if the season is early winter or spring when rotavirus and norovirus are prevalent, CwG must be considered [4–6]. Although the mean interval between enteric symptom onset and seizure onset in CwG is roughly 2 days, some patients may experience seizures before enteric symptoms, meaning that clinicians should exercise caution during early winter and spring, when the prevalence of CwG is especially high [7]. In clinical settings, a fever accompanying an AGE episode is not a rare scenario. High-grade fever accompanying AGE may induce seizures, particularly among infants and young children, who are more susceptible to febrile stimuli due to immaturity of the brain [2].

Febrile seizures typically occur in children from 6 months to 5 years of age in association with fever over 38 °C, who do not have evidence of an intracranial cause, another definable cause of seizure (e.g., electrolyte imbalance, hypoglycemia, drug use, or drug withdrawal), or a history of an afebrile seizure. In most cases, febrile seizures occur within the first day of the fever. The seizure usually lasts for a few seconds to at most 15 minutes (usually less than 5 minutes), followed by a brief postictal period of drowsiness, and does not recur within 24 hours [8, 9].

In clinical settings it is necessary to characterize the seizure to determine the nature of examination and treatment, although distinguishing febrile and afebrile gastroenteritis-related seizures as separate entities may be difficult. Convulsions are very common phenomena in children, but there is still insufficient data that compare the characteristics of febrile and afebrile seizures during a mild AGE episode [2, 10].

Material and Methods

Data were collected retrospectively from the medical records of consecutive children admitted to our hospital due to seizures associated with mild gastroenteritis from October 2021 to April 2022, in the period of the year when gastrointestinal infections are most common in young children. We defined "mild AGE" as a single AGE episode without moderate to severe complications, such as dehydration, electrolyte imbalance, or hypoglycemia.

The inclusion criteria for patients in this study were as follows: being previously healthy, aged from 6 months to 6 years, with normal neurological development, and negative history of epilepsy. The exclusion criteria included having a history of meningitis, encephalitis, encephalopathy, cerebral trauma, brain tumor, hypoxia, or any other underlying diseases of the central nervous system. Patients were categorized into two groups: febrile group included children who had a central body temperature higher than 38 °C within 24 h of AGE-related seizures; and afebrile group of patients with an average temperature throughout the AGE course. Background, demographic data, clinical and microbiological characteristics, neurophysiological and neuroradiological presentations were compared in the two groups. The data were analyzed using the Statistical Package for Social Science for Windows. The chi-squared (χ^2) was used to compare categorical variables according to the analyzed sample size and the student t-test was used to compare continuous variables between the febrile and afebrile group. The $p < 0.05$ was considered statistically significant.

Results

During the study period from October 2021 to April 2022, 31 children with febrile and afebrile seizures and mild gastroenteritis were admitted to the Pediatric Clinic in Novi Sad. The patients were divided in two groups – 20 febrile patients and 11 afebrile patients **(Graph 1)**. The seizures were more frequent in male (58%) than in female (42%) patients. The mean age in febrile patients was 21.5 months, and 16.8 months in afebrile. The youngest patient was 6 months old, and the oldest 68 months old. Diarrhea was the most common symptom: 14 patients (45%) presented only with diarrhea, 11 patients (35.5%) had both diarrhea and vomiting, and 6 patients (29.5%) experienced only vomiting. Sixteen patients were examined for causative enteropathogens. The most commonly identified enteropathogen was rotavirus (43.75%), followed by adenovirus (18.75%) and coxsackievirus B (6.25%). Three patients (18.75%) presented only with severe acute respiratory syndrome coronavirus 2. One patient had bacterial gastroenteritis, with Salmonella enteritidis isolated from the stool, and one patient had concomitant infection with rotavirus and Campylobacter jejuni.

The comparison of medical history data showed that 4 patients in the febrile group and 3 patients in

Graph 1. Patients with febrile and afebrile seizures associated with mild gastroenteritis
Grafikon 1. *Pacijenti sa febrilnim i afebrilnim napadima udruženi sa akutni gastroenteritisom*

Table 1. Clinical-demographic characteristics of patients with febrile and afebrile seizures associated with mild acute gastroenteritis
Tabela 1. *Kliničko-demografske karakteristika pacijenata sa febrilnim ili afebrilnim napadima udruženi sa blagim akutnim gastroenteritisom*

	Febrile/*Febrilni* (n/*br.*=20)	Afebrile/*Afebrilni* (n/*br.*=11)	p value/*p vrednost*
Age in months (mean, standard deviation and range)/*Uzrast u mesecima (srednja vrednost standardna devijacija, raspon)*	21.5 +/- 12.3 (11 – 68)	16.8 +/- 9.4 (6 – 36)	p > 0.05
Male gender/*Muški pol*	11	7	p > 0.05
Past history of febrile seizures *Pozitivna anamneza o ranijim febrilnim napadima*	4 (20%)	3 (27%)	p > 0.05
Family history of febrile seizures or epilepsy/*Pozitivna porodična anamneza o febrilnim napadima ili epilepsiji*	8 (40%)	4 (36.4%)	p > 0.05
Seizure semiology/*Semiologija napada*			
Generalized tonic-clonic seizure *Generalizovani tonično-klonični napad*	20 (100%)	7 (63.6%)	p < 0.05
Generalized atonic seizure *Generalizovani atonični napad*	/	2 (18.2%)	
Partial seizure/*Parcijalni napad*	/	2 (18.2%)	
Patients with cluster seizures *Pacijenti sa klaster napadima*	4 (20%)	6 (54.5%)	p < 0.05
Seizure frequency/*Učestalost napada*	1.3 +/- 0.6 (range 1-3)	3.63 +/-3.04 (range 1 - 10)	p < 0.05
Seizure duration > 5 minutes *Trajanje napada >5 minuta*	7 (35%)	/	p < 0.01
Interval from the onset of gastrointestinal symptoms/*Interval od početka gastrointestinalnih tegoba*	1.5 +/-0.82 (1-4 days)	1.72 +/-0.9 (1-3 days)	p > 0.05

the afebrile group had a history of previous febrile seizures **(Table 1)**. Family history of febrile seizures or epilepsy was positive in 4 patients in the afebrile group and in 8 patients in the febrile group. One patient from the febrile group that presented with convulsions had a positive past history of febrile seizures and a positive family history. As of the seizure semiology, generalized tonic-clonic seizure was the most prevalent in both groups. Two patients presented with partial seizure and two patients had generalized atonic seizure, all of them from the afebrile group. Ten patients had clustered seizures. There were 6 patients in the afebrile group who had two or more seizures, that is from one to ten episodes. Furthermore, there were 4 patients in the febrile group who had multiple seizures ranging from one to three episodes. Seven patients had a seizure that lasted longer than 5 minutes and all of them were from the febrile group. We observed intervals between the onset of acute gastroenteritis symptoms and the first seizure, and most of the patients from both groups presented with a seizure in the first day of sickness (54.8%). Normal neuroimaging findings were reported in all patients. Five patients had abnormal electroencephalographic findings, with temporary abnormalities like slow background activity and sharp wave discharge. Emergency anticonvulsant treatment was administered to children who had prolonged or repeated seizures. Diazepam or midazolam were used as first line treatment. Twelve patients responded well to the initial treatment; however, 5 patients were unresponsive to the repeated doses of benzodiazepines and received phenobarbital. None of the patients was discharged with continuous anticonvulsant therapy.

Discussion

It is well known that seizures are one of the complications of acute gastroenteritis in pediatric patients. Although seizures may be explained by hypoglycemia, electrolyte imbalance and dehydration, patients included in this study had normal laboratory findings. Benign convulsions associated with gastroenteritis are a relatively newly recognized entity described by Mooroka et al. in 1982. Since then, several studies have described it, as well as the similarities between CwG and febrile seizures [1, 2, 4–6, 11, 12]. In our study, clinical and demographic characteristics of febrile and afebrile seizures associated with acute gastroenteritis were analyzed. We found that the afebrile and febrile patients with AGE-related seizures shared similar clinical and laboratory features; however, there were still some distinct characteristics between the two groups.

When it comes to the age at which seizures occur, our data are similar to previously published papers about CwG [2–4, 12, 13]. Studies have shown that their incidence is similar in both sexes, with few reports of female dominance, with a male to female ratio of 1: 1.5 - 1.8 [5, 10]. Our study showed male predominance with 58% of male patients. As described in many studies, the most commonly identified enteropathogen was rotavirus [2, 3, 5, 11]. The finding of seasonal clustering of CwG cases strongly suggests the role of infectious pathogens, specifically rotavirus as the possible cause of benign convulsions. Several researches have been performed to detect the exact virus-dependent mechanism in febrile CwG, but this pathogenesis still remains unclear [10, 12–14]. Most of the patients presented with diarrhea and seizures on the first day of sickness. Reports of other studies show that afebrile patients have longer intervals between the onset of enteric symptom and seizures than febrile patients [2, 4, 5, 7]. Some patients may even experience seizures before enteric symptoms [5, 7, 11]. When it comes to the interval between the onset of gastrointestinal symptoms and seizure onset, our study showed no statistical significance between the two groups, as reported in a study conducted by Kawano et al. [15]. The previously conducted studies showed that there were significant differences between the two groups when it comes to past history of febrile seizures and positive family history of febrile seizures or epilepsy [2, 13, 15]. Our study showed no statistically significant difference. However, comparison of seizure characteristics in the febrile and afebrile group revealed some significant differences. The majority of seizure types associated with CwG are known to be generalized seizures, focal features such as lateral eye deviation or complex partial seizures [4, 6, 9]. Most of our patients from both groups experienced a generalized tonic-clonic seizure, with 4 patients from afebrile group experiencing partial or generalized atonic seizures, with a significantly higher prevalence. The CwG is characterized by clusters of attacks, and children with CwG are at a higher risk of experiencing another seizure within 24 hours of the first seizure [3, 4, 6].

The duration of each seizure mostly ranged from 30 seconds to less than 5 minutes. Seven patients from febrile group presented with convulsions and two of them experienced seizures lasting around 30 minutes. The convulsions were treated with first line therapy - diazepam and midazolam, with good therapeutic response [16]. We registered statistically significant differences between the two groups, since data obtained from other studies differed, showing no significant difference between the two groups [2, 13]. Although many studies in the past showed good prognosis of CwG, in recent years, with the increase in follow-up studies being conducted, it was found that children with CwG have some risk of seizure recurrence. Furthermore, if the age of seizure onset is ≤ 18 months and if there is a positive family history of epilepsy or febrile seizures, these children should be closely followed up within 6 - 12 months from the first episode [17].

Conclusion

Distinguishing febrile and afebrile gastroenteritis-related seizures as separate entities may be difficult, since fever accompanying acute gastroenteritis in children is not a rare finding. It is still unclear what effect fever has on the onset of gastroenteritis-associated seizures, and whether febrile and afebrile seizures have distinctly different pathophysiology. Further follow up studies are needed to better understand characteristics and prognosis of benign convulsions associated with mild gastroenteritis. Comprehensive knowledge of pediatricians should help to avoid unnecessary diagnostic tests and usage of anticonvulsants.

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SELF-ASSESSMENT OF THE RISK OF SEXUALLY TRANSMITTED DISEASES

SAMOPROCENA RIZIKA ZA DOBIJANJE POLNO PRENOSIVIH BOLESTI

Aleksandra BULOVIĆ[1, 2], Jelena ĐURICA[1, 2], Miloš NIŠAVIĆ[1, 3] and Vanja ANDRIĆ[1, 2]

Summary

Introduction. Sexually transmitted diseases can be prevented, but it is necessary to know how the infection is transmitted and be aware of the possibility of infection that will lead to change in behavior. Regular testing for sexually transmitted infections is also of crucial importance to prevent its further spread and the development of complications of the infection. The aim of this study was to examine the incidence of risky behaviors in the population of men who have sex with men, their self-assessment of the risk of sexually transmitted diseases, as well as the incidence of testing for these infections. **Material and Methods**. The study was conducted in the territory of the City of Novi Sad in the population of 185 men who have sex with men. The research method was an anonymous online survey that respondents filled out on a voluntary basis, with previously provided information about the research. **Results**. Of the total number of respondents, 39% claimed that they had unprotected sex with at least one partner in the previous year. Among the respondents who had unprotected sex in the past year, only 12% believe that they are at high risk of sexually transmitted diseases, and 42% of them have not been tested for sexually transmitted diseases in the past year. **Conclusion.** In conclusion, a large number of untested people practice risky sex and have a poor perception of the risk of sexually transmitted diseases. The common reason for not getting tested is fear or lack of information about testing.

Key words: Sexually Transmitted Diseases; Self-Assessment; Risk Assessment; HIV; HIV Testing; Sexual Behavior; Health Risk Behaviors

Sažetak

Uvod. Polno prenosive infekcije se mogu sprečiti, ali je potrebno znanje o načinu prenošenja infekcije, kao i svest o mogućnosti infekcije, koji će dovesti do promene ponašanja. Od krucijalnog je značaja i redovno testiranje na polno prenosive infekcije zbog sprečavanja daljeg širenja infekcije, kao i sprečavanja razvoja komplikacija infekcije kod pojedinaca. Cilj ovog rada bio je da se ispita učestalost rizičnog ponašanja u populaciji muškaraca koji imaju seks sa muškarcima, njihova samoprocena rizika od dobijanja polno prenosivih infekcija, kao i učestalost testiranja ispitanika na ove infekcije. **Materijal i metode.** Istraživanje je sprovedeno na teritoriji grada Novog Sada u okviru populacije muškaraca koji imaju seks sa muškarcima na uzorku od 185 ispitanika. Metod istraživanja je bila anonimna onlajn anketa koju su ispitanici popunjavali na dobrovoljnoj bazi, uz prethodno dat tekst o informacijama u vezi sa istraživanjem. **Rezultati.** Od ukupnog broja ispitanika, 39% je navelo da je imalo nezaštićene seksualne odnose sa najmanje jednim partnerom tokom prethodne godine. U okviru grupe ispitanika koji su imali nezaštićene seksualne odnose u poslednjih godinu dana, samo 12% smatra da je u visokom riziku za dobijanje seksualno prenosivih bolesti, a 42% njih se nije testiralo na polno prenosive bolesti u poslednjih godinu dana. **Zaključak.** U zaključku veliki broj netestiranih praktikuje rizične seksualne odnose i ima lošu percepciju o riziku za dobijanje polno prenosivih bolesti. Razlog netestiranja je često strah ili nedovoljna informisanost o testiranju.

Ključne reči: polno prenosive bolesti; samoprocena; procena rizika; HIV; testiranje na HIV; seksualno ponašanje; ponašanje rizično po zdravlje

Introduction

According to the latest data, about 3,300 people in Serbia are positive for human immunodeficiency virus (HIV), while there are 37,700,000 people with HIV in the world [1, 2]. In order to prevent further growth in the incidence of HIV, it is important to inform the population about the ways the virus is transmitted, its clinical manifestations, as well as various testing options. As far as HIV is concerned, humans are the only reservoir of infection, and the sources of infection are body fluids: blood, semen, vaginal secretions, and breast milk. The HIV infection is transmitted sexually, parenterally (blood) and vertically. The sexual route of transmission is the most common and the receptive anal intercourse is considered to be the most risky for virus transmission [3]. Other sexually transmitted diseases (STDs) that often accompany HIV are hepatitis B, hepatitis C and syphilis [4]. Early diagnosis of infection is crucial for the further course of the disease, so in that context, self-assessment of the risk of infection is important, so that the individual is aware of the need for testing. Risk perception of infection is an assessment of the individual's own risk of STDs. One assesses the risk based on their own opinion

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Abbreviations

MSM – men who have sex with men
HIV – human immunodeficiency virus
STDs – sexually transmitted diseases
PrEP – pre-exposure prophylaxis
cART – combination antiretroviral therapy

about how much they were at risk of infection. It can be a strong motivating factor for reducing risk behaviors, increasing the number of tested, and thus reducing the risk of infection. Testing for STDs is done for epidemiological and clinical reasons. Epidemiological reasons include possible exposure to HIV, such as unprotected sexual intercourse, intravenous drug use, as well as contact with an infected person or blood by medical staff. Clinical reasons for testing imply testing due to the presence of symptoms. In addition to diagnosis as a measure to prevent the spread of STDs, for their early detection and adequate treatment, one should also think about preventing infection in general. Fortunately, today there are a number of measures that individuals can take to prevent the spread of STDs. Condoms are the best way to prevent STDs, but a great number of people still engage in risky sexual behavior despite the risk of infection. This raises the question of whether the problem is the lack of information about the protection during sexual intercourse and STDs in general, or the behavior of individuals with adequate knowledge of STDs. For this reason, education on preventive measures should be conducted so that they are accepted and adequately implemented.

Due to the fact that classical preventive measures did not give adequate results in slowing down the growing trend of HIV, there was a need to improve prevention with new methods. One of them is pre-exposure prophylaxis (PrEP) with antiretroviral drugs. It includes a combination of two drugs, tenofovir disoproxil fumarate and emtricitabine, which can be used daily or as needed. The World Health Organization recommends PrEP to people who are at significant risk of HIV infection, and this includes the population of men who have sex with men (MSM). According to the conducted studies, the safety and effectiveness of PrEP is over 90%, which gives it a significant place in the prevention of HIV infection. The HIV testing is necessary before starting to use PrEP. This is important because there is a possibility of developing resistance if the person is already HIV positive. Despite prophylaxis, it is necessary to continue regular testing, because early detection of the disease is important in preventing the spread of infection and a better outcome of treatment with early application of adequate therapy [5]. In addition to PrEP, which reduces the risk of infection, there is a very effective post-exposure procedure. Namely, the use of antiretroviral drugs early enough after exposure to HIV can reduce the risk of infection by more than 80% [6].

Thanks to the existence of combination antiretroviral therapy (cART), the idea of HIV as a chronic disease has emerged. Chronic HIV infection destroys the immune system and thus creates a basis for the development of a large number of other diseases, especially those found in the acquired immunodeficiency syndrome (AIDS) stage. Therefore, the emphasis should be placed on early detection of HIV infection, regular testing and other modalities of prevention [7].

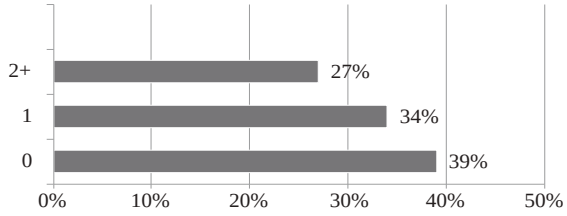
The goals of this research were to determine the incidence of risky behavior in the population of MSM, the level of risk perception of STDs in MSM, and to determine the frequency of testing for STDs in relation to risky behavior in the population of MSM.

Material and Methods

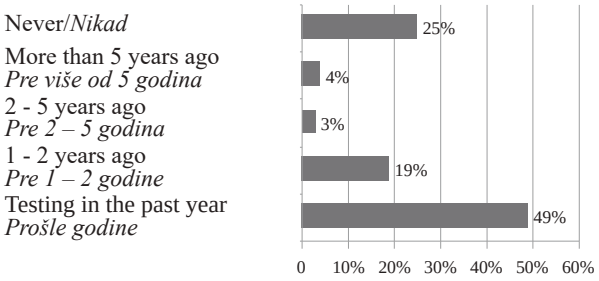
The study was conducted in the territory of the City of Novi Sad in the population of 185 MSM. The research method was an anonymous online survey posted on www.gayromeo.com. The surveyed population were all persons who were active on the site during the survey and wanted to complete an anonymous online survey. The participants were contacted via personal message with a request to participate in the study. Out of the total number of respondents, 30 surveys were filled out incorrectly, and 155 respondents were included as the final sample. The survey consisted of 12 questions with multiple-choice answers. The questions about the age, level of education, number of sexual partners, use of protection in relationships, and finally risk perception of STDs. The next set of questions were related to STD testing in terms of frequency, reasons for and against testing, and the place of testing. The basic method in data processing was the method of descriptive statistics in Excel, as a tool for calculation, tabular and graphical presentation.

Results

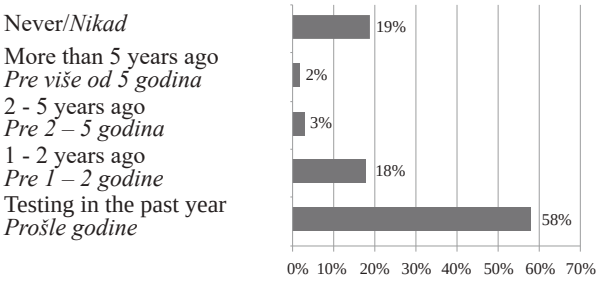
The total number of completed surveys was 185, of which 30 were incorrectly or incompletely filled out, and for that reason the research included 155 surveys for statistical analysis. A total of 155 men participated in the survey, most of whom were aged between 25 and 34 years, to be exact 68 of them (44%). None of the respondents were aged between 55 - 64 years, but 1% of the respondents were over 65. Also, the level of education of the respondents



Graph 1. The number of sexual partners with whom the sex was unprotected (in the past year)
Grafikon 1. *Broj seksualnih partnera sa kojima je odnos bio bez zaštite (u poslednjih godinu dana)*



Graph 2. Time of testing for STDs in the whole sample
Grafikon 2. *Vreme testiranja na polno prenosive bolesti u celom ispitivanom uzorku*



Graph 3. Time of testing for STDs in the group of respondents who engaged in risky behavior
Grafikon 3. *Vreme testiranja na polno prenosive infekcije u grupi ispitanika koji su naveli rizično ponašanje*

was analyzed and as many as 108 (70%) have attained university education, while only 1% have attained only primary education. The risky behavior of the respondents was further analyzed. Of 155 respondents, 104 (67%) answered that they had more than five partners in the past five years, while 30 (19%) respondents had 2 - 4 partners, and 21 had 0 - 1 (14%) partners in the past five years. The next question also referred to the risk factors, but in terms of unprotected sex. Interestingly, almost two-thirds of respondents (61%) had unprotected sex in the past year, and half of them with more than two partners in that period **(Graph 1)**. Regarding the time of testing for STDs, the frequency of testing in the whole sample indicates that the percentage of tested subjects in the previous year is 49%, and the percentage of respondents who have never been tested is 25%. **Graph 2** presents data related to testing periods in the whole sample. Furthermore, we analyzed the number of persons tested for STDs in the group of respondents who had unprotected sex in the past year (94 respondents). Only 58% of the respondents from this group were tested for STDs, and as many as 19% from this group have never been tested. **Graph 3** shows that as many as one fifth of the respondents have never been tested for STD's, although they practiced unprotected sex. Most of the respondents were tested in the past year. A total of 80 (52%) respondents answered that they had sex with several partners in the same period. The problem is that out of 80 respondents who had sex with several partners in the same period, 58 had sex without a condom. Therefore, the risk of spreading sexually transmitted infections among these subjects increases significantly. Out of 155 respondents, only 20 (13%) answered that they had sex with new partners without condoms, while 135 (87%) answered that they use condoms when starting sexual relations with a new partner. The issue with this question is that the respondents were asked about their first intercourse with a new partner, which does not mean that they did not later decide to have unprotected sex. Although the percentage of persons practicing unprotected sex with new partners is low, 80% had multiple partners at the same time, 70% had unprotected sex in the past year, and 90% had more than 5 sexual partners in the past 5 years. Respondents were asked to assess their own risk of STDs and 84 (54%) answered that there was no risk, 58 (38%) answered that the risk was

Table 1. Reasons for getting tested for STDs
Tabela 1. *Razlozi testiranja na polno prenosive bolesti*

Statement/*Izjava*	Number of respondents/*Broj ispitanika*	
	No./*Br.*	%
Because of traveling abroad or because of getting insurance *Zbog putovanja u inostranstvo ili zbog dobijanja osiguranja*	8	4%
As part of a routine check-up for STDs *Kao deo rutinske provere na polno prenosive bolesti*	63	29%
As part of a routine health check/*Kao deo rutinske provere zdravlja*	57	27%
I want to stop using a condom in a relationship *Želim da prestanem da koristim kondom u vezi*	13	6%
I was afraid of my own risk and/or risk of my partner *Plašio sam se sopstvenog rizika i/ili rizika za partnera*	27	13%
The doctor recommended that I get tested/*Doktor mi je preporučio da se testiram*	7	3%
Due to risky sexual behavior (sex without a condom) *Zbog rizičnog seksualnog ponašanja (seksualni odnos bez kondoma)*	33	15%
Other/*Ostalo*	6	3%

Legenda: STDs - polno prenosive bolesti

Table 2. Reasons why respondents did not get tested
Tabela 2. *Razlozi zbog kojih se ispitanici nisu testirali*

Statement/*Izjava*	Number of respondents/*Broj ispitanika*	
	No./*Br.*	%
I am afraid to take the test/*Imam strah od testiranja*	13	15%
There was no need, I always use a condom *Nije bilo potrebe uvek koristim kondom*	18	21%
I don't like dealing with the health care system *Ne volim da imam dodira sa zdravstvenim sistemom*	2	2%
I am afraid of being stigmatized and discriminated *Plašim se stigme, diskriminacije*	6	7%
I have a fear of needles and getting blood drawn *Imam strah od igala i vađenja krvi*	5	6%
I fear of the test results/*Plašim se rezultata*	11	13%
I am afraid of being seen getting tested by someone I know *Plašim se da me neko poznat ne vidi da se testiram*	11	13%
I didn't know where to get tested/*Nisam znao gde da se testiram*	11	13%
I am not sure if I need to pay for it/*Nisam siguran da li se plaća*	5	6%
I am afraid of the legal consequences if I am HIV+ *Plašim se pravnih posledica ukoliko dobijem rezultat da sam HIV +*	2	2%
I don't have enough knowledge and information about the importance of HIV testing *Nemam dovoljno znanja i informacija o značaju potrebe testiranja na HIV*	1	1%
Other/*Ostalo*	2	2%

Legenda: HIV - virus humane imunodeficijencije

Table 3. Places where the examinees got tested for STDs
Tabela 3. *Mesto testiranja na polno prenosive bolesti*

Statement *Izjava*	Number of respondents/*Broj ispitanika*	
	No./*Br.*	%
Private laboratories/*Privatne laboratorije*	31	27%
In a hospital/*U bolnici*	9	8%
Institute of Public Health/*Institut za javno zdravlje*	59	51%
Institute for Student Health Care/*Zavod za zdravstvenu zaštitu studenata*	3	2%
Free of charge testing offered by non-governmental organizations *Deo akcija nevladinih organizacija*	6	5%
Elsewhere/*Negde drugde*	8	7%

medium, while only 13 (8%) answered that there was a high risk of STDs. It is also important to perform a risk assessment analysis for those who had unprotected sex in the past year. Of 94 men, 47 (50%) believe the risk is low or non-existent, 36 (38%) think they are at medium risk of STDs, and only 11 (12%) think they are at high risk of getting STDs. It is extremely interesting and important that half of the respondents who have unprotected sex believe that they are not at risk of STDs. This is certainly a sign of a very poor risk perception of half of the respondents who are at real risk of STDs.

We were further interested in the reasons for getting tested for STDs. The greatest number, i.e. 63 respondents, answered that they get tested as part of a routine STD test, which speaks in favor of the fact that a certain number of respondents are aware of the risk. It is interesting that only 15% of respondents get tested because they are aware of their risky behavior and almost the same percentage because they have to (because of a visa, for example). Other results are shown as a percentage in **Table 1**. The research also examined the reasons why the respondents were not tested. Most of the respondents answered that there was no need for testing. About a fifth of respondents do not get tested for fear of testing, positive results, or being recognized. All results are shown in **Table 2.** As for the place of getting tested for STDs, most of the respondents, i.e. 59 of them, named the Institute of Public Health. Other results are shown as a percentage in **Table 3**.

Discussion

Risk perception of the risk of STDs is primarily related to knowledge about the existence of risk, and then to the perception of one's own behavior

that may lead to infection. The importance of self-assessment of the risk of STDs is extremely important for early detection of infection and timely treatment. If not treated in time, all STDs may lead to permanent consequences and serious health damage. On the other hand, the importance of STD risk perception is important for STD prophylaxis. People who are aware of the risks are more likely to use protective measures. In the case of HIV infection, there is also a possibility of PrEP, which has proven to be a very effective method of prevention. The survey we conducted dealt with the assessment of risky behavior, and determining the awareness of risky behavior. Finally, we wanted to determine whether awareness of risky behavior encouraged respondents to get tested for STDs. This is extremely important, because without awareness of the risk, the person is less likely to get tested. If a person does not have a perception of risky behavior, they are less likely to get tested and find out their status, i.e. they may further spread the infection.

In this survey, most men were in the age group between 25 and 34, which is logical considering that this is an online survey, i.e. people who use internet were selected. The number of partners mentioned by the respondents is relatively high, so we can assume that the respondents gave an honest answer, and 67% of respondents answered that they had more than 5 partners in the past 5 years. It is a worrying fact that 61% of those surveyed answered they had unprotected sex with at least one partner in the past year. This is a relatively high percentage, but according to the literature, it is not an unusual result. According to a research in China, the percentage of people who had unprotected sex in the last year was also high and amounted to 51% [8], while a research conducted in the United States showed a trend of declined use of condom in the past few years, as well as an increase in new HIV cases in the younger population, because they are not aware that the absence of symptoms does not mean the absence of infection [9]. There is also an increase in the number of sexual partners, and this is a problem because of the great number of unprotected sexual intercourses and poses a risk of STDs. In our survey, 61% of respondents said they had engaged in unprotected sex in the past year. Of the total sample, 13% claimed they had sex with a new partner without a condom. If we analyze only this group of respondents, 80% of them claimed they had multiple partners at the same time, 70% had risky sexual intercourse in the past year, and 90% had more than 5 partners in the same period. We come to the conclusion that, although this number is small, it is still significant due to the number of partners and the lack of protection against STDs. According to a survey conducted in the Netherlands in the population of MSM who have never been tested for STDs, 36% had unprotected sex with at least one person of unknown HIV status in the past year [10]. When it comes to risk perception for HIV and other STDs, of 61% of respondents who had unprotected sex in the past year, only 12% believe that they are at high risk of STDs, and 50% believe that the risk is low or non-existent. Perception of risk of infection is a key to testing, and in the study, 54% of the total sample rated their risk of STDs as low or non-existent. In the group of respondents who had risky sex in the past year, a statistical analysis of those tested for STDs was performed, and it was concluded that 58% had been tested for STDs in the past year, which means that 42% of respondents who were at risk had not been tested. Of the total sample, 49% of respondents were tested for STDs in the last year, and as many as 25% of them have never been tested before. These results support the results of a survey in Germany where 35% of respondents had never been tested, and of those who had unprotected sex in the past year, almost 50% had not been tested in the same period [11]. Comparing the results, we found that 50% of respondents who had unprotected sex in the past year assessed their risk as low or non-existent. This means that a large number of respondents who practice unprotected sex have a poor perception of their own risk. According to a study conducted in the United States by the Center of Disease Control as part of the National HIV Behavioral Curvature System project, one third of HIV-positive participants in the project did not know they were infected with the virus and claimed that they had unprotected sex recently [12]. This again supports the fact that every risky sex carries the risk of infection and testing is very important to prevent further spread of the infection due to the unknown HIV status.

Reasons for testing were also examined, and most examinees answered that routine health screening or routine testing for STDs were the reasons. Only 21% of respondents answered that they were tested because of risky behavior, and the research shows that 61% of respondents had unprotected sex in the past year, which again supports the poor perception of risk by those who engage in risky sexual behavior. The same results were obtained in a study in the United Kingdom, where most respondents answered that they were tested for routine control, preoperative, etc., and a very small number were tested because they were advised by a doctor [13]. Most of the tests were done at the Institute of Public Health, which may indicate that there is a lack of information about free, anonymous HIV testing outside health institutions. When it comes to the reason why the respondents did not get tested, the highest percentage answered that they always use a condom and therefore believe that there is no need for testing, and the second reason was fear of testing. This was confirmed by a research in China, where fear of testing, stigma and discrimination was found to be an important factor in low STDs testing [14]. Testing for STDs provides early treatment and a better treatment outcome; however, in order to prevent infection, education on prophylactic measures of protection against STDs is needed. In addition to classic preventive measures, awareness of prophylactic measures, such as PrEP and post-exposure prophylaxis should be raised, as they have proven to be effective in a large percentage.

All the information, as well as free testing, can be obtained from non-governmental organizations such as the "Crvena Linija", where people can get tested anonymously without fear of stigma or discrimination, which was noted as the reason for not getting tested by a great percentage of respondents. Reducing risky behavior, as well as more frequent testing for STDs is extremely important for the health of individuals, and thus for the health of the entire population, because it allows early diagnosis of infection and prevention of its further spread. That is why it is crucial to raise awareness about risky behavior, preventive measures, and importance of regular testing and early detection of the disease.

Conclusion

The research showed that 54% of respondents assessed their risk of sexually transmitted diseases as low or non-existent. We also concluded that in the population of men who have sex with men there are a great number of those who engage in risky sex without protection and 61% of them claimed that they had unprotected sex in the past year. The study also showed that the risk assessment for sexually transmitted diseases is poor, since 50% of examinees who reported risky behavior claimed that the risk of infection is low or non-existent. The worrying fact is that 58% of respondents who reported risky behavior had never been tested for sexually transmitted diseases. Sexually transmitted diseases are spread due to the smaller number of individuals who get tested, because a great number do not use protection during sexual intercourse. Also, the research showed that most of the untested men were not tested due to fear of results, the test itself, lack of anonymity, and lack of information about testing. Of the total number of examinees, 78% answered that they were tested at the Institute of Public Health and private laboratories, meaning that the awareness of safe anonymous testing should be raised. In conclusion, there is a need to raise awareness about the risks, improve knowledge about sexually transmitted diseases, their transmission, ways of protection, and all this should be done using posters, brochures, through the media, education in schools and many other ways. Risk groups such as men who have sex with men should also get informed about places where they can be tested, anonymously, without fear of stigma and discrimination in order to prevent further spread of infection, promote risk awareness, because prevention and early diagnosis are key to preventing the spread of sexually transmitted diseases.

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FUNCTIONAL OUTCOMES AFTER SURGICAL TREATMENT OF ANTERIOR SOFT-TISSUE SHOULDER INSTABILITY USING A MINIMALLY INVASIVE ANTERIOR APPROACH

FUNKCIONALNI REZULTATI LEČENJA PREDNJE MEKOTKIVNE NESTABILNOSTI RAMENA MINIMALNO INVAZIVNIM PREDNJIM PRISTUPOM

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Summary

Introduction. The purpose of this paper is to present and analyze the results of treatment of anterior soft-tissue shoulder instability using an open surgical technique with a minimally invasive anterior approach, as well as to emphasize the benefits of using an open surgical procedure in high-risk patients. **Material and Methods**. All patients underwent surgery at the Clinic of Orthopedic Surgery and Traumatology in Novi Sad in the period between January 2013 and September 2017. Out of 138 patients undergoing surgery for anterior shoulder instability, 40 patients came for follow-up examination. The average age of subjects was 27 ± 6. Medical history was taken from each patient and the range of motion and muscle strength of the operated shoulder was examined. The subjects filled out a questionnaire regarding the functional status of the operated shoulder, their experience in resuming sports activities, and their subjective feeling of pain. The Constant-Murley score was used to assess the postoperative results. **Results**. Postoperatively, the mean Constant-Murley score was 90.3 ± 11.5, while 87.5% patients had excellent and good results. Compared to the contralateral uninjured shoulder, there was a statistically significant difference ($p < 0.05$) in the Constant-Murley score, in external rotation of the abducted shoulder (13.2° ± 10.4°), as well as in shoulder adduction (10.25° ± 9.7°). Out of 35 patients who were athletes, 27 continued to actively engage in sports following the surgical treatment. Four patients had a re-dislocation (10%). **Conclusion**. Open surgical treatment of the anterior shoulder joint instability using a minimally invasive anterior approach is a reliable, time-tested procedure that provides favorable clinical results in young high-risk contact and overhead athletes with timely diagnosis and surgical care.

Key words: Open, Bankart; Shoulder; Anterior; Instability;

Sažetak

Uvod. Cilj ovog rada je prikaz i analiza rezultata lečenja prednje mekotkivne nestabilnosti ramena otvorenom hirurškom tehnikom minimalno invazivnim prednjim pristupom i ukazivanje na značaj primene otvorene procedure kod visokorizičnih pacijenata. **Materijal i metode**. Svi pacijenti su operisani na Klinici za ortopedsku hirurgiju i traumatologiju u Novom Sadu u periodu od januara 2013. do septembra 2017. godine. Od 138 operisanih pacijenata sa prednjom nestabilnosti ramena, 40 pacijenata se odazvalo na kontrolu. Prosečna starost ispitanika bila je 27 ± 6 godina. Svim pacijentima je uzeta anamneza i izvršen pregled obima pokreta i mišićne snage operisanog ramena. Ispitanici su popunjavali upitnik u vezi sa funkcionalnim stanjem operisanog ramena, povratkom sportu i subjektivnim osećajem bola. Za procenu postoperativnih rezultata korišćena je Konstantova bodovna skala. **Rezultati.** Postoperativno srednja vrednost Konstantove bodovne skale iznosila je 90,3 ± 11,5, dok je odličan i dobar rezultat imalo 87,5% pacijenata. U poređenju sa suprotnim nepovređenim ramenom, postojala je statistički značajna razlika ($p < 0,05$) u Konstantovoj bodovnoj skali, u spoljašnjoj rotaciji obdukovanog ramena (13,2° ± 10,4°), kao i u adukovanom položaju ramena (10,25° ± 9,7°). Od 35 pacijenata koji su se prethodno izjasnili kao sportisti, 27 je nastavilo da se aktivno bavi sportom nakon operativnog lečenja. Četiri pacijenta je imalo redislokaciju (10%). **Zaključak**. Otvoreni hirurški tretman prednje nestabilnosti zgloba ramena minimalno invazivnim prednjim pristupom je pouzdana, vremenski testirana procedura koja daje dobre kliničke rezultate, kod visokorizičnih mladih, kontaktnih i *overhead* sportista koji su pravovremeno dijagnostikovani i hirurški zbrinuti.

Ključne reči: Otvoreni, Bankart; Rame; Prednja; Nestabilnost;

Introduction

Shoulder joint injuries are common and there has been a noticeable increase in the number of such injuries in the last three decades [1–3]. Anterior dislocations are most common and they account for 90% of all shoulder dislocations [4]. They are the result of a considerable force, landing on an outstretched arm or a sudden and violent abduction and external rotation of the shoulder joint [5] leading to severe disability and limitations in daily and sports activities. Conservative treatment of anterior shoulder dislocation is

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Abbreviations
ISIS – instability severity index score

not a recommended treatment option in young athletes due to a risk of developing shoulder instability following the initial dislocation which occurs in over half of patients between the ages of 20 and 30 years, and up to 80% of patients under the age of 20 [6, 7]. High risk of dislocation recurrence, up to 80%, affects athletes who play overhead sports (the arms are lifted over the head), contact sports, and those with avulsion of the glenoid labrum verified by nuclear magnetic resonance imaging [8].

Anterior shoulder stabilization is the most common and most successful method of surgical treatment of unidirectional soft-tissue shoulder instability [9]. There are two types of surgical procedures: soft-tissue procedures with the objective of repositioning the glenoid labrum and the glenohumeral ligaments into the anatomical position with minimal damage to other shoulder joint structures [9, 10], and additional bone grafting procedures which are used to rebuild the damaged anterior border of the glenoid [11, 12]. The glenoid labrum is placed into the anatomical position around the edge of the glenoid fossa by means of open surgical or arthroscopic techniques. The open surgical procedure has been the gold standard for treating anterior shoulder instability up to the year 2000 [13] when the development of arthroscopic procedures and the improvement of arthroscopic instruments and materials started leading to excellent postoperative results [14]. However, over the years, the percentage of re-dislocations following arthroscopic procedures approached the percentage of re-dislocations occurring after the open surgical procedure [15, 16].

The purpose of this paper is to present and analyze the results of treatment of anterior soft-tissue shoulder instability using an open surgical technique with a minimally invasive anterior approach, as well as to emphasize the benefits of using open surgical procedures in high-risk patients.

Material and Methods

This retrospective study was performed with the approval of the Ethics Committee of the Clinical Center of Vojvodina. During the period between January 2013 and September 2017, 138 patients were treated for anterior shoulder joint instability using open, minimally invasive anterior approach surgery at the Clinic of Orthopedic Surgery and Traumatology of the Clinical Center of Vojvodina in Novi Sad. This study included 40 patients who came for follow-up examination **(Table 1)**. The sample included 34 men (85%) and 6 women (15%). The average age of the subjects was 27 ± 6, whereas 52.5% were between 20 and 29 years old. The most common mechanism of injury was a forced abduction and flexion of the arm in 80% of the cases. Initial dislocation occurred as a result of sports activities in 32 patients (80%). As much as 55% of athletes in this study were in overhead and contact sports. Half of the patients had more than 10 shoulder joint dislocations before the surgery, and nine of them experienced more than twenty dislocations. All patients had unidirectional instability determined by clinical examination of the affected shoulder.

All the patients underwent shoulder stabilization by means of open surgical technique with a minimally invasive anterior approach. Indications for soft-tissue shoulder stabilization include recurrent dislocations following non-operative treatment, avulsion of the glenoid labrum with bone defect of the glenoid surface < 13.5%, avulsion with an accompanying on-track Hill Sachs lesion (HSL) and/or humeral avulsion of glenohumeral ligament (HAGL) lesion [17–19], instability severity index score (ISIS) < 7 [20].

Open surgical procedure was performed instead of arthroscopic treatment, due to the fact that all of the subjects had a high risk of re-dislocation and that more than a half of them had more than ten luxations prior to surgical treatment. The anterolateral approach was used with an incision of up to 5 cm in the middle between the coracoid process of the scapula and the greater tubercle of the humerus instead of the more extensile deltopectoral approach. A part of the detached glenoid labrum and the anterior capsule of the shoulder joint were reattached to the anterior border of the glenoid using three or more anchors (Zimmer Biomet JuggerKnot Soft Anchor 1.5 mm). In the process of surgical wound closure, a repetition of the subscapularis was made using a modified Neer technique [21]. Rehabilitation was provided in accordance with the recommendations outlined by Hayes [5].

The evaluation of outcomes was performed using the Constant-Murley score [22] which involves a combination of objective physical examination regarding the range of motion of the operated shoulder (40 points) and muscle strength (25 points), and the subjective measurements of patients in terms of the activities of daily living (20 points) and the level of pain measured using the visual analogue scale (15 points). The external rotation range of motion was measured in two positions. In the first position, the arm was in the adducted position (the shoulder joint was at 0° of abduction with 90° of elbow flexion), while in the second position the arm was in the abducted position (the shoulder joint was at 90° of abduction with 90° of elbow flexion). The values of the operated and the healthy shoulder were compared in each subject. Student T-test was used to analyze the results.

Exclusion criteria in this study were previous surgical interventions on either the operated or non-operated shoulder, multidirectional instability, presence of instability in both shoulders, glenoid bone defect > 13.5%, ISIS > 7.

Results

The average duration of postoperative follow-up was 34 ± 2 months. The Constant-Murley scores of the operated and non-operated shoulder were compared, as well as the external rotation range of motion of the operated and non-operated shoulder measured in two

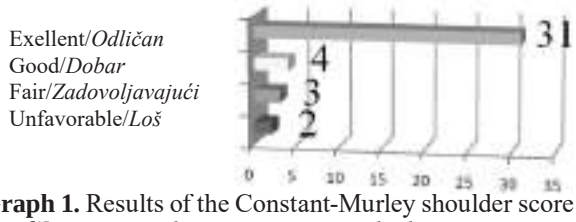
Table 1. Study group characteristics
Tabela 1. *Karakteristike ispitivane grupe*

		No *Br.*	%
Gender *Pol*	Male/*Muško*	34	85
	Female/*Žensko*	6	15
Age *Starost*	< 20	6	15
	20–29	21	52.5
	30–39	9	22.5
	> 40	4	10
Shoulder instability *Nestabilnost ramena*	Left/*Levo*	23	57.5
	Right/*Desno*	17	42.5
	Dominant/*Dominantno*	19	47.5
	Non-dominant/*Nedominantno*	21	52.5
Mechanism of injury *Mehanizam povrede*	Forceful abduction and external rotation/*Forsirana abdukcija i spoljašnja rotacija*	32	80
	Fall on outstretched arm/*Pad na opruženu ruku*	6	15
	High energy trauma/*Povreda usled jakog intenziteta*	2	5
Etiology *Etiologija*	Sports/*Sportska aktivnost*	32	80
	Daily activities/*Svakodnevna aktivnost*	6	15
	Motor vehicle trauma/*Saobraćajni traumatizam*	2	5
Sports *Sport*	Combat/*Borilački*	7	17.5
	Handball/*Rukomet*	5	12.5
	Skiing/*Skijanje*	4	10
	Football/*Fudbal*	3	7.5
	Volleyball/*Odbojka*	3	7.5
	Basketball/*Košarka*	2	5
	Water polo/*Vaterpolo*	2	5
	Other sports/*Ostali sportovi*	9	22.5
	Non-athletes/*Nesportisti*	5	12.5
Level of sports *Nivo sporta*	Professional/*Profesionalan*	8	20
	Recriational/*Rekreativni*	27	67.5
	Non-athletes/*Nesportisti*	5	12.5

positions. A statistically significant difference ($p < 0.05$) was observed in all compared parameters.

The average Constant-Murley score was 90.3 ± 11.5 for the operated shoulder, and 98.2 ± 1.2 for non-operated shoulder. According to the Constant-Murley score, excellent outcome was achieved in 31 patients, good in 4 patients, fair in 3 patients, and unfavorable in 2 patients **(Graph 1)**.

The difference in the external rotation range of motion between the operated and the non-operated shoulder in the adducted position was 10.25° ± 9.7°, while in the abducted position it was 13.2° ± 10.4°.



Graph 1. Results of the Constant-Murley shoulder score
Grafikon 1. *Rezultati Konstant-Marli skora*

After surgery, 77.1% (27) of subjects continued to actively engage in sports at the same or lower level; 21 subjects continued participating in recreational sports activities; and 6 professional athletes continued their respective sports at the same or higher level.

Following the surgical treatment, four subjects (10%) had a re-dislocation. All four subjects reported a subsequent injury as the cause of instability of the operated shoulder. One patient experienced luxation and was subjected to revision Latarjet [12] procedure, while the other three patients had subluxations and presented without further issues after physical therapy. None of the patients experienced postoperative infections or neurological complications.

Discussion

In the last decades, there has been an intensive development of methods and procedures for the treatment of anterior shoulder instability. The most affected population are physically active working age young men and it is the case in this study as well. The sample included 34 men (85%) and 6 women (15%).

The average age of patients was 27 (from 18 to 43 years of age), and more than half of them were between 20 and 29 years old. The injuries mostly occurred in the course of sports activities, and the most common mechanism was violent abduction and external rotation of the arm. Epidemiologic data in our test group do not differ from the test groups in Harris et al. [23], Naviaser et al. [24], Zacchilli & Owens [4], and Longo et al. [25].

The Constant-Murley score is an internationally accepted score used to follow the outcomes of surgical treatment of the anterior shoulder instability, and it involves comparison of the level of pain, range of motion, muscle strength, and the level of functionality in the activities of daily living of the operated and non-operated shoulder. The average Constant-Murley score in this study for the operated shoulder was 90.3 ± 11.5. Harris et al. [23] analyzed 26 studies including 731 subjects who underwent open surgical technique and determined an average Constant-Murley score of 82.2. According to the Constant-Murley score, excellent and good results were achieved in 87.5% of subjects, fair results in 7.5%, and unfavorable results in 5% of patients. This is in line with the study performed by Pavlik et al. [26] who also used the Constant-Murley score: excellent and good results were achieved in 88% and a fair result in 12% of patients. Stone & Pearsall [27] found that excellent and good results were achieved in 92.1%. It may be concluded that the functional results of patients in this study are comparable to the results gathered by the aforementioned authors.

Our study compared the average external rotation deficit with the arm in adduction of the operated and non-operated shoulder and it was 10.25° ± 9.7°, while the average value of the external rotation deficit with the arm in abduction was 13.2° ± 10.4°. The external rotation deficit of the operated shoulder in our sample was in line with the studies conducted by Lai et al. [28], Boileau et al. [21], Yamamoto et al. [29], Autor et al. [30] who reported average values of the external rotation deficit between 6° and 17°. Naviaser et al. [24] reported an average external rotation deficit over 4°, in both in adduction and abduction. They attribute lower deficit to the capsular release technique described in their study. The deficit in the maximum external rotation following the minimally invasive open surgical stabilization of the shoulder is an acceptable deficiency of the open surgical technique which in our opinion causes no limitations in daily and sports activities of the patients.

In our research, 35 patients were athletes. The subjects mostly played contact and overhead sports (55%). Following the surgery, 27 (77.1%) resumed their sports activities. Yamamoto et al. [29] reported that 38 (75%) out of 51 athletes who played contact sports and who were treated using an open surgical technique continued their sports activities, while 13 (25%) quit sports. Naviaser et al. [24] included 107 athletes in their study; 98 (91%) of them resumed sports activities, and 2 out of the 9 remaining subjects quit sports as a result of functional limitations of the operated shoulder. The percentage of patients who resumed sports activities after the surgical treatment indicates that the open minimally invasive surgical technique for the anterior shoulder stabilization is a reliable procedure in the treatment of high-risk athletes.

In our study, instability of the operated shoulder occurred in four subjects (10%). All four subjects claim that it was caused by a subsequent injury. Berendes et al. [31] reported a re-disclocation rate of 9.7%. Boileau et al. [21] reported 11%. In their 2012 meta-analysis, Murray et al. [32] recorded a re-disclocation rate of 7.5% in a sample of 775 athletes following an open surgical procedure. Harris et al. [23] analyzed 26 papers in their study and determined a mean re-dislocation of 8%. The study included 731 patients who underwent an open surgical technique. Yamamoto et al. [29] compared the percentages of re-dislocatios in athletes in contact (10%) and non-contact (5%) sports and reached a conclusion that contact sports is a risk factor for re-dislocation, given the double dislocation recurrence rate. Virk et al. [33] reported a slightly greater re-dislocation rate of 16%, however, they explained that all patients experienced additional trauma. The percentage of complications in our study was in line with the aforementioned studies by different authors; correct determination of indications for operative treatment of patients suffering from anterior shoulder instability is highly important to achieve satisfactory clinical results.

The limitations of this study include a small sample size, inability to reach patients to perform a follow-up examination, short follow-up period, as well as the subjectivity of patients when filling the questionnaire.

During the last two decades, there has been a tendency towards a reduced use of open surgical procedure in treating anterior shoulder instability in favor of arthroscopic and bone grafting procedures. In 2016, Virk et al. [33] found that in case of open surgical procedure, complications tend to occur later (34.2 months) than in case of arthroscopic procedure (12.6 months), which leads to the conclusion that open surgical procedure is more suitable for high-risk patients. In 2020, Reider [34] pointed out that more and more orthopedic surgeons use the open surgical anterior soft-tissue stabilization procedure as an alternative to the arthroscopic procedure when treating high-risk patients.

The treatment of the anterior soft-tissue shoulder instability is a current topic of discussion amongst orthopedic surgeons at various conferences and a subject of numerous studies. Our opinion is that additional research is needed, as well as comparison between open surgical and arthroscopic techniques in order to reach a clear consensus regarding the indications for the type of operative treatment in high-risk patients.

Conclusion

Shoulder instability most commonly occurs in men between 20 and 29 years of age and athletes who play contact and overhead sports are at higher risk. Following surgical treatment, 80% of patients have no limitations in daily activities, while 77.1% of athletes resume sports activities.

Open surgical treatment of the anterior shoulder joint instability using a minimally invasive anterior ap-

proach is a reliable, time-tested procedure which leads to favorable clinical results in high-risk young contact and overhead athletes with proper, timely diagnosis, and surgical care.

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PEER INFLUENCE ON MARIJUANA USE AMONG ADOLESCENTS IN NOVI SAD

UTICAJ VRŠNJAKA NA UPOTREBU MARIHUANE KOD ADOLESCENATA U NOVOM SADU

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Summary

Introduction. Cannabis use in adolescence has a major impact on the individual, family and community, whereas the effects are cumulative and contribute to social, physical and mental problems. Socializing with peers who use psychoactive substances can significantly increase the likelihood of adolescent cannabis use. The aim of this study was to determine the prevalence of cannabis use among adolescents in Novi Sad, as well as the differences in prevalence depending on the risky behavior of their friends depending on the relationships between them. **Material and Methods.** The research was conducted as a cross-sectional study in 2017 and included 1,067 first-grade students from 19 high schools in Novi Sad. The research instrument was a questionnaire of the European School Survey Project on Alcohol and Other Drugs. **Results.** The prevalence of marijuana abuse in Novi Sad was 12% and it was twice higher among students from the city (13.1%) or suburban areas (13.6%) than in students from villages (5.8%) ($p < 0.05$). Marijuana use was significantly more prevalent among students whose most/all friends smoked (23.1%) than among those whose friends did not smoke (10.1%) or only a few smoked (5.5%) ($p < 0.001$). Respondents whose friends use alcohol were significantly more likely to use marijuana (15.2%) than those who have only a few such friends (6.4%) or none (10.5%) ($p < 0.001$). More than half of students whose friends use marijuana have tried it (54%), while among those who do not have such friends, only 3% have used marijuana ($p < 0.001$). **Conclusion.** The prevalence of marijuana use in adolescents in Novi Sad is high. Peer risk behaviors influence adolescent cannabis use.

Key words: Marijuana Use; Peer Group; Adolescent; Risk Factors; Health Risk Behaviors; Students

Sažetak

Uvod. Upotreba marihuane u periodu adolescencije ima veliki uticaj na pojedinca, porodicu i zajednicu, a efekti su kumulativni i doprinose socijalnim, fizičkim i mentalnim problemima. Druženje sa vršnjacima koji koriste psihoaktivne supstancije može značajno da poveća verovatnoću upotrebe marihuane kod adolescenata. Cilj rada bio je utvrđivanje prevalencije upotrebe marihuane kod adolescenata u Novom Sadu, kao i razlika u prevalencijama u zavisnosti od rizičnih ponašanja njihovih prijatelja i u zavisnosti od odnosa sa prijateljima. **Materijal i metode.** Istraživanje je sprovedeno kao studija preseka 2017. godine i obuhvatilo je 1.067 učenika prvih razreda iz 19 srednjih škola u Novom Sadu. Instrument istraživanja je bio upitnik Evropske školske ankete o zloupotrebi alkohola i drugih droga. **Rezultati.** Prevalencija zloupotrebe marihuane u Novom Sadu bila je 12% i dvostruko je veća kod učenika iz grada (13,1%) ili prigradskog naselja (13,6%) u odnosu na ispitanike sa sela (5,8%) ($p < 0,05$). Upotreba marihuane je bila značajno zastupljenija među učenicima čiji prijatelji, većina/svi, puše (23,1%) nego kod onih čiji prijatelji ne puše (10,1%) ili samo nekoliko njih (5,5%) ($p < 0,001$). Ispitanici čiji prijatelji koriste alkohol su značajno češće koristili marihuanu (15,2%) od onih ispitanika koji imaju samo nekoliko takvih prijatelja (6,4%) ili ih nemaju (10,5%) ($p < 0,001$). Više od polovine učenika, čiji svi ili većina prijatelja koriste marihuanu, probalo je marihuanu, (54%), dok među onima koji nemaju takve prijatelje samo 3% koristilo je marihuanu ($p < 0,001$). **Zaključak.** Prevalencija upotrebe marihuane kod adolescenata u Novom Sadu je visoka. Rizična ponašanja vršnjaka utiču na upotrebu marihuane kod adolescenata.

Ključne reči: zloupotreba marihuane; vršnjačke grupe; adolescenti; faktori rizika; ponašanje rizično po zdravlje; studenti

Introduction

Adolescence is the period from 10 to 19 years and it is the transitional stage from childhood to adulthood [1]. It is the phase of life when foundations and patterns of healthy behavior of the future adult person are established [2]. Many risky behaviors begin precisely during this period and are major challenges for public health [3]. Abuse of psychoactive substances among adolescents is a significant public health problem in many countries [4, 5]. The most commonly used illegal drug around the world is marijuana, i.e. cannabis [6, 7]. According to the data of the European School Survey Project on Alcohol and Other Drugs (ESPAD) conducted in 35 European countries, every third sixteen-year-old used marijuana at least once in their lives (16%) [6]. According to the data of the European Monitoring Center for Drugs and Drug Addiction, cannabis, as the most commonly abused illegal drug among young people in Europe, was used by 9.8 million young people between the ages of 8 and 24 in 2017 [15]. According to data from the ESPAD project in Serbia conducted in 2011, 4% of girls and 9% of young men have tried marijuana at least once in their lives. The fact that 24% of adolescent girls and 27%

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Abbreviations
ESPAD – European School Survey Project on Alcohol and Other Drugs

of adolescent boys believe that marijuana is easily accessible to them is worrying [7]. In Novi Sad, every tenth young man (10.0%) and every sixteenth girl (6.4%) (sixteen-year-olds) have tried marijuana at least once in their lives. About 1% of high school first graders have used marijuana more than 40 times in their lifetime [9]. Research shows that alcohol and marijuana abuse often occur together. The reasons for this are the cumulative or complementary effects of these two substances, their availability, price and social desirability [10, 11].

Factors that affect the health of adolescents act at different levels: individual (gender, age, knowledge and skills), family, community, cultural standards, and mass media [12]. Adolescent behavior is influenced by many different factors and according to the social learning theory adolescents learn behaviors by observing and imitating the behavior of family members, leaders and others [13]. In addition to the family, the most common sources of social influence are peers and that was confirmed by several studies [14–16]. Ferguson et al. reported that the peer influence on the use of psychoactive substances is greater than the influence of the family, the environment and the media [15], which is also confirmed by other authors [9, 17]. Especially important is the influence of peers who use different psychoactive substances (such as alcohol and marijuana). Socializing with such peers significantly increases the likelihood of using marijuana [14, 15]. It is assumed that peers who use psychoactive substances share information, attitudes, values, and norms regarding drug abuse and thus create a social context for substance abuse [18]. However, it is not entirely clear whether peer behaviors increase an adolescent's risk of engaging in problem behaviors (socialization effect) or whether a predisposition to problematic behavior simply increases the risk of associating with problematic peer groups (selection effect) [14]. Adolescents are more likely to engage in a risky behavior in a group than alone. Some adolescents, due to a limited degree of self-confidence, are not able to act independently of the influence of peers, and in order to raise their social status, they use marijuana [3, 19]. Adolescents are more likely to try marijuana if they are offered by close friends they trust [19]. The peer influence is particularly significant because in the adolescent period children spend more and more time with their peers and less time with their parents [20].

The aim of this paper was to determine the prevalence of marijuana use among adolescents in Novi Sad, to assess the differences in the prevalence of marijuana use by adolescents in Novi Sad associated with risky behavior of their friends, and to assess the differences in the prevalence of marijuana use among adolescents in Novi Sad associated with risky behavior of their friends and their relationships.

Material and Methods

The research is part of the project of the Institute of Public Health of Vojvodina and the City Administration for Health of the City of Novi Sad. The research was conducted as a cross-sectional study in the period from December 1 to December 26, 2017 using the methodology of the ESPAD. The target population included high school first-grade students from 19 high schools in the territory of the municipality of Novi Sad: Jovan Jovanović Zmaj Grammar School, Svetozar Marković Grammar School, Laza Kostić Grammar School, Isidora Sekulić Grammar School, Medical High School "April 7", Bogdan Šuput High School of Design, Mihajlo Pupin School of Electrical Engineering, Pinki Traffic High School, High School of Mechanical Engineering, Mileva Marić Einstein Technical School, Pavle Savić Technical School, High School of Agriculture, Isidor Bajić High School of Music, High Ballet School, Karlovci Grammar School, E-Grammar School, Sveti Arhangel Medical High School, and Clerical High School of Saint Arsenije Sremac.

The research included students who were in class on the day of the survey, while students who were not in class and those who dropped out of school, were not included in the study. The research instrument was the questionnaire of the ESPAD. The survey was conducted by trained interviewers from the Institute of Public Health of Vojvodina and students of the Faculty of Medicine in Novi Sad. Students were surveyed in classrooms during one school lesson (45 minutes), without the presence of teachers. The students filled out self-completion questionnaires. Before starting to fill in the questionnaire, all the participants were informed that filling in the questionnaire was anonymous and voluntary. Students who decided to participate in the research signed an informed consent to participate in the research. In order to ensure anonymity, these informed consents were submitted separately from the completed questionnaires. The survey included 1,236 first-grade students (550 boys and 637 girls) from 65 classes. Since the target group included students born in 2002, 1,067 students (95% of respondents) born in 2002 were included in the final analysis. A total of 146 questionnaires filled in by students born in 2000 were excluded from the statistical analysis, as well as 23 questionnaires where data on gender and date of birth were missing. The study was approved by the Ethics Committee of the Institute of Public Health of Vojvodina.

Data on the prevalence of marijuana use were obtained based on the question "How many times have you used marijuana (weed, joint) or hashish (cannabis) in your lifetime?". For the purposes of analysis, the responses were grouped into two categories: students who never used marijuana in their lifetime and those who used marijuana at least once in their lifetime. Data on peer risky behaviors were obtained based on questions about the number of friends who smoke cigarettes, drink alcoholic beverages, get drunk, smoke marijuana, use tranquilizers, ecstasy, or inha-

lants. Relationships with friends were assessed based on answers to questions about how often they receive emotional support and attention from their best friend, as well as based on questions about how satisfied they are with their relationships with friends. The Statistical Package for Social Sciences version 11.0, was used for statistical data processing. Descriptive statistics methods were used to describe the target population. The χ^2 test was used to determine the differences in the prevalence of marijuana use between individual groups of respondents. Values of $p < 0.05$ were considered statistically significant.

Results

The research included 1,067 first-grade students from 19 high schools, with slightly more girls (55%) than boys (45%). More than half of the respondents completed the elementary school eighth grade with excellent results (59.7%). Other data on the characteristics of the respondents are shown in **Table 1**.

The prevalence of marijuana use during life was slightly higher among young men (13%) compared to girls (11%), however, this difference was not statistically significant ($\chi^2 = 0.997$; $p = 0.318$). According to the place of residence, the prevalence of marijuana use was twice as high among students living in the city (13.1%) or suburban settlements (13.6%) compared to respondents from rural areas (5.8%) ($\chi^2 = 8.275$; $p = 0.016$). The prevalence of marijuana use was significantly higher among students who had good or poor grades at the end of the eighth grade (26.6%) compared to those who had very good (10.6%) or excellent grades (9.3%) ($\chi^2 = 17.776$; $p < 0.001$) **(Table 2)**.

Every fourth student stated that most or all of their friends smoked cigarettes (26.3%), 57.8% had several friends who smoked, and 15.9% of students did not have any such friends. Marijuana use was significantly more prevalent among students who stated that most of their friends smoked (23.1%) than among those who had fewer friends who smoked ($\chi^2 = 57.519$; $p < 0.001$). Almost half of the respondents answered that most or all of their friends drank alcoholic beverages (46.9%), 42.6% that they have only a few such friends and 10.6% of students did not have a single friend who drank alcoholic beverages. Students whose most or all friends drank alcohol, used marijuana at least once in their lives (15.2%) compared to those who have few or no such friends ($\chi^2 = 17.825$; $p < 0.001$). About a quarter of students stated that most or all of their friends get drunk (23.2%), 52.7% estimated that they have only a few such friends and 24.1% had none such friends. Almost every fourth respondent (22.6%) whose all or most friends get drunk tried marijuana, while significantly fewer respondents without (6.7%) or a few (7.8%) friends who get drunk tried marijuana ($\chi^2 = 41.871$; $p < 0.001$) **(Table 3)**.

Every third student stated that they had several friends who used marijuana (34.6%), and 5.3% of students answered that all or most of their friends used this psychoactive substance. More than half of the students whose all or most friends used marijuana tried marijuana (54%). Among students whose friends did not use marijuana, only 3% tried this drug ($\chi^2 = 154.167$; $p < 0.001$) **(Table 4)**. The largest percentage of students have no friends who used tranquilizers without a doctor's prescription (80.7%), 15.2% have a few such friends, and 1.7% have most/all such friends. As many as 73.3% of students whose most friends used sedatives tried marijuana, significantly more compared to students whose few friends (25%) or none of their friends (7.2%) used sedatives ($\chi^2 = 102.565$; $p < 0.001$). Every sixth student has several friends who used ecstasy (16.4%), 2.9% stated that most or all of their friends used ecstasy, and 80.7% said that they did not have any such friends. The prevalence of marijuana abuse is significantly higher among students whose most/all (63%) or few (28%) friends take ec-

Table 1. Demographic and socio-economic characteristics of respondents
Tabela 1. *Demografske i socio-ekonomske karakteristike ispitanika*

Characteristics of the respondents *Karakternstike ispitanika*	Number of students (•0) *Broj učenika (n)*	Percentage (%) *Procenat (%)*
Gender/*Pol*		
Male/*Muški*	480	45.0
Female/*Ženski*	587	55.0
Place of living/*Mesto stanovanja*		
City/*Grad*	637	59.9
Suburb/*Prigradsko naselje*	236	22.2
Rural areas/*Selo*	191	18.0
Material status of the family in relation to others/*Materijalno stanje porodice u odnosu na druge*		
Better/*Bolje*	346	34.4
The same/*Isto*	514	51.1
Worse/*Lošije*	145	14.4
Student success at the end of the 8th grade/*Uspeh na kraju 8. razreda*		
Excellent/*Odličan*	602	59.7
Very good/*Vrlo dobar*	340	33.7
Good or insufficient/*Dobar ili dovoljan*	66	6.5

Table 2. Prevalence of marijuana use among adolescents in Novi Sad in 2017 according to demographic and socio-economic characteristics
Tabela 2. *Prevalencija upotrebe marihuane kod adolescenata u Novom Sadu u 2017. godini, prema demografskim i socio-ekonomskim karakteristikama*

	Lifetime use of marijuana *Upotreba marihuane tokom života*				p/*p*
	Never/*Nikad*		At least once/*Bar jednom*		
	n/*br.*	%	n/*br.*	%	
Gender/*Pol*					
Male/*Muški*	416	87.0	62	13.0	Z^O.997; p=0.318
Female/*Ženski*	519	89.0	64	11.0	
Place of living/*Mesto stanovanja*					
City/*Grad*	550	86.9	83	13.1	y-%215-, p=0.016
Suburb/*Prigradsko naselje*	204	86.4	32	13.6	
The countryside/*Selo*	179	94.2	11	5.8	
Student success at the end of the 8rd grade/*Uspeh na kraju 8. razreda*					
Excellent/*Odličan*	544	90.7	56	9.3	xM 7.776; pO.001
Very good/*Vrlo dobar*	304	89.4	36	10.6	
Good or insufficient/*Dobar ili dovoljan*	47	73.4	17	26.6	
Material status of the family in relation to others/*Materijalno stanje porodipe u odnosu na druge*					
Better/*Bolje*	307	89.2	37	10.8	χ^2—0.151; p=0.927
Same/*Isto*	457	88.9	57	11.1	
Worse/*Lošije*	125	88.0	17	12.0	

stasy compared to students whose friends did not use this illegal drug (5.7%) ($\chi^2 = 147.443$; $p < 0.001$). The largest percentage of adolescents do not have a single friend who used inhalants (89.9%), 8.3% have several such friends and 1.8% had most or all such friends. Among the respondents whose all friends used inhalants, 82.4% tried marijuana, while significantly lower percentages of marijuana abuse were recorded among respondents whose few (19.3%) or no friends (8.8%) used inhalants ($\chi^2 = 99.409$; $p < 0.001$) **(Table 4)**.

When asked about receiving emotional support from their best friend, about 80% of students estimated that they received it almost always and often (78.9%), and every fifth person said that they rarely or never received it (21.1%). Among students who rarely received support from their best friend, 15.9% of them tried marijuana at least once in their lives, which is significantly more compared to respondents who often received support from their best friend (9.6%). ($\chi^2 = 6.929$; $p = 0.008$). Every fifth adolescent

Table 3. Prevalence of marijuana use among adolescents in Novi Sad in 2017 in regard to the smoking habits and alcohol consumption of their friends
Tabela 3. *Prevalencija upotrebe marihuane kod adolescenata u Novom Sadu u 2017. godini u zavisnosti od navike pušenja i konzumacije alkohola njihovih prijatelja*

	Lifetime use of marijuana *Upotreba marihuane tokom života*				p/*p*
	Never/*Nikad*		At least once/*Bar jednom*		
	n/*br.*	%	n/*br.*	%	
Friends smoke cigarettes/*Prijatelji puše cigarete*					
None/*Nijedan*	143	89.9	16	10.1	χ^2=57.519; pcO.001
A few/*Nekoliko*	548	94.5	32	5.5	
Most or all/*Većina ili svi*	200	76.9	60	23.1	
Friends drink alcoholic beverages/*Prijatelji piju alkoholna pića*					
None/*Nijedan*	94	89.5	11	10.5	χ^2=17.825; pO.OOl
A few/*Nekoliko*	398	93.6	27	6.4	
Most or all/*Većina ili svi*	397	84.8	71	15.2	
Friends get drunk/*Prijatelji se opijaju*					
None/*Nijedan*	224	93.3	16	6.7	χ^2=41.871; pO.OOl
A few/*Nekoliko*	484	92.2	41	7.8	
Most or all/*Većina ili svi*	178	77.4	52	22.6	

Table 4. Prevalence of marijuana use among adolescents in Novi Sad in 2017 in regard to the use of illegal drugs by their friends
Tabela 4. *Prevalencija upotrebe marihuane kod adolescenata u Novom Sadu u 2017. godini u zavisnosti od upotrebe ilegalnih droga njihovih prijatelja*

	Lifetime use of marijuana *Upotreba marihuane tokom života*				p/*p*
	Never/*Nikad*		At least once/*Bar jednom*		
	n/*br.*	%	n/*br.*	%	
Friends smoke marijuana/*Prijatelji puše marihuanu*					
None/*Nijedan*	583	97.0	18	3.0	xM54.167; pO.001
A few/*Nekoliko*	283	81.8	63	18.2	
Most or all/*Većina ili svi*	23	46.0	27	54.0	
Friends use sedatives/*Prijatelji koriste sedative*					
None/*Nijedan*	770	92.8	60	7.2	XM02.565; pO.001
A few/*Nekoliko*	114	75.0	38	25.0	
Most or all/*Većina ili svi*	4	26.7	11	73.3	
Friends use ecstasy/*Prijatelji uzimaju ekstazi*					
None/*Nijedan*	762	94.3	46	5.7	χ^2— 147.443; pcO.OOl
A few/*Nekoliko*	118	72.0	46	28.0	
Most or all/*Većina ili svi*	10	37.0	17	63.0	
Friends use inhalants/*Prijatelji koriste inhalanse*					
None/*Nijedan*	820	91.2	79	8.8	Г-99.409; p<0.001
A few/*Nekoliko*	67	80.7	16	19.3	
Most or all/*Većina ili svi*	3	17.6	14	82.4	

answered that they only sometimes or never received attention from their best friend (21.2%), and 78.7% believed that they received it almost always or often. Among respondents who believed that their best friends almost always or often cared for them, there was a significantly lower prevalence of marijuana use (9.5%) compared to those who believed that their best friends sometimes or never cared for them (16.3%) ($\chi^2 = 8.107$; p = 0.004) **(Table 5)**. The majority of students were satisfied or very satisfied with the relationships with their friends (92.5%). No significant differences were found in the use of marijuana among students who were satisfied and those who were not satisfied with the relationships with their friends ($\chi^2 = 1.175$; p = 0.27) **(Table 5)**.

Discussion

The research was conducted among high school students from Novi Sad using the ESPAD method. The aim of the study was to assess the prevalence of marijuana use among adolescents and differences in prevalence of risky behavior of their friends and relationships with them. Every eighth high school first-

Table 5. Prevalence of marijuana use among adolescents in Novi Sad in 2017 in regard to the relationship with friends
Tabela 5. *Prevalencija upotrebe marihuane kod adolescenata u Novom Sadu u 2017. godini u zavisnosti od odnosa sa prijateljima*

	Lifetime use of marijuana *Upotreba marihuane tokom života*				p/*p*
	Never/*Nikad*		At least once/*Bar jednom*		
	n/*br.*	%	n/*br.*	%	
Emotional support from the best friend/*Emocionalna podrška od najboljeg prijatelja*					
Almost always or often/*Skoro uvek ili često*	727	90.4	77	9.6	χ^2=6.929; p=0.008
Sometimes, rarely or never/*Ponekad, retko ili nikada*	180	84.1	34	15.9	
Attention from the best friend/*Briga od strane najboljeg prijatelja*					
Almost always or often/*Skoro uvek ili često*	727	90.5	76	9.5	χ^2=8.107; p=0.004
Sometimes, rarely or never/*Ponekad, retko ili nikada*	180	83.7	35	16.3	
Satisfaction with relationships with friends/*Zadovoljstvo odnosima sa prijateljima*					
Satisfied/*Zadovoljni*	830	89.5	97	10.5	$\chi^{2=}$ 1.175; p=0.278
Dissatisfied, neither satisfied nor dissatisfied or there is no such person/*Nezadovoljni/ni zadovoljni ni nezadovoljni ili nema takvu osobu*	65	65.5	11	14.5	

grader in Novi Sad used marijuana at least once in their lives. Compared to study conducted in 2012 in Novi Sad, an increase in prevalence was recorded from 8% to 12% [9]. Compared to adolescents in Europe, where the prevalence of cannabis use is 16%, the prevalence of drug abuse is lower among high school students of Novi Sad. The prevalence in Novi Sad is three times lower compared to the Czech Republic, which has the highest prevalence of marijuana use (37%) out of all the countries included in the ESPAD survey. Countries where the prevalence is similar to that in Novi Sad are Denmark (12%), Georgia (11.0%), Hungary (13%) and Malta (13%) [6]. Lifetime prevalence of marijuana abuse is higher among young men (13%) than among girls (11%), but not significantly. In both sexes, among Novi Sad students, there was an increase in the abuse of cannabis compared to 2012, especially among girls, whose prevalence increased from 6.4% to 11% [9]. In most European countries, the prevalence is also higher in boys compared to girls [6, 7]. Twice as many students from the city and suburbs used marijuana compared to students living in the rural areas, which is in line with research conducted in Serbia in 2008, according to which young people from urban areas regularly use illegal drugs more often than adolescents from smaller cities and rural areas [21]. This research showed that the prevalence of marijuana use was significantly higher among students who had good or poor results (failed, repeated the grade) at the end of the elementary school eighth grade, compared to students who had very good or excellent results. Multiple studies have shown that early marijuana use is associated with poor school performance [22, 23]. The link between early marijuana use and education is hypothesized to be due to the social context in which cannabis is used. Early cannabis use appears to be associated with the adoption of anti-conventional lifestyle characterized by belonging to delinquent and substance-using peers, even dropping out of school [23, 24]. In addition, the research shows that the use of marijuana leads to a decline in mental functions [25], but also those adolescents who start using marijuana have a lower IQ compared to their peers who do not use it [26]. Adolescents' behavior is greatly influenced by the behavior of their peers [20] and even at this age it is stronger than the influence of the family [15, 17]. The influence of peers on the use of marijuana is strongest in the adolescent period, and then significantly decreases in the mid-twenties [14]. A group of authors from New Zealand found that peer influence on marijuana use was significantly greater in 14- to 15-year-olds than in 20- to 21-year-olds [27]. The prevalence of marijuana use among adolescents in Novi Sad is significantly higher among students whose most (or all) friends smoke cigarettes, consume alcohol, or use marijuana. The fact that more than half of the students whose friends smoke marijuana also use it, while on the other hand, only 3% of respondents who do not have friends who use marijuana have used it. Other studies also confirm that adolescents who have friends who consume psychoactive substances use marijuana in a higher percentage than adolescents whose peers do not approve of this behavior [28]. Peer approval or use of marijuana can be a strong motivator for an adolescent to also try marijuana [29]. It is also possible that adolescents who use psychoactive substances find friends who have similar behavior patterns, as stated by authors from Canada [30]. It is considered that the use of psychoactive substances has a significant social role. If adolescents start using cigarettes, alcohol or marijuana, new social opportunities open up for them, such as new friendships and situations where the use of psychoactive substances dominates. Not only do friends influence marijuana use, by creating situations in which marijuana is used, but also the use of psychoactive substances can be the entry ticket to new friendships [30]. Adolescents in Novi Sad who felt they had less support and attention from their best friends used marijuana more often. The influence of an adolescent's best friend stands out as the strongest form of peer influence on marijuana use. His influence is stronger than the influence of parents and other peers [31]. On the other hand, according to research from California on the effects of socialization on the use of marijuana, the stronger influence of peers is felt among adolescents whose relationship is reciprocal (friends mutually influence each other), because it is precisely such a relationship that allows a young person to try this drug, following the example of a peer [19]. Negative experiences in peer relationships increase the risk of marijuana use, and in this context marijuana use is seen as an attempt to reduce the impact of these negative experiences [32]. Although this research provided insight into the prevalence of marijuana use and the existence of an association between adolescent marijuana use and risky peer behaviors, it also has its limitations. One of the main limitations of the study is that it is a cross-sectional study that does not allow establishing cause-and-effect relationships. Despite this shortcoming, significant data were obtained on marijuana use patterns that can be used for designing preventive programs aimed at preventing adolescent marijuana use.

Conclusion

The prevalence of marijuana use among adolescents in Novi Sad is high and amounts to 12%. In regard to the place of residence, the prevalence of marijuana abuse is twice as high among students who live in the city or suburbs compared to respondents from the rural areas. The prevalence of marijuana use is significantly higher among students who had good or poor results at the end of the elementary school eighth grade compared to those who had very good or excellent results. Peers have a significant influence on adolescent marijuana use. The prevalence of marijuana use among adolescents in Novi Sad is significantly higher among students whose friends smoke cigarettes, drink alcoholic beverages, and get drunk, smoke marijuana, use tranquilizers, ecstasy or inhalants. The prevalence is also higher among students who feel that they do not receive enough support and attention from their best friend.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
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SPONTANEUS RUPTURE OF THE LEFT VENOUS ANGLE ANEURYSM – A CASE REPORT

SPONTANA RUPTURA ANEURIZME LEVOG VENSKOG UGLA – PRIKAZ SLUČAJA

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Summary

Introduction. Upper extremity venous aneurysms and aneurysms of the neck are rare, unlike the lower extremity venous aneurysms. Only a few cases of upper extremity venous aneurysms have been described in the literature. The aim of the study was to find the best way to treat upper extremity venous aneurysms and the aneurysms of the neck region. **Case Report.** A 40-year-old female patient reported to the Emergency Center due to the swelling in the supraclavicular region. Color Doppler ultrasonography was performed and a saccular subclavian aneurysm was found, at the junction with the internal jugular vein, with signs of rupture presenting with locoregional hematoma spillage measuring 19 x 13 mm. Complete laboratory tests were performed, followed by computed tomography phlebography, where a partially thrombosed aneurysm was described in the angle between the internal jugular vein and subclavian vein, with a maximum diameter of 25 mm. The patient was hospitalized and treated conservatively. Six days after the onset of symptoms, magnetic resonance phlebography was performed, which did not show the previously described aneurysm of the left venous angle. Three months after the onset of symptoms, a control magnetic resonance phlebography was performed, which showed an aneurysm in the region of the junction of the left internal jugular vein and subclavian vein again, with a maximum diameter of 20 x 13 mm. **Conclusion.** Clinical examination and color Doppler ultrasound should certainly be the first-line of diagnosis, while magnetic resonance phlebography and computed tomography phlebography are the gold standard for aneurysm monitoring. Asymptomatic aneurysms and aneurysms with mild symptoms are best treated conservatively.

Key words: Aneurysm; Subclavian Vein; Phlebography; Tomography, X-Ray Computed; Magnetic Resonance Imaging; Signs and Symptoms; Diagnosis; Rupture

Sažetak

Uvod. Aneurizme vena gornjih ekstremiteta i regije vrata su retkost za razliku od aneurizmi vena donjih ekstremiteta. Samo nekoliko slučajeva aneurizmi vena gornjih ekstremiteta je opisano u literaturi. Cilj rada bilo je nalaženje načina lečenja venskih aneurizmi gonjih ekstremiteta i regije vrata. **Prikaz slučaja.** Pacijentkinja stara 40 godina javila se u urgentni centar zbog pojave otoka u supraklavikularnoj regiji. Urađena je dopler ultrasonografija, gde je opisana sakularna aneurizma potključne vene, neposredno pre spajanja sa unutrašnjom jugularnom venom, sa znacima rupture u vidu razlivenog hematoma dimenzija 19 x 13 mm. Urađena su kompletna laboratorijska ispitivanja, a potom i kompjuterizovana venografija gde je opisana parcijalno trombozirana aneurizma u uglu između unutrašnje jugularne vene i potključne vene, maksimalnog dijametra 25 mm. Pacijentkinja je hospitalizovana i konzervativno lečena. Šest dana od nastanka simptoma urađena je magnetno-rezonantna venografija, na kojoj nije bila prisutna ranije opisana aneurizma levog venskog ugla. Tri meseca od nastanka simptoma, kontrolna magnetnorezonantna flebografija je urađena, na kojoj je ponovo opisana aneurizma u regiji spoja unutrašnje jugularne vene i potključne vene, maksimalnog dijametra 20 x 13 mm. **Zaključak.** Prva linija u dijagnostici je svakako klinički pregled i Dopler ultrasonografija, dok za monitoring aneurizme magnetnorezonantna venografija i venografija kompjuterizovanom tomografijom predstavljaju zlatni standard. Asimptomatske aneurizme i aneurizme sa blagom kliničkom slikom najbolje je konzervativno tretirati.

Ključne reči: aneurizma; potključna vena; flebografija; CT; magnetna rezonanca; znaci i simptomi; dijagnoza; ruptura

Introduction

Upper extremity venous aneurysms and aneurysms of the neck region are rare, unlike the lower extremity venous aneurysms [1]. Only a few cases of venous aneurysms of the upper extremities are described in the literature [2–4]. Contrary to lower extremity venous aneurysms, they are mostly asymptomatic and have mild complications [5]. Clinically, they are mostly painless non-pulsatile masses in the neck region that increase with Valsalva maneuver [1]. In addition to clinical examination, color Doppler ultrasound (CDUS), computed tomography (CT) phlebography and magnetic reso-

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Abbreviations

CDUS – color Doppler ultrasound
LMWH – low molecular weight heparin
CC – craniocaudal
LL – latero-lateral
CT – computed tomography
MR – magnetic resonance

nance (MR) phlebography are also used in the diagnosis.

The complications are rare, and only a few cases with complications, including rupture or pulmonary thromboembolism, have been reported in the literature [6–8].

Currently, there is no clear algorithm for the treatment of symptomatic and asymptomatic upper extremity venous aneurysms. There are only recommendations for open surgical treatment of symptomatic aneurysms if the conditions are met. We recently treated a patient with a large symptomatic subclavian venous aneurysm, which forms the basis of this report.

Case Report

A 40-year-old female patient reported to the Emergency Center due to the appearance of edema in the left supraclavicular region. The edema appeared spontaneously the day before, without previous trauma and was not accompanied by other symptoms.

The patient presented with hypertension, without other comorbidities. She denied previous surgeries and central venous cannulation, as well as trauma in the left supraclavicular region.

During the examination, the patient was hemodynamically stable, conscious and communicative. Clinically, there was a soft edema in the left supraclavicular region, which was completely painless. During the Valsalva maneuver, there was a slight increase in the edema.

The CDUS was performed and a saccular subclavian venous aneurysm was found at the junction with the internal jugular vein, presenting with locoregional hematoma spillage measuring 19 x 13 mm **(Figure 1)**.

Complete laboratory tests were performed, followed by CT phlebography **(Figure 2)**, where a partially thrombosed aneurysm was described in the angle between the internal jugular vein and subclavian vein, with a maximum diameter of 25 mm. There was also a hematoma in the supraclavicular and left neck region and diffuse edema of subcutaneous adipose tissue. The neck structures were shifted to the right by about 3 mm, and the lumen of the trachea was normal.

The patient was hospitalized at the Vascular and Endovascular Surgery Clinic. Since the patient had no subjective problems other than edema, she was hemodynamically stable, and the laboratory findings were within reference limits, conservative treatment was initiated. The patient was prescribed anticoagulant therapy, prophylactic doses of low molecular weight heparin (LMWH), as well as analgesics, gastroprotective agents and infusion solutions. Two days later, a control CT scan was performed **(Figure 3)** and showed a reduction of the aneurysm to a maximum diameter of about 15mm, with complete reduction of the thrombotic mass with only the circulating lumen of the aneurysm. Significant regression of the locoregional hematoma spillage was also described, and the neck structures were less shifted.

Figure 1. CDUS on the first day of the onset of symptoms – left subclavian venous aneurysm with hematoma
Slika 1. *Dopler ultrasonografija prvog dana od nastanka simptoma – aneurizma leve potključne vene sa hematomom*

Figure 2. CT phlebography two days after the onset of symptoms – a partially thrombosed aneurysm in the angle between internal jugular vein and subclavian vein, with a maximum diameter of 25 mm and hematoma of the supraclavicular and left neck region with a shift of the neck structures
Slika 2. *Kompjuterizovana flebografija dva dana nakon nastanka simptoma – parcijalna tromboza aneurizme u uglu između unutrašnje jugularne vene i potključne vene, sa maksimalnim dijametrom od 25 mm i hematomom supraklavikularno u regije vrata sa leve strane, kao i dislokacijom struktura vrata*

Figure 3. CT phlebography two days after the onset of symptoms - reduction of the aneurysm to a maximum diameter of about 15 mm, with a complete reduction of the thrombotic mass
Slika 3. *Kompjuterizovana flebografija dva dana nakon početka simptoma – smanjenje aneurizme na maksimalni dijametar oko 15 mm, sa kompletnom redukcijom trombotičnih masa*

Six days after the onset of symptoms, MR phlebography was performed and it did not show the previously present aneurysm in the left venous angle

Figure 4. MR phlebography six days after the onset of symptoms – without previously described aneurysm of the left venous angle
Slika 4. *Magnetno-rezonantna flebografija šest dana nakon početka simptoma – bez prethodno opisane aneurizme levog venskog ugla*

(Figure 4). The patient was hemodynamically stable during the entire hospitalization, with clinically significant regression of the edema in the supraclavicular region. The patient was discharged for further home treatment six days after the onset of symptoms. After discharge, the patient was tested for thrombophilia, and it was confirmed that she was a heterozygous carrier of the V Leiden mutation.

Three months after the onset of symptoms, control MR phlebography was performed, which showed an aneurysm in the region of the junction of the left internal jugular vein and subclavian vein again, with a maximum diameter of 20 x 13 mm, craniocaudal (CC) x latero-lateral (LL), and a larger circulating lumen compared to the first CT finding **(Figure 5)**. Considering that the patient did not have clinical symptoms at that time, and that there was no increase in mass in the supraclavicular region during the Valsalva maneuver, the decision was made to further continue conservative treatment.

Figure 5. MR phlebography three months after the onset of symptoms - aneurysm in the region of the junction of the left internal jugular vein and subclavian vein, with a maximum diameter of 20 x 13 mm (CC x LL)
Slika 5. *Magnetno-rezonantna flebografija tri meseca nakon početka simptoma – aneurizma u regiji spoja leve unutrašnje jugularne vene i potključne vene, sa maksimalnim dijametrom 20 x 13 mm (KK x LL)*

Discussion

An aneurysm is a concentric or eccentric, permanent segmental enlargement of a blood vessel wall, at least 1.5 times its normal diameter [9]. Venous aneurysms are rare and the first was described in 1928 [10]. Yao et al. described three categories of venous aneurysms: congenital, traumatic and acquired [5]. Sometimes aneurysms occur spontaneously, of unclear cause, as in our case. Venous

aneurysms in the region of the neck and upper extremities are rare, and only a few cases have been described in the literature [6–8].

Most venous aneurysms are asymptomatic painless non-pulsatile masses which increase with Valsalva maneuver [1]. The differential diagnosis is quite broad and includes enlargement of lymphatic nodes, thyroid gland, cysts, lipomas, as well as malignancies and metastatic changes [11]. In our case, the aneurysm manifested as a non-pulsatile edema in the left supraclavicular fossa, painless on palpation.

Aneurysm in our patient was diagnosed only after the development of one of the most serious complications, rupture. In addition to rupture, complications include thrombosis or embolism, compression of surrounding structures and venous obstruction [11].

Unfortunately, in most patients, the diagnosis is made only after the development of some of the symptoms. There is no clear diagnostic algorithm for the diagnosis of venous aneurysms of the upper extremity and neck region. The most common and first-line diagnostic procedure is certainly the CDUS, while in case of complications, additional diagnostic procedures by means of CT phlebography, MR phlebography, and even invasive angiography are recommended.

There is currently no clear treatment protocol for venous aneurysms of the upper extremities and neck region. According to the available literature, some authors [3–5, 12] surgically treated aneurysms, while in a small number of cases they were treated conservatively [4]. Aneurysm resection theoretically eliminates the risk of serious complications, such as rupture and embolization. Some authors argue that asymptomatic aneurysms should always be operated, while other authors believe that surgery is necessary only in case of serious complications and development of symptoms. However, surgical treatment of venous aneurysms of the neck and upper extremities, due to the anatomical position, carries an increased risk of injury to surrounding structures. In our case, we decided for conservative treatment due to the localization of the aneurysm, increased risk of intraoperative injury to surrounding structures, as well as mild symptoms that resolved completely after conservative treatment. Unfortunately, we still do not have a large series of cases to show which type of treatment would be the most optimal.

Conclusion

Upper extremity venous aneurysms and aneurysms of the neck region are rare and they are mostly diagnosed only after the development of complications. Clinical examination and color Doppler ultrasound should certainly be the first-line of diagnosis, while magnetic resonance phlebography and computed tomography phlebography are the gold standard for aneurysm monitoring. Asymptomatic aneurysms and aneurysms with mild symptoms are best treated conservatively.

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SPONTANEOUS PNEUMOMEDIASTINUM WITH PNEUMOTHORAX, PNEUMORRHACHIS AND PNEUMOPERITONEUM IN A CHILD – A CASE REPORT

SPONTANI PNEUMOMEDIJASTINUM SA PNEUMOTORAKSOM, PNEUMORAHISOM I PNEUMOPERITONEUMOM KOD DETETA – PRIKAZ SLUČAJA

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Summary

Introduction. Pneumomediastinum is defined as the presence of free air in the mediastinum. Primary, idiopathic, spontaneous pneumomediastinum is very rare and it affects healthy children with no identifiable cause. Secondary pneumomediastinum may be caused by underlying respiratory disorders, iatrogenic causes or trauma. The most common clinical sign of pneumomediastinum is subcutaneous emphysema, and the most common symptoms are acute chest pain and dyspnea. The diagnosis is confirmed by a chest X-ray or chest computed tomography. Pneumomediastinum is rarely associated with pneumothorax, pneumoperitoneum, and pneumorrhachis. **Case Report.** In this report, we present a case of a spontaneous pneumomediastinum in a child aged 2 years and 6 months. A child was admitted to our hospital due to massive subcutaneous emphysema. On admission, the patient was without a history of chest trauma or any chronic respiratory tract diseases. He had a mild upper respiratory tract infection 6 days before admission. The diagnosis of pneumomediastinum was confirmed by chest X-ray and computed tomography. After conservative treatment, on the eighth day of hospitalization, there was a complete regression of the pneumomediastinum with normalization of the clinical and radiological findings. **Conclusion.** Spontaneous pneumomediastinum is the most common benign condition that spontaneously regresses after conservative treatment. Life-threatening complications require surgical decompression. The use of antibiotic therapy in the prophylaxis of mediastinitis has not been proven to be useful. Opinions on the routine use of chest computed tomography in patients with spontaneous pneumomediastinum are still not uniform.

Key words: Mediastinal Emphysema; Pneumothorax; Pneumoperitoneum; Pneumorrhachis; Child; Signs and Symptoms; Radiology

Sažetak

Uvod. Pneumomedijastinum se definiše kao prisustvo slobodnog vazduha u medijastinumu. Primarni, idiopatski, spontani pneumomedijastinum se javlja jako retko kod zdrave dece, bez poznatog uzroka. Sekundarni pneumomedijastinum može biti uzrokovan bolestima respiratornog trakta, jatrogenim faktorima ili traumom. Najčešći klinički znak pneumomedijastinuma je supkutani emfizem, a najčešći simptomi su akutni bol u grudima i dispnea. Dijagnoza se potvrđuje na osnovu rendgenskog snimka grudnog koša ili kompjuterizovane tomografije grudnog koša. Pneumomedijastinum je retko udružen sa pneumotoraksom, pneumoperitoneumom i pneumorahisom. **Prikaz slučaja.** Opisan je slučaj pneumomedijastinuma kod deteta uzrasta dve godine i šest meseci. Dete je primljeno u našu bolnicu zbog masivnog supkutanog emfizema. Nije imalo traumu grudnog koša niti hronične bolesti respiratornog trakta. Dete je imalo blagu infekciju gornjih respiratornih puteva šest dana pre prijema u bolnicu. Dijagnoza pneumomedijastinuma potvrđena je radiografijom i kompjuterizovanom tomografijom grudnog koša. Nakon primene konzervativnog tretmana osmog dana hospitalizacije došlo je do potpune regresije pneumomedijastinuma uz normalizaciju kliničkog i radiološkog nalaza. **Zaključak.** Spontani pneumomedijastinum je najčešće benigno stanje koje spontano regredira nakon konzervativnog tretmana. Životno ugrožavajuće komplikacije zahtevaju hiruršku dekompresiju. Nije dokazana korist od primene antibiotske terapije u profilaksi medijastinitisa. Stavovi o rutinskoj primeni kompjuterizovane tomografije grudnog koša kod pacijenata sa spontanim pneumomedijastinumom još uvek nisu unifromni.

Ključne reči: pneumomedijastinum; pneumotoraks; pneumoperitoneum; pneumorahis; dete; znaci i simptomi; radiologija

Introduction

Pneumomediastinum, defined as the presence of free air in the mediastinum, is a rare condition in children [1]. Primary, idiopathic, spontaneous pneumomediastinum occurs most often in healthy children with no identifiable cause. On the other hand, secondary pneumomediastinum may be caused by disorders of the respiratory tract (such as asthma, infections of the respiratory tract, interstitial lung disease, foreign body aspiration, etc.), iatrogenic causes (such as mechanical ventilation, endoscopy, intubation, central venous access procedures, thoracostomy, and chest or abdominal surgery) or trauma (esophageal rupture, bronchial injury) [1–3].

Rarely, pneumomediastinum may be associated with pneumothorax, pneumorrhachis, and pneumoperitoneum. Pneumothorax is defined as free air in the pleural space and can be spontaneous or traumatic. Pneumorrhachis is the presence of free air in the spinal

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Abbreviations
CRP – C-reactive protein
CT – computed tomography

canal and can be primary (spontaneous) or secondary. Spontaneous pneumorrhachis is usually asymptomatic and extra-dural, while secondary pneumorrhachis is most often intra-dural and symptomatic [4, 5].

The most common clinical manifestations of spontaneous pneumomediastinum are subcutaneous emphysema, acute chest pain, and dyspnea [6, 7]. The medical history, clinical findings, and radiological imaging, chest X-ray and chest computed tomography (CT) are sufficient to confirm the diagnosis of the pneumomediastinum. In rare cases, such as suspected foreign body aspiration or esophageal rupture, endoscopic evaluation should also be considered [6–8].

In most patients, spontaneous pneumomediastinum is a benign condition with a high rate of complete regression after conservative treatment. Rarely, pneumomediastinum may be a life-threatening condition that requires immediate diagnosis and surgical treatment [8, 9].

Case Report

A male child aged 2 years and 6 months presented with nasal secretion and dry cough six days before admission to our hospital. The child had a fever for two days. On admission, facial and neck swelling was observed, without dyspnea or any other symptom. Medical history ruled out the possibility of chest trauma. Apart from the delay in speech development, he was a healthy child without any respiratory diseases.

On admission, the boy was afebrile, his respiratory rate was normal and oxygen saturation was 97% on room air. His cheeks, neck, and upper part of the thoracic wall were extremely swollen, palpation of these body parts revealed crepitations. Chest auscultation was normal, as well as the rest of physical findings. The neurological status was also normal. The C-reactive protein (CRP) was 9.33 mg/L, with normal blood count, normal blood gas exchange, and regular biochemical findings. The alpha-1 antitrypsin level was in the reference range. Blood cultures and serological tests for viruses were negative. A chest X-ray was done and revealed subcutaneous emphysema and pneumomediastinum **(Figures 1 and 2)**. Chest CT confirmed pneumomediastinum associated with massive diffuse subcutaneous emphysema affecting the head, neck and chest walls **(Figures 3, 4 and 5).** There was a small amount of free air in the upper retroperitoneum, upper anterior abdomen (pneumoperitoneum), and spinal canal (pneumorrhachis) **(Figure 6).** A smaller partial pneumothorax in the apex of the left lung was also confirmed **(Figure 4).** Signs of interstitial emphysema have been described on both sides of the lungs, mostly in the left apical and lingular segment (described as the Macklin effect), without any other lung parenchymal disorders. The electrocardiogram and echocardiographic findings were normal.

The boy was examined by a pulmonologist and a pediatric thoracic surgeon. He was treated conservatively with monitoring of his vital signs during the

Figure 1. Anteroposterior chest X-ray showing pneumomediastinum and subcutaneous emphysema
Slika 1. *Rendgenografija grudnog koša u anteroposteriornoj projekciji: pneumomedijastinum i supkutani emfizem*

Figure 2. Lateral neck X-ray shows subcutaneous emphysema of the neck soft tissues. Lateral chest X-ray confirmed pneumomediastinum and chest subcutaneous emphysema
Slika 2. *Rendgenografija vrata u lateralnoj projekciji: subkutani emfizem mekih tkiva vrata. Rendgenografija grudnog koša u lateralnoj projekciji: pneumomedijastinum i supkutani emfizem grudnog koša*

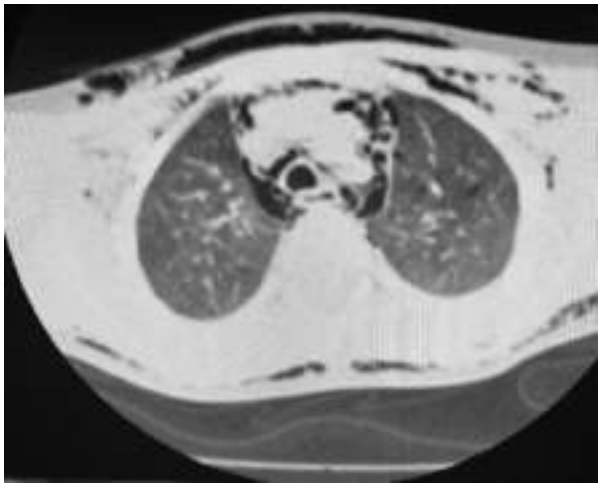

Figure 3. Chest CT shows pneumomediastinum and subcutaneous emphysema
Slika 3. *Kompjuterizovana tomografija grudnog koša: pneumomedijastinum i supkutani emfizem*

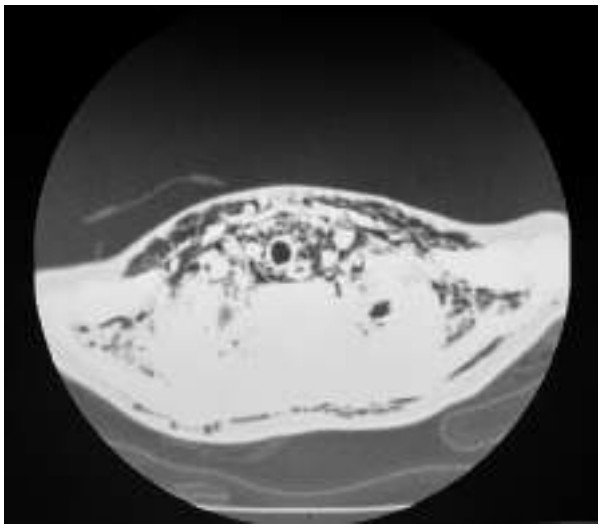

Figure 4. CT of the upper part of the chest shows chest wall emphysema and a smaller partial pneumothorax in the apex of the left lung
Slika 4. *Kompjuterizovana tomografija gornjih partija grudnog koša: emfizem struktura torakalnog zida i mali parcijalni pneumotoraks u predelu apeksa levog plućnog krila*

follow-up. Empirical intravenous antibiotic therapy was introduced, but it was discontinued when negative blood cultures were obtained, the child was afebrile without any signs of infection and the CRP values decreased. On the eighth day of hospitalization a complete spontaneous regression of the subcutaneous emphysema and pneumomediastinum was observed, with normalization of the clinical and radiological findings.

Discussion

Spontaneous pneumomediastinum in children is a rare and mostly benign clinical entity. It is defined as

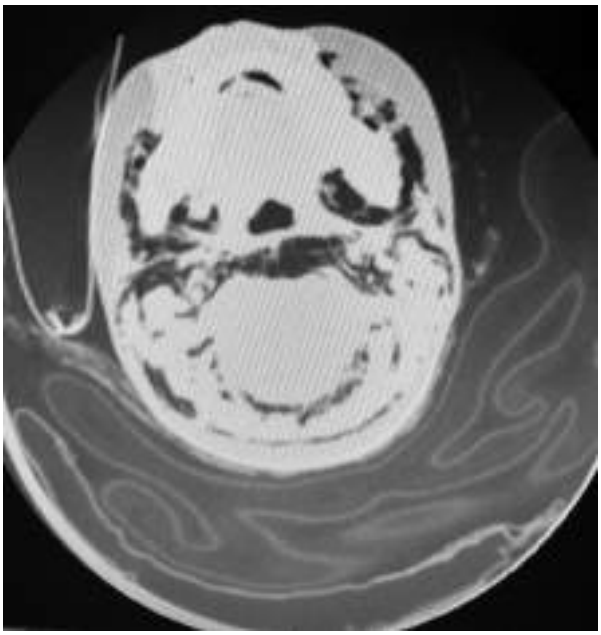

Figure 5. CT of the head (suprahyoid neck region) shows subcutaneous and deep neck emphysema
Slika 5. *Kompjuterizovana tomografija glave (suprahioidni region vrata): supkutani emfizem i emfizem dubokih struktura suprahioidnog regiona vrata*

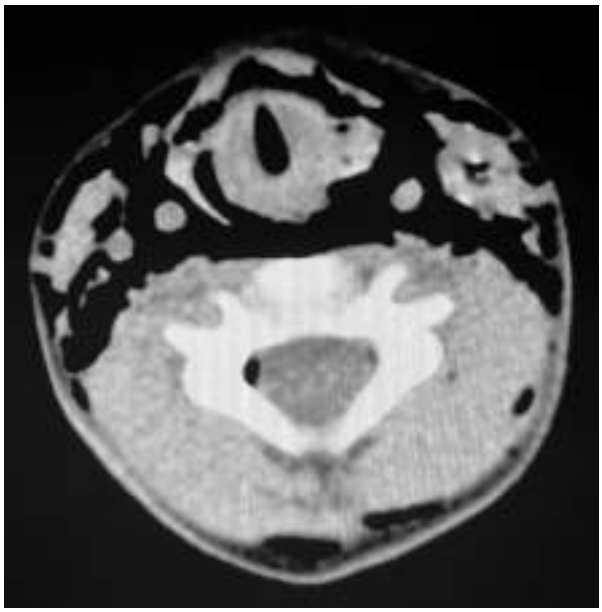

Figure 6. CT of the infrahyoid neck shows pneumorrhachis
Slika 6. *Kompjuterizovana tomografija infrahioidnog dela vrata: pneumorahis*

the presence of free air in the mediastinal space in the absence of previous respiratory disease, chest trauma, or iatrogenic causes [1–3]. Primary spontaneous pneumomediastinum affects healthy children. Voluntary alterations in the breathing pattern (playing a wind instrument, pulmonary function tests, smoking of cannabis) or involuntary breathing pattern alterations (in-

tense physical activity, coughing and vomiting) are described as possible triggers. Secondary pneumomediastinum develops in children with certain respiratory diseases, iatrogenic causes or trauma. In the case of pneumomediastinum, it is very important to rule out predisposing conditions that would require immediate specific treatment [3, 6–9]. Our patient was without a history of trauma and without any respiratory disease at the time of admission, so the diagnosis of primary spontaneous pneumomediastinum was established. Pneumomediastinum presented 6 days after a mild acute upper respiratory tract infection.

Pneumomediastinum occurs as a result of increased intra-alveolar pressure, which causes alveolar rupture. The alveolar free air then enters the mediastinum through the peribronchial and perivascular lung spaces [9, 10]. Since there are no fascial barriers surrounding the posterior mediastinum, mediastinal air may spread into the spinal canal (pneumorrhachis), soft tissues (subcutaneous emphysema), pericardium (pneumopericardium), and peritoneum (pneumoperitoneum) [4]. The neck and mediastinum communicate with the peritoneal cavity and retroperitoneum through a common visceral space that inverts the esophagus and trachea and follows the esophagus through the diaphragmatic hiatus. This can explain the airflow from the mediastinum into the peritoneum [5]. Our patient had pneumomediastinum associated with a smaller partial pneumothorax, pneumorrhachis and pneumoperitoneum.

Epidemiological data on pneumomediastinum in children are not precisely determined, but it is evident that pneumomediastinum is an extremely rare condition in pediatric population [3]. The incidence of spontaneous pneumomediastinum in children under the age of 18 is 1/8000 to 1/15000, with the first peak at the age of 6 months to 4 years, and the second peak between the age of 15 and 18 years. The incidence of neonatal pneumomediastinum is 1.7 - 2.5/1000 [1, 11]. Our patient was 2 years and 6 months old, being classified in the first peak age group. There is no available data in the literature about the incidence of the association of pneumomediastinum, pneumothorax, pneumoperitoneum, and pneumorrhachis. To the best of our knowledge, this is the first case report that describes this association in children.

The clinical manifestations of pneumomediastinum are determined by the amount of free air in the mediastinum and by the underlying condition. Although symptoms of spontaneous pneumomediastinum may be mild, secondary pneumomediastinum may be potentially lethal, depending on the underlying disease [3]. The most common clinical presentations include facial and neck swelling as a sign of subcutaneous emphysema, acute chest pain, and dyspnea. The chest pain is usually retrosternal radiating to the back, shoulders, and arms. It is more common in patients with primary spontaneous pneumomediastinum than in patients with secondary pneumomediastinum. Other symptoms and signs include cough, shortness of breath, speech difficulties, cyanosis, dysphagia, and wheezing [9–11]. At the time of admission, our patient had facial and neck swelling, without any other symptoms. Hamman's sign is characteristic in pneumomediastinum with subcutaneous emphysema, but it is rare (11.6%). It represents the crepitations detected by cardiac auscultation [1, 8]. In our patient, palpation of the cheeks, neck, and chest revealed crepitation, while the auscultatory finding on the lungs was normal. Hamman's sign was not recorded.

Radiological evaluation is required to confirm the diagnosis of pneumomediastinum. Chest X-ray is the basic diagnostic tool, while lateral neck radiography is more sensitive for free air detection in the soft neck tissues [12–14]. On chest X-ray, pneumomediastinum presents with lucent, vertical streaks or bubbles of gas within the mediastinum, which also can extend into the neck or chest wall. The characteristic radiological signs are the ring sign (free air surrounds the pulmonary artery), thymic sail sign (free air causes thymus elevation), continuous diaphragm sign (the superior surface of the diaphragm is surrounded by mediastinal air), and double bronchial wall sign (both sides of the bronchial wall are visible due to presence of air in the mediastinum) [3, 10]. In our patient, the frontal and lateral chest X-ray and lateral neck radiography confirmed the diagnosis of pneumomediastinum with subcutaneous emphysema of the neck and chest walls.

There are still different attitudes towards the routine use of chest CT in patients with pneumomediastinum. Some recent studies support the use of the chest CT to determine the possible underlying cause of pneumomediastinum and to assess the amount of free air in the mediastinum and surrounding spaces [10, 13, 15]. Furthermore, recent data show that about 30% of children with pneumomediastinum have a normal chest X-ray [3]. Other studies do not recommend routine use of additional radiological tools due to radiation exposure [2]. In our patient, chest CT was performed due to prominent clinical signs of subcutaneous emphysema. The pneumomediastinum with diffuse massive subcutaneous emphysema on the head, neck and chest walls was described.

In 1944, Macklin and Macklin first observed that released air from an alveolar rupture centripetally dissects through the pulmonary interstitium along the bronchovascular sheaths. Then the released alveolar air is directed to the pulmonary hila and into the mediastinum. The Macklin effect appears on chest CT as linear collection of free air in the mediastinum contiguous to the bronchovascular sheaths [16], as it was the case in our patient.

Pneumomediastinum is very rarely associated with pneumothorax, pneumorrhachis, pneumopericardium, and pneumoperitoneum [13–15]. In our patient, a smaller partial pneumothorax in the apex of the left lung was detected on CT, as well as interstitial emphysema. Also, a small amount of free air in the spinal canal and upper part of the retroperitoneum was described. Pneumopericardium was not apparent. Pneumomediastinum was probably caused by a small partial pneumothorax.

Severe complications, such as respiratory distress and cardiac disorders, are caused by airway and heart compression by a large amount of free air in the me-

diastinum. Massive pneumothorax or pneumopericardium are life-threatening conditions and require surgical decompression (thoracic drainage or video-assisted thoracoscopy). Gas embolism and laryngeal compression are also described [13, 14, 17].

The majority of patients with primary spontaneous pneumomediastinum should be treated conservatively (analgesics, monitoring, bed rest, avoiding triggering factors such as Valsalva maneuver, physical activity, and vomiting). Complete spontaneous regression is expected during 3 to 15 days [3, 12–15], which was the case in our patient. Physical activity should not be strictly limited after recovery [3]. The treatment of the secondary pneumomediastinum is determined by the underlying disease [12–15].

The use of antibiotics in the treatment of pneumomediastinum is controversial. Although antibiotics may be used to prevent mediastinitis and soft tissue infections of the neck, recent research has not proven the benefit of prophylactic antibiotic use [8, 12, 13]. However, antibiotics are indicated in patients with confirmed infection of the respiratory tract, bronchial tree trauma, or esophageal trauma [3]. In our patient, antibiotic therapy was initiated empirically, but it was discontinued in the further course.

Patients with spontaneous pneumomediastinum without severe complications have a good prognosis, high survival rate, and minimal risk of recurrence [11–15].

Conclusion

Spontaneous pneumomediastinum, pneumothorax, pneumorrhachis, and pneumoperitoneum are usually benign but potentially life-threatening conditions in children. In the majority of the patients, conservative treatment results in complete spontaneous regression. Life-threatening complications require immediate surgical decompression. Antibiotic therapy in mediastinitis prophylaxis has not been proven to be useful in recent studies. The opinions on the routine use of chest computed tomography in patients with spontaneous pneumomediastinum are still not uniform. Recent studies suggest that patients without complications of spontaneous pneumomediastinum should not be exposed to radiation, but more evidence is needed to confirm this assumption.

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ADVANTAGES OF SPINAL ANESTHESIA IN ORTHOPEDIC SURGERY

PREDNOSTI SPINALNE ANESTEZIJE U ORTOPEDSKOJ HIRURGIJI

Milica GOJKOVIĆ[1], Milanka TATIĆ[2, 3] and Sanja MARIČIĆ PRIJIĆ[3, 4]

Summary

Introduction. Spinal anesthesia is one of the oldest and most commonly used regional anesthesia techniques. It is based on the injection of a local anesthetic into the subarachnoid space, during which there is a transient interruption of impulse conduction in the spinal nerve roots. **Application of spinal anesthesia.** The use of spinal anesthesia depends on the following factors: the site of the surgical procedure, the type and duration of the surgical procedure, the degree of necessary surgical relaxation, and presence of accompanying diseases. **Local anesthetics used in spinal anesthesia.** There are two types local anesthetics used in spinal anesthesia. These are local anesthetics of the ester and amide type. Most frequently applied local anesthetics are those of the amide type. **Orthopedic procedures under spinal anesthesia.** The most common surgical procedures in orthopedic surgery performed under spinal anesthesia are hip, knee and ankle surgeries. **Complications of spinal anesthesia.** The most common complications of spinal anesthesia are hypotension, bradycardia, urinary retention, and postpuncture headache. **Conclusion.** The advantages of spinal over general anesthesia in orthopedic surgery include lower incidence of respiratory and myocardial depression, better peripheral tissue perfusion, minimal coagulation system disorders and prolonged postoperative analgesia.

Key words: Anesthesia, Spinal; Anesthetics, Local; Orthopedic Procedures; Arthroscopy; Intraoperative Complications; Classification

Sažetak

Uvod. Spinalna anestezija je jedna od najstarijih i najprimenjivih tehnika regionalne anestezije. Zasnovana je na ubrizgavanju lokalnog anestetika u subarahnoidalni prostor pri čemu dolazi do tranzitornog prekida sprovođenja impulsa u spinalnim nervnim korenovima. **Primena spinalne anestezije** zavisi od sledećih faktora: mesta hiruškog zahvata, vrste i dužine trajanja operativnog zahvata, stepena potrebne hiruške relaksacije i propratnih oboljenja bolesnika. **Lokalni anestetici koji se koriste u spinalnoj anesteziji.** Postoje dve vrste lokalnih anestetika koji se koriste u spinalnoj anesteziji. To su lokalni anestetici esterskog i amidnog tipa. Najčešće se primenjuju lokalni anestetici amidnog tipa. **Operacije u ortopediji koje se izvode u spinalnoj anesteziji.** Najčešći operativni zahvati u ortopedskoj hirurgiji koji se izvode u spinalnoj anesteziji su operacije kuka, kolena i skočnog zgloba. **Komplikacije spinalne anestezije.** Najučestalije komplikacije spinalne anestezije su: hipotenzija, bradikardija, retencija urina i postpunkciona glavobolja. **Zaključak.** Prednosti spinalne nad opštom anestezijom u ortopedskoj hirurgiji su: manja učestalost respiratorne i miokardne depresije, bolja periferna tkivna perfuzija, minimalni poremećaji koagulacijskog sistema i prolongirana postoperativna analgezija.

Ključne reči: spinalna anestezija; lokalni anestetici; ortopedske procedure; artroskopija; intraoperativne komplikacije; klasifikacija

Introduction

Orthopedic surgery is a great challenge for anesthesiologists in the context of the patient's general condition, type of surgical procedure, and the patient's position during surgery [1]. Orthopedic surgery includes surgical procedures on the bone and joint system and soft tissues of the extremities. Elderly people make up the largest number of patients who need orthopedic surgery and the majority of them have chronic diseases. Regarding the accompanying diseases in the elderly patients, when choosing the type of anesthesia in orthopedic surgery, anesthesiologists must take into account the overall patient's condition, not only the part that is significant for surgery. Preoperative assessment and preparation is one of the most important steps in the perioperative process and optimization. Geriatric patients who undergo orthopedic surgery are a high-risk group of patients. As for the high-risk patients, the following factors contribute a lot: accompanying diseases, limited functional capacity, postoperative systemic inflammatory response, massive blood loss, and post-operative pain [1, 2]. Orthopedic surgeries may be performed under general anesthesia, neuraxial block (spinal anesthesia), peripheral or central blocks. The choice of anesthesia depends on chronic diseases, pre-

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Abbreviations
SPA – spinal anesthesia
ASA – American Society of Anesthesiologists

vious anesthesiological complications, and potential hemodynamic and respiratory problems [2].

Spinal anesthesia: mechanism of action and performance approaches

Spinal anesthesia (neuraxial block) is one of the oldest and most commonly used techniques of regional anesthesia. In the last decade, it became widely used due to good intraoperative and postoperative analgesia as well as faster postoperative recovery of patients [3]. It is based on the injection of a local anesthetic into the subarachnoid space, during which there is a transient interruption of impulse conduction in the spinal nerve roots [4].

The primary sites of action of local anesthetics are the dorsal root ganglia, ventral of spinal nerves, autonomic nerve fibers, and mixed nerve trunk [5]. Distribution and effects of anesthesia are controlled in short time intervals, from two to five minutes. The beginning of the spinal anesthesia is associated with a feeling of warmth in the feet. The motor function is completely blocked at the site of greatest concentration of the local anesthetic. The sensory blockade is usually two to four segments higher, sympathetic blockade involves two to four more segments in cranial position. The most frequent approach for spinal anesthesia is medical approach, whereas the alternative approaches are paramedial and Taylor's approach [6] **(Figure 1)**.

Types of local anesthetics

There are two types of local anesthetics that are used in spinal anesthesia (SPA). These are local anesthetics of the ester and amide type. The most frequently applied local anesthetics are those of the amide type. The most important local anesthetics for hypobaric and isobaric SPA are: 0.5% bupivacaine, 0.5% ropivacaine - local anesthetics that have long-term impact. The group of mid-acting local anesthetics include: 2 - 4% mepivacaine or 2% prilocaine or 2 - 5% lidocaine. Hyperbaric SPA is based on adding glucose (5 - 10%) to the local anesthetic by using the method of baricity in liquor and by adjusting the position of the patient in order to determine the level of anesthesia. In isobaric SPA, the

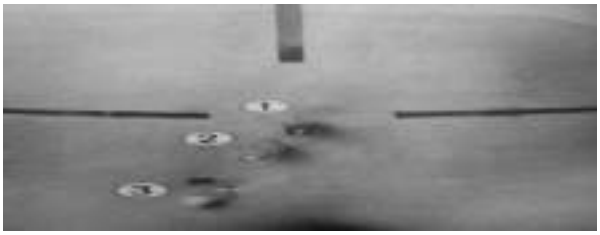

Figure 1. 1) Medial 2) Paramedial 3) Taylor's approach [2]
Slika 1. *1) Medijalni 2) Paramedijalni 3) Tejlorov pristup* [2]

patient's position has no significant impact onto the anesthesia distribution. By slow injection, the local anesthetic remains at the site of injection, whereas by faster injection or barbotage, a higher level of anesthesia is achieved. In the United Stated and England, local anesthetics of the ester group (0.5 - 1% tetracaine) are most frequently used for single blockades.

Unilateral SPA is used in orthopedic surgical procedures on lower extremities, so the front and back nerves are blocked only on the side that is being operated. Spinal nerves on the other side are not blocked. This is especially significant for smaller blockade of sympathetic nervous system and smaller risk from arterial hypotension. Advantages of unilateral anesthesia are hemodynamic stability, quick recovery from anesthesia, convenience for outpatient surgery, and better patient compliance. Application of SPA depends on the following factors: the setting of the surgical procedure, type and duration of surgical procedure, degree of the necessary surgical relaxation, and presence of comorbidities. Advantages of SPA are: lower incidence of respiratory and myocardial depression, better peripheral tissue perfusion due to sympathetic block, less intraoperative bleeding, and minimal disorders of coagulation system [6, 7] **(Table 1).**

Significance and indications for SPA in orthopedic patients include:
- Patients with a full stomach
- Difficult intubation
- Medical history data of malignant hyperthermia
- Muscle diseases
- Cardiopulmonary diseases
- Metabolic diseases
- Hepatorenal diseases
- High spinal cord injury.

Positive aspects of SPA include technical simplicity, quick effect, good quality, and no systemic toxic-

Table 1. Advantages and disadvantages of local anesthetics used in orthopedic surgery
Tabela 1. *Prednosti i nedostaci lokalnih anestetika koji se koriste u ortopedskoj hirurgiji*

	Advantages/*Prednosti*	Disadvantages/*Nedostaci*
Bupivacaine *Bupivakain*	Faster motor block *Brži nastanak motornog bloka*	Worse hemodynamic stability with hypotension and bradycardia/*Lošija hemodinamička stabilnost-nastanak hipotenzije, bradikardije*
Levobupivacaine *Levobupivakain*	Lower toxicity, better hemodynamic stability *Manja toksičnost, bolja hemodinamička stabilnost*	Slower block onset *Sporiji nastanak bloka*
Marcain Heavy *Marcain Heavy*	Faster block onset *Brži nastanak bloka*	Worse hemodynamic stability, hypothesion, bradycardia/*Lošija hemodinamička stabilnost, hipotenzija, bradikardija*

Table 2. American Society of Anesthesiologists (ASA) classification
Tabela 2. *ASA klasifikacija - Klasifikacija Američkog anesteziološkog društva*

ASA I – a healthy patient without organ disease with a localized pathological process ***ASA I*** *– zdrav bolesnik bez organskog oboljenja sa lokalizovanim patološkim procesom*
ASA II – a patient with mild systemic disease without functional limitations ***ASA II*** *– bolesnik sa blagom sistemskom bolešću bez funkcionalnih ograničenja*
ASA III – a patient with moderate to severe systemic disease causing functional limitations ***ASA III*** *– bolesnik sa umerenom do teškom sistemskom bolešću koja dovodi do funkcionalnih ograničenja*
ASA IV – a patient with severe systemic disease which is a constant threat to life making life functions difficult ***ASA IV*** *– bolesnik sa teškom sistemskom bolešću koja ugrožava život i otežava životne funkcije*
ASA V – a moribund patient with little possibility for survival with or without surgery ***ASA V*** *– moribundni bolesnik sa malom verovatnoćom za preživljavanje sa operacijom i bez nje*

ity. In orthopedic surgery, SPA has a great significance due to good postoperative analgesia, increased intestinal motility, thromboembolism prophylaxis due to sympathetic blockades and advantages for surgery in outpatient clinics, and positive economic impact. Upon the surgical procedure performed under SPA, the following data are entered in the protocol and in the check-up list: general data on the patient, aim of the blockade, patient's position, applied local anesthetic, patient's opinion during the blockade, and complications if they occurred [7].

Orthopedic surgical procedures under spinal anesthesia

Hip, knee and ankle joint surgeries are the most frequent procedures in orthopedic surgery which are performed under SPA.

Arthroscopic surgery of the hip, knee, shoulder, ankle, and elbow is a procedure that is more and more performed in outpatient clinics. The final decision on patients that will undergo surgery at outpatient clinics and the type of anesthesia is brought by an anesthesiologist. According to the American Society of Anesthesiologists (ASA) patients are divided into five groups and those with comorbidities who belong to the ASA classification III/IV cannot be candidates for surgery in outpatient clinics **(Table 2)** [8, 9].

Arthroscopic knee surgery may be performed under SPA. In order to provide good surgical conditions and prevent postpuncture headache, it is necessary to use thin Quincke needles or pencil point needles. The SPA is suitable for performing ligament reconstruction surgery. Sports injuries are the most common causes of anterior cruciate ligament injury [10, 11].

Hip arthroplasty is performed in anterior and lateral position. Obese patients and patients with arthritis are a high-risk group and they need to be in lateral position. Patients in lateral position are inclined to obtain less oxygen, which results in altered ventilation-perfusion relation. There are controversial data regarding the origin of respiratory complications when it comes to anesthesia type [12].

Knee arthroplasty is the most common orthopedic procedure in the elderly population. The SPA has an advantage regarding the postoperative pain, respiratory and myocardial depression, and better peripheral perfusion of tissues due to sympathetic block. Multimodal analgesia is applied in order to provide better postoperative pain control as well as early mobilization, but periarticular infiltration analgesia is also more and more frequent. The SPA is especially significant in patients with estimated difficult intubation [13].

Regarding the fact that in the scope of orthopedic surgery most patients are elderly, ASA III/IV patients with ischemic heart disease, with ejection fraction under < 40% and lung hypotension should undergo orthopedic surgery under general anesthesia [14, 15].

Complications of spinal anesthesia

Beside the positive aspects of SPA, complications that may occur are: complications during the blockades (vasovagal syncope), complications immediately upon injecting and during the phase of fixation of the local anesthetic (hypotension, high and total SPA), and complications in early postoperative period (urinary retention), complications in the late postoperative period (postdural puncture headache) and neurological complications [16]. Neurological complications are very rare; if there is any doubt regarding the neurological complication, it is necessary to consult the neurologist as soon as possible. Neurological complications are manifested as arachnoiditis, myelitis, spinal or epidural abscess, cauda equina syndrome, and anterior spinal artery syndrome [17].

Conclusion

Spinal anesthesia has a wide range of applications in orthopedic surgery. The advantages of this type of anesthesia include excellent muscle relaxation and postoperative analgesia, increased intestinal motility, prophylaxis of thromboembolism, convenience in outpatient surgery, and economic and reliable monitoring. The decision on the choice of anesthesia is made by anesthesiologists who take into account the patient's general condition based on the American Society of Anesthesiologists classification, including the patient's age and previous anesthesiological complications. Beside the advantages, the frequency of potential complications is also taken into consideration, as well as the absolute and relative contraindications.

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

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

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Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

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

∗ Organizacija kao autor

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

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∗ Sažetak u časopisu

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

Knjige i druge monografije

∗ Jedan ili više autora

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

∗ Urednik (urednici) kao autor (autori)

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

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∗ Disertacija

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

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

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

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

∗ Kompjuterska datoteka

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

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

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

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

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

6. Dodatne obaveze

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

INFORMATION FOR AUTHORS

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

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

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

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

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

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

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

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

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

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

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

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

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

Preparation of the manuscript

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

The covering letter:

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

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

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

The manuscript:

General instructions.

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

The manuscript should contain the following elements:

1. The title page.

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

2. Summary.

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

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

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

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

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

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

3. The text of the paper.

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

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

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

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

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

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

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

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

Articles in journals

∗ *A standard article*

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

∗ *An organization as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

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

∗ *An issue with supplement*

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

∗ *A summary in a journal*

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

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

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

∗ *A chapter in a book*

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

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

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

∗ *Monographs in electronic format*

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

∗ *A computer file*

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

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

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

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

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

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

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

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

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

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

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

6. Additional requirements

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