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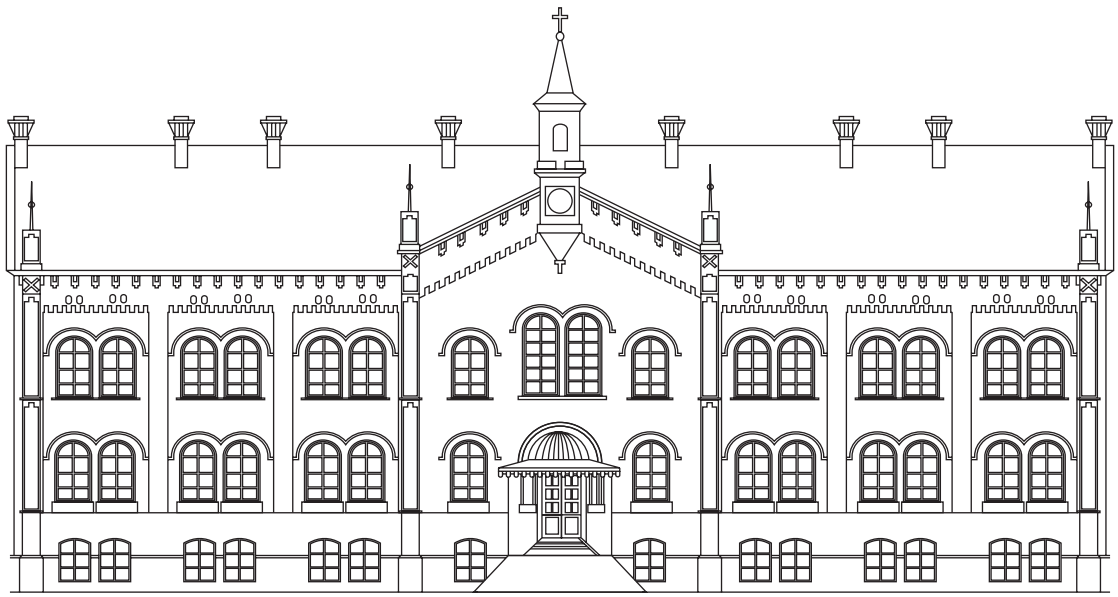

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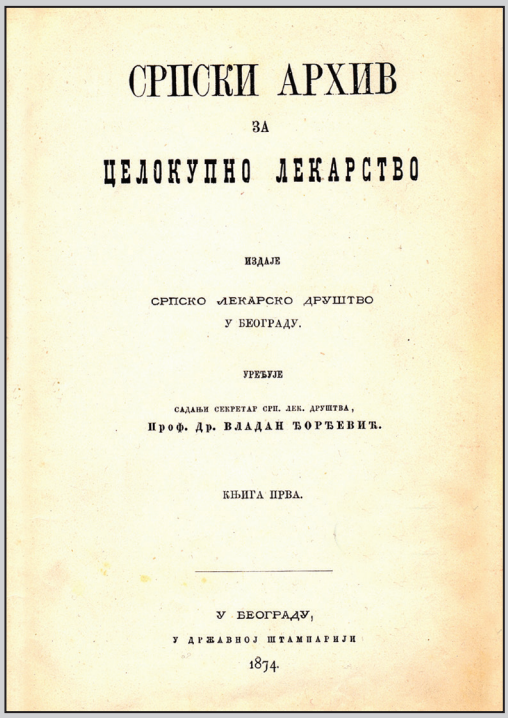

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ЗА

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1874.

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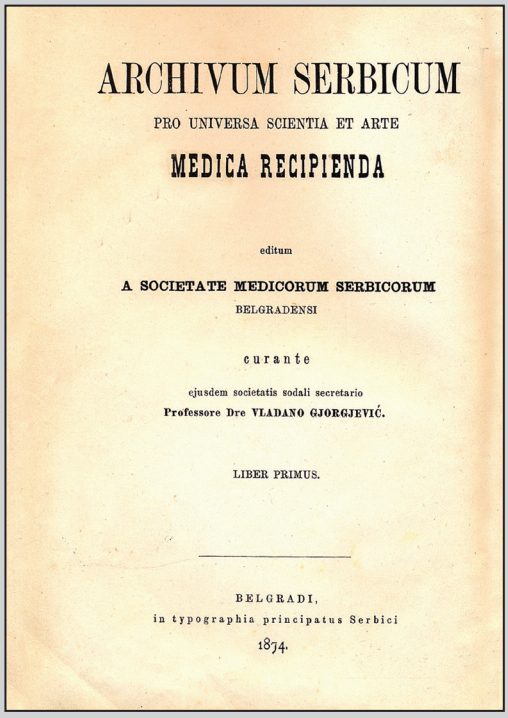

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Efficacy of the anterior and middle superior alveolar nerve block in achieving pulpal anesthesia of maxillary teeth

Slavoljub Tomić[1], Lado Davidović[2], Đorđe Božović[3], Mihael Stanojević[3], Smiljka Cicmil[4], Zoran Tatić[5], Marija Bubalo[5], Ljubomir Todorović[6]

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SUMMARY

Introduction The anterior and middle superior alveolar (AMSA) nerve block is an alternative technique of local anesthesia in the maxilla, unpredictably efficient for pulpal anesthesia.
The aim of this study was to determine the anesthetic efficacy of the AMSA injection for pulpal anesthesia, using computer-controlled injection system or conventional syringe, and two local anesthetic solutions with or without adrenaline.

Methods The authors administered two AMSA injections during two separate appointments, utilizing the computer-controlled system and conventional syringe to 40 subjects, divided into two groups of 20 subjects each depending on the local anesthetic used. A pulp tester was used to test the achieved anesthesia of the central and lateral incisors, canine, first and second premolars, and the first molar in 10-minute cycles over a period of 60 minutes. Duration of anesthesia for all the mentioned teeth was also determined for both the anesthetic solutions and ways of application.

Results The AMSA injection with both types of equipment was successful, showing slow onset, satisfying intensity, and declining duration of pulpal anesthesia at the last two measurements. Local anesthetic with vasoconstrictor exhibited a significantly longer pulpal anesthesia.

Conclusion The AMSA nerve block could be recommended for achieving pulpal anesthesia of maxillary teeth from the region of the first incisor to the second premolar.

Keywords: AMSA nerve block; pulpal anesthesia; maxillary teeth

INTRODUCTION

Traditionally, local anesthesia for the many dental procedures in the maxilla is achieved by administering an infiltration injection on the buccal or labial aspect of the targeted tooth. However, this technique is sometimes inadequate for relieving pain during tooth extraction in cases of teeth affected by acute periodontal infection; also, paresis of muscles of facial expression, which occurs to some degree, may interfere with aesthetic dental work in the region. The anterior and middle superior alveolar (AMSA) nerve block, introduced in 1998, represents an alternative technique that might compensate the mentioned shortcomings [1]. It derives its name from the fact that both the anterior and the middle (if existing) alveolar nerves are blocked, providing anesthesia of several maxillary teeth (including incisors, canines, both premolars and mesial roots of the first molars) [2].

Some studies have shown that effective pulpal anesthesia after the AMSA nerve block is questionable [3–6]. Moreover, palatal injections with the conventional syringe are known to be unpleasant and painful. Several studies have shown that computer-assisted injection system technique resulted in less pain than the conventional syringe [7–10]. Therefore, conventional syringes, according to some researches, were claimed to be too unpredictable to be recommended for clinical use as the first choice [3]. Finally, there are no available studies in the literature that compare success of the AMSA injection in achieving pulpal anesthesia depending on the type of local anesthetic solution.

This prospective, randomized, double-blind study (concerning the anesthetic used) was aimed at determining the efficacy of the

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AMSA nerve block for pulpal anesthesia, applied with a computer-controlled injection system or a conventional syringe, when local anesthetics with different contents of adrenaline were used.

METHODS

The clinical trial was conducted at the Faculty of Medicine in Foča, Bosnia and Herzegovina. The study protocol was approved by the Ethical Committee of the Faculty of Medicine (registration number 01-8/111, issued 11/2/2009). The study was conducted in accordance with the accepted ethical standards for research practice (guidelines of the Declaration of Helsinki of 1975, as revised in 1983). All participants signed an informed consent form.

Subjects

Forty adult subjects of both sexes, with intact teeth from the first molar on one side to the first molar on the other side, voluntarily participated in this study. All participants were in good health (determined by a written medical health form), ranging from 20 to 25 years of age, and not taking any medication that could alter their pain perception. Participants were students of the Faculty of Dental Medicine in Foča, University of East Sarajevo.

Method

All the participants were divided into two groups of 20 participants each, depending on the content of adrenaline in the local anesthetic used – 0.9 mL of 3% mepivacaine plain (Septanest®, Septodont, Saint-Maur-des-Fosses, France) and 0.9 mL of 4% articaine with adrenaline 1:100,000 (Ubistesin forte®, 3M ESPE, Seefeld, Germany).

All subjects randomly received two AMSA injections at two separate appointments, the time between the sessions being at least one week. All the participants received the AMSA injection using computer-controlled injection system at the first appointment, and the same amount of appropriate local anesthetic solution with a conventional syringe at the other appointment. In total, 80 injections were administered and each subject served as his/her own control. Forty AMSA injections were administered on the left side, and the same number on the right side. The side of the injection was randomly chosen for the first injection.

All the participants received the AMSA nerve block as previously described [1, 2]. They were positioned supine in the dental chair, with slight hyperextension of the neck in order to have good accessibility and visibility (Figure 1). They were informed that the procedure will last slightly longer than usually, especially when receiving a computer-controlled injection (approximately 3 minutes).

The depth of anesthesia for all the mentioned teeth was monitored with the electric pulp tester of 10 mA, with a scale of 0–10. Every 10 minutes within an hour, the pulp tester recorded the level of anesthesia, seven times in total. The mandibular intact canine was used as control. No response to the maximum output of the pulp tester was used as the criterion for good pulpal anesthesia. Also, for the same subjects, the duration of anesthesia was determined, regardless of the way of administration.

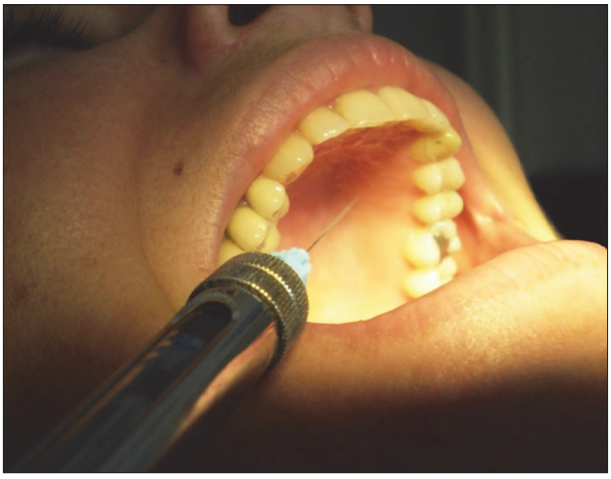

Figure 1. The anterior and middle superior alveolar nerve block done with conventional syringe and slight hyperextension of the neck

Statistical analysis

Data was analyzed using Kruskal–Wallis test and exact Wilcoxon rank sum test, using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Statistical significance of p-values was determined in relation to Bonferroni correction α value ($\alpha_1 = 0.05 / 3 = 0.0167$). For graphical data display, MS Office Excel 2003 (Microsoft, Redmond, WA, USA) was used.

RESULTS

Essentially, the results of the intensity of pulpal anesthesia of the central and lateral incisors were similar when articaine was used, regardless of the equipment used for anesthesia. The intensity of pulpal anesthesia of the mentioned teeth was less intense when mepivacaine was used, regardless of the equipment (Figures 2 and 3). Based on the obtained results, a statistically significant difference in the intensity of anesthesia was observed after the use of anesthetics with adrenaline compared to that without the vasoconstrictor ($p < 0.05$).

Concerning the success of pulpal anesthesia of canines and premolars, intensity of the achieved anesthesia, for the whole observational period (60 minutes), was better when articaine was used, regardless of the equipment used. The intensity of anesthesia decreased when mepivacaine had been already used after second measurement, regardless of the equipment used (Figures 4, 5, 6). Regardless of the mode of administration, a statistically significant difference existed in the intensity of anesthesia achieved with different anesthetic solutions ($p < 0.05$).

Anesthesia of the first molar achieved by mepivacaine was not satisfactory; anesthesia achieved by articaine with adrenaline was better but short-lived, regardless of the

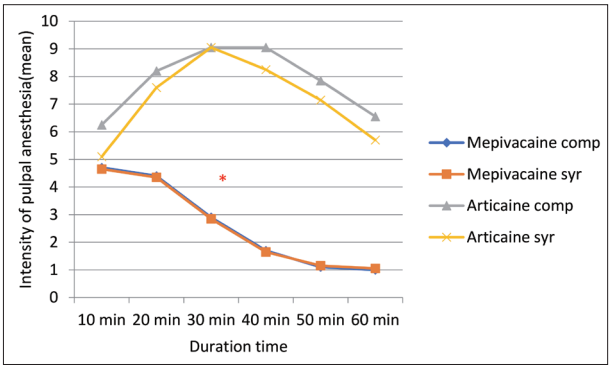

Figure 2. Intensity of central incisor pulpal anesthesia as determined by the lack of response to electrical pulp testing

*p < 0.05, statistically significant difference in the intensity of pulp anesthesia between two different anesthetic solutions, regardless of the manner of administration after the second measurement and further on

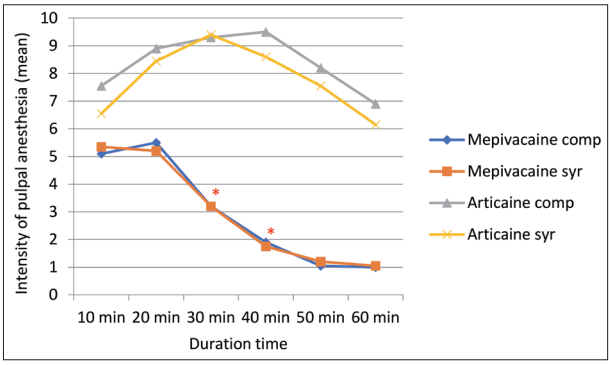

Figure 3. Intensity of lateral incisor pulpal anesthesia as determined by the lack of response to electrical pulp testing

*p < 0.05, statistically significant difference in the intensity of pulp anesthesia between two different anesthetic solutions, regardless of the manner of administration after the second and third measurement

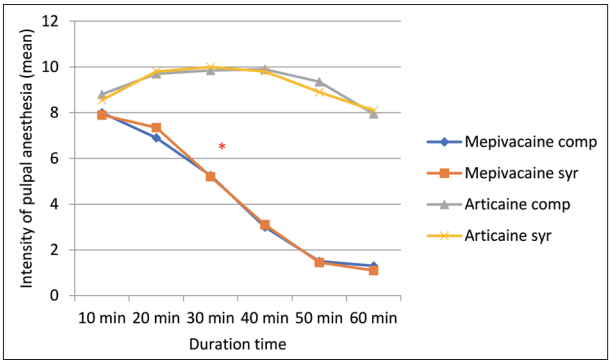

Figure 4. Intensity of canine pulpal anesthesia as determined by the lack or response to electrical pulp testing

*p < 0.05, statistically significant difference in the intensity of pulp anesthesia between two different anesthetic solutions, regardless of the manner of administration after the third measurement and further on

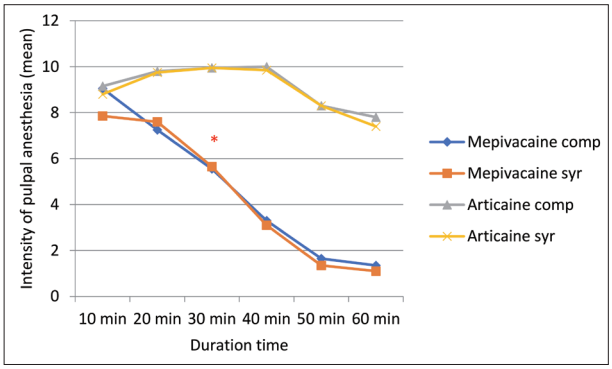

Figure 5. Intensity of the first premolar pulpal anesthesia as determined by the lack of response to electrical pulp testing

*p < 0.05, statistically significant difference in the intensity of pulp anesthesia between two different anesthetic solutions, regardless of the manner of administration after the third measurement and further on

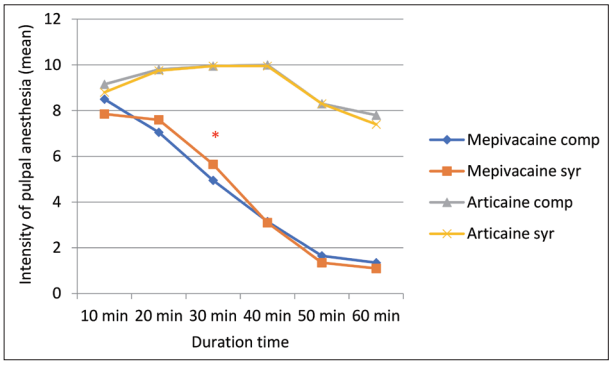

Figure 6. Intensity of the second premolar pulpal anesthesia as determined by the lack of response to electrical pulp testing

*p < 0.05, statistically significant difference in the intensity of pulp anesthesia between two different anesthetic solutions, regardless of the manner of administration after the third measurement and further on

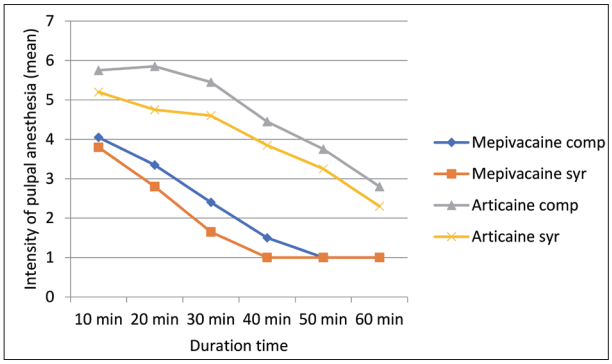

Figure 7. Intensity of the first molar pulpal anesthesia as determined by the lack of response to electrical pulp testing

*p > 0.05, there is no statistical significance in any parameter, neither in the application mode nor in the type of local anesthetic solution

equipment used (Figure 7). In regard to the first molar, statistical significance was not found in the intensity of anesthesia, regardless of the type of local anesthetic solution and the manner of application ($p > 0.05$).

Regarding the length of anesthesia, the descriptive data, presented in Tables 1 and 2, clearly indicates that the duration of anesthesia was significantly shorter when anesthetic without vasoconstrictor was used.

DISCUSSION

The use of no response to 10 mA (maximum output of the pulp tester), as a criterion for complete pulpal anesthesia, was based on the clinical studies by Dreven et al. [11] and Certosimo and Archer [12].

It is believed that the palatal application of anesthetics to achieve the AMSA block is more efficient if the Wand system (Milestone Scientific, Inc., Livingston, NJ, USA)

Table 1. Descriptive data on the duration of anesthesia for all teeth (in minutes) in relation to the equipment used

Type of anesthetic	Anaeject device	Carpule syringe	Total
Mepivacaine plain			
n	20	20	40
Average (SD)	41 (5.68)	40 (5.77)	40.50 (5.6)
Median (range)	40 (35–50)	40 (30–50)	40 (30–50)
Articaine with vasoconstrictor			
n	20	20	40
Average (SD)	81.5 (8.18)	77 (12.06)	79.25 (10.29)
Median (range)	82.5 (65–90)	80 (55–90)	82.5 (55–90)

There is a statistically significant difference in the duration of anesthesia in relation to the type of the anesthetic (Kruskal–Wallis test; $\chi^2 = 40.518$; $p = 1.59 \times 10^{-9}$)

Table 2. The results of testing the duration of anesthesia in relation to the types of anesthetic (regardless of the way of administration)

Group	Exact Wilcoxon rank-sum test	
	W	p#
Mepivacaine vs. articaine	0	1.45×10^{-11}

#Significance of p-value is determined in relation to the Bonferroni correction ($\alpha_1 = 0.05 / 3 = 0.0167$)

is used instead a classic syringe [13, 14]. However, the results of this study indicate that the use of conventional syringe might be practically equally effective as the use of the computer-controlled injection system equipment.

Concerning the presence of vasoconstrictor in the anesthetic solution, the use of local anesthetics with adrenaline resulted in successful pulpal anesthesia for all the mentioned teeth except the first molar, regardless the equipment used. Some studies have shown that 4% articaine with adrenaline in the 1:100,000 ratio has significantly lower effect than 2% mepivacaine with adrenaline in the 1:100,000 ratio, in the width of the anesthetic field and the duration of anesthesia [15].

The use of the AMSA injection for clinical anesthesia of the mentioned five teeth and bucco-mesial root of the first molar may be accepted as advantageous because with only one injection, all these teeth (upper incisors, canine, and both premolars) can be anesthetized for almost 60 minutes, without numbness of the lips and muscles of facial expression [16]. The main theoretical advantage of this AMSA nerve block is that it reduces the number of injections and the quantity of anesthetic solution administered in comparison with the conventional supra-periosteal infiltrative anesthesia applied in multiple injections for each tooth. There is also evidence that the effect of AMSA is equal to a total of five supra-periosteal injections on one side of the maxilla, with less discomfort and less anesthetics [17].

According to our results, the AMSA injection seems to be successful for clinical requirements of pulpal anesthesia of both incisors, canines and premolars. This success is largely dictated by the pattern of diffusion of the local anesthetic solution across the bony canal from the palatal nutritive canal and the region of upper dental plexus. This is the reason the AMSA injection has been called a nerve block. It is possible that the success of the AMSA injection in anesthesia of the first molar might somehow depend on the presence/absence of the medial superior alveolar nerve, whose absence was found in 30–72% in a cadaver dissection study [18]. The superior alveolar nerve's course lateral to the maxillary sinus and the greater palatine nerve travels through the hard palate. This difficult three-dimensional anatomy has led some dentists and oral surgeons to a critical misunderstanding of the development of the AMSA nerve block. In one research, authors concluded that the AMSA and palatal-anterior superior alveolar nerve blocks, as currently described, are not based on accurate anatomy [19]. A similar study of a comparative evaluation of anesthetic efficacy showed that 4% articaine proved to be more effective than 2% lidocaine in securing anesthesia of maxillary anterior teeth and premolars [20]. The advantages of the AMSA injection when compared to conventional infiltration can be particularly evident in patients who may be sensitive to vasoconstrictors. Thus, the results found here seem to indicate that the AMSA injection could be considered an alternative to the standard infiltration technique for patients in whom increased vasoconstrictor concentrations may be undesirable, especially in multiple endodontic procedures.

CONCLUSION

Having in mind all the presented results, the AMSA nerve block used for pulpal anesthesia was quite successful. Therefore, the AMSA nerve block may be recommended for clinical use in endodontics. In conclusion, we can add that anesthetic solution without a vasoconstrictor can be used for short-term procedures, regardless of the significantly short duration in relation to anesthetics with a vasoconstrictor.

Conflict of interest: None declared.

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Успешност блока предњих и средњих горњих алвеоларних нерава у постизању анестезије зубне пулпе горњих зуба

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САЖЕТАК

Увод Успешност блока предњих и средњих горњих алвеоларних нерава (блок *AMSA*), алтернативне технике локалне анестезије горњих зуба, непредвидива је када је у питању постизање анестезије зубне пулпе ових зуба.

Циљ ове студије био је да утврди ефикасност блока *AMSA* у постизању анестезије зубне пулпе применом компјутерски контролисаног система за апликацију локалне анестезије или класичне карпул-бризгалице и коришћењем два локална анестетичка раствора, са адреналином или без њега.

Методе Аутори су дали инјекције за блок *AMSA* у две одвојене посете, користећи компјутерски контролисани систем за апликацију локалног анестетика или конвенционалну карпул-бризгалицу за 40 испитаника, подељених у две групе од по 20 испитаника у зависности од примењеног локалног анестетичког раствора. Пулп-тестером је на сваких 10 минута у току једног сата одређиван интензитет постигнуте анестезије пулпе централног и латералног секутића, очњака, оба преткутњака и првог кутњака. Такође, одређивана је и дужина трајања анестезије за поменуте зубе у односу на примењене анестетичке растворе и начин апликације.

Резултати Блок *AMSA* је био успешан после примене обе врсте бризгалице и карактерисао се спорим почетком, задовољавајућим интензитетом, као и опадањем интензитета приликом последња два мерења. Локални анестетички раствор са вазоконстриктором показао је статистички значајно дуже трајање анестезије.

Закључак Блок *AMSA* се може препоручити за анестезирање пулпе горњих зуба, од централног секутића до другог преткутњака.

Кључне речи: локална анестезија; анестезија пулпе; горњи зуби

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Hybrid imaging of vascular graft infection by positron emission tomography with computed tomography using fluorine-18-labeled fluorodeoxyglucose: the Serbian National PET Center experience

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SUMMARY

Introduction Positron emission tomography (PET) with computed tomography (CT) using fluorine-18-labeled fluorodeoxyglucose (^{18}F-FDG PET/CT) is a hybrid diagnostic method based on the cell's glucose uptake detection, which correlates with the degree of disease activity. While other diagnostic procedures fail to evaluate functional tissue, ^{18}F-FDG PET/CT can be helpful in discovering active disease in patients with vascular graft infection.

Methods This cohort retrospective study included 22 patients (17 male, five female; aged 61.7 ± 16.1) with suspected vascular graft infection. Blood analyses and CT were performed in all patients. Degree of glucose uptake was evaluated visually and semiquantitatively using maximal standardized uptake value (SUVmax). Findings were considered positive if focal fluoro-deoxyglucose (FDG) accumulation was greater in vascular graft projection than other parts of the blood vessel and liver.

Results The sighs of active disease were found in 19 patients (86%) (16 male, three female) at the level of implanted vascular grafts: six aortobifemoral (27%), four aortoiliac (18.2%), four of abdominal aorta (18.2%), two of thoracic aorta (9.1%), two femoral (9.1%), one femoropopliteal (4.5%) (SUVmax 7.9 ± 2.4). Two patients were considered true and one false negative- due to antibiotic usage, which reduces FDG uptake. PET/CT helped in treatment alteration of 12 patients, seven (31.8%) started new medicament therapy, five (22.7%) had a surgical graft replacement. Overall sensitivity of this method is 95%, specificity 100%, positive predictive value 100%, negative predictive value 66.6%, accuracy 95.4%.

Conclusion ^{18}F-FDG PET/CT is a useful diagnostic method in detection of active vascular graft infection with high diagnostic accuracy, which is important in avoiding unnecessary surgery and appropriate therapy planning.

Keywords: ^{18}F-FDG PET/CT; SUVmax; vascular graft; infection

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide [1]. Endovascular interventions rarely end up with infection, but in cases of infected prosthetic vascular graft, morbidity and mortality are high [2].

Infection and inflammation of cardiovascular system can be clinically presented by numerous nonspecific symptoms, which make them even more difficult to be recognized. Right diagnosis is made based on blood tests, hemoculture, ultrasound, and computed tomography (CT) [3, 4]. The most common causes of an infection are bacteria *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* and *Enterococcus* [5, 6]. Medicament treatment implies elimination of an infective agent by various antibiotics (Tetracycline, Methicillin, Penicillin), but the treatment of choice for graft infections is surgical removal and graft replacement [7, 8], which is why an accurate diagnosis is important to avoid unnecessary surgery.

Nowadays, positron emission tomography (PET) with CT using fluorine-18-labeled fluorodeoxyglucose (^{18}F-FDG PET/CT) is used to assess the sights of an increased metabolism of glucose, such as in neoplastic cells, which is why PET/CT is mostly used in oncology [9, 10]. However, ^{18}F-FDG PET/CT can identify the source of an infection or inflammation relying on its ability to recognize functional changes of the tissue, unlike radiologic modalities, which evaluate only morphology [11, 12]. Therefore, our aim was to evaluate the importance of ^{18}F-FDG PET/CT in patients with suspected vascular graft infection, to detect the extent and degree of active disease.

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METHODS

Patients

In this cohort retrospective study were included 22 patients (17 male and five female; aged 61.7 ± 16.1) with persistent systemic manifestations (fever, weakness, chills, muscle pain), who were referred to ^{18}F-FDG PET/CT examination, to National PET Center of Clinical Center of Serbia, in the period between September 2012 to June 2018, to confirm vascular graft infection. Biochemical blood analyses, hemocultutre and CT were performed in all patients. The criteria for inclusion in this study and indications for ^{18}F-FDG PET/CT scan were as follows: suspicion of a recurrent cardiovascular infection based on positive hemoculture and blood analyses (elevated C-reactive protein, sedimentation) or fever of unknown origin in patients with positive medical history of graft implantation, as well as patients with follow up of at least six months. The criteria for exclusion were blood glucose level above 11 mmol/l, application of corticosteroid therapy, the existence of malignant disease and recent chemo/radiotherapy. All the patients gave their written consent to participate in the study which was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee.

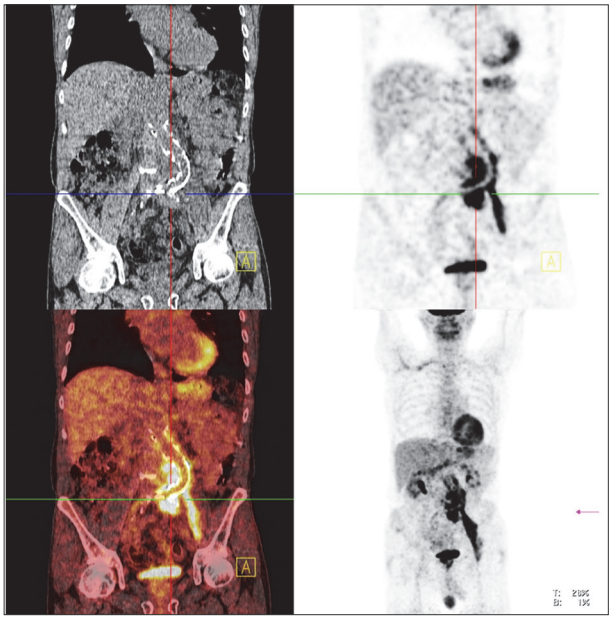

Figure 1. Coronal plane of unenhanced low dose CT, PET, fused PET/CT and maximal intensity projection. Focally increased uptake of FDG is showed in a projection of soft tissue lesions along vascular graft of abdominal aorta (SUVmax 9.3).

CT – computed tomography; PET – positron emission tomography; FDG – positron emission tomography; SUVmax – maximal standardized uptake value

Fluorine-18 labeled fluorodeoxyglucose examination

A 64-slice hybrid PET/CT (Biograph, TruePoint64, Siemens Medical Solutions, Inc. USA) was used for scanning, which was initiated one hour after intravenous injection of ^{18}F-FDG. Imaging was performed from the base of the skull to the mid tights, by non-contrast-enhanced low dose CT and PET. CT, PET, and fused PET/CT images were then demonstrated for interpretation on the workstation. Level of metabolic activity was analyzed visually and semiquantitatively using the maximal standardized uptake value (SUVmax), which was calculated according to the patient's weight and admitted radioactivity. ^{18}F-FDG PET/CT findings were found to be positive in cases of focal glucose uptake that is higher in a projection of implanted vascular graft than the accumulation in other parts of the blood vessel and liver.

Findings of ^{18}F- FDG PET/CT examination were compared to the bacterial culture results of an infected vascular graft from surgery, and results of clinical follow-up of at least six months.

Statistical analyses

The results were showed as mean ± standard deviation (SD). The ^{18}F-FDG PET/CT and CT diagnostic values were calculated by specificity, sensitivity, positive predictive value, negative predictive value and accuracy.

RESULTS

The sights of pathological ^{18}F-FDG uptake were found in 19 out of 22 patients (86.4%) (16 male and three female), which were considered true positive. Increased glucose metabolism was showed in a projection of implanted vascular grafts: six aortobifemoral (27%), four aortoiliac (18.2%), four of abdominal aorta (18.2%) (Figure 1), two of thoracic aorta (9.1%), two femoral (9.1%) and 1 femoropopliteal (4.5%) (Figure 2). Mean SUVmax values of an active disease were 7.9 + 2.4 (Table 1). Out of 19 true positive patients, 13 (68.4%) had manifested symptoms such as fever, swelling, weakness and pain of an affected limb and 11 (57.9%) had leukocytosis and elevated C-reactive protein.

Out of three negative patients, two were considered true negative and one was false negative – due to antibiotic usage in a period of examination, which reduces ^{18}F-FDG uptake.

^{18}F-FDG PET/CT helped in treatment alteration of 12 patients, seven (31.8%) started a new medicament therapy (antibiotic) and five (22.7%) had a surgical graft replacement during which an infective agent was proved (*Staphylococcus species*), while seven patients remained on the same therapy as the disease was still active on PET/CT (Table 2).

Four patients (three men and one woman) had a control ^{18}F-FDG PET/CT in order to evaluate therapy response. Recurrent disease was found in one patient after the antibiotic interruption.

CT failed to detect graft infection in 14 patients (63.3%). In eight patients the results correlated to ^{18}F-FDG PET/CT, five were true positive and three were true negative. Calculated sensitivity of CT is very low (26.3%), with higher specificity (66.7%). However, overall sensitivity of ^{18}F-FDG PET/CT is 95%, specificity 100%, positive predictive value 100%, negative predictive value 66.6%, accuracy 95.4%.

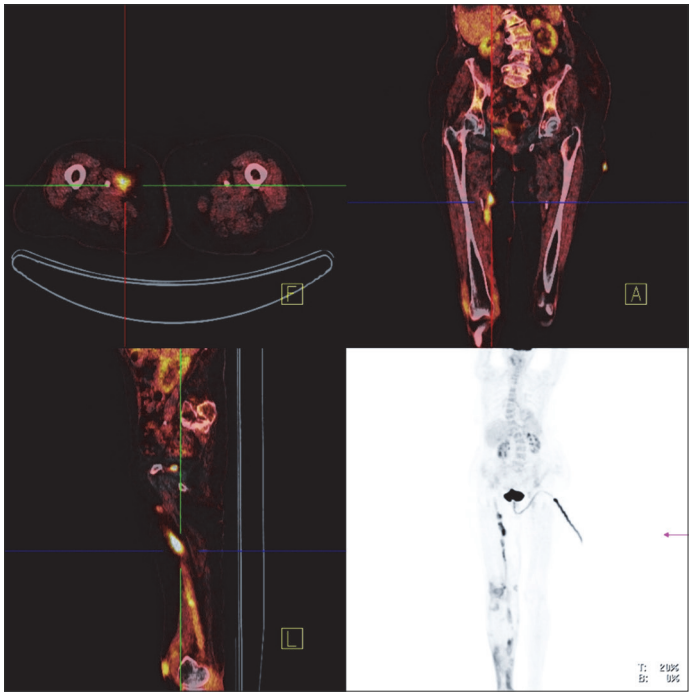

Figure 2. Transversal, coronal, and sagittal plane of FDG PET/CT and maximal intensity projection. Focally increased accumulation of FDG is showed in a projection of right femoropopliteal vascular graft (SUVmax 6.1).

FDG – positron emission tomography; PET – positron emission tomography; CT – computed tomography; SUVmax – maximal standardized uptake value

Table 1. Average values of SUVmax based on PET/CT finding

Parameters	True positive	True negative	False negative
n (%)	19 (86.4%)	2 (9.1%)	1 (4.5%)
SUVmax + SD	7.92 + 2.40	1.1 + 0.2	1.9

SUVmax – maximal standardized uptake value; PET – positron emission tomography; CT – computed tomography

Table 2. Number of patients who received a new treatment or prolonged with the same therapy after 18F-FDG PET/CT examination

Parameters	Antibiotics	Surgery	Total
New treatment	7	5	12
No change in treatment	7	0	7
Total	14	5	19

^{18}F-FDG PET/CT – fluorine-18-labeled fluorodeoxyglucose

DISCUSSION

Mortality of vascular graft infection has high rates, which is why the appropriate diagnosis is a priority, especially when infection is asymptomatic. Because of the high glucose uptake of inflammatory cells, ^{18}F-FDG PET/CT is an appropriate tool to use in detecting suspected inflammation and infection [13].

Diagnostic tool of choice in a progressive vascular graft infection is CT; however, the frequency of false negative results is relatively high, which is why ^{18}F-FDG PET/CT was introduced as an alternative modality for infectious lesions [14]. In our study, 63.6% of findings were false negative on CT, in comparison to one false negative on ^{18}F-FDG PET/CT. This can be explained by the fact that both sensitivity and specificity of CT decrease in chronic infection [4, 15].

False-negative finding in one patient was a result of antibiotic therapy used in a period of PET/CT examination. In the study of Guenther et al. [16], one patient was also considered false negative for the same reason. Antibiotics reduce inflammation and accumulation of radiopharmaceutical, which can undermine the diagnostic accuracy. In addition, subacute and low-grade infections may also be problematic to interpret, which is why it is important to take all into account – clinical, biochemical and diagnostic findings in the final conclusion [17].

The results of our study show high sensitivity (95%) and specificity (100%) of ^{18}F-FDG PET/CT in detection of vascular graft infection, similar to those in the paper of Keidar et al. [18], who reported sensitivity of 93% and specificity of 91%, as well in other papers [19, 20]. However, specificity may vary, which can be explained by physiological uptake in postoperative inflammation, healing tissue or chronic inflammatory reactions induced by the graft [15, 16, 21]. ^{18}F-FDG PET/CT had better diagnostic performance than CT in this study, similar to the results of other studies [4, 22].

One of this study's exclusion criteria was high glucose level, over 11 mmol/L. However, a study by Rabkin et al. [23], proved that hyperglycemia might reduce the sensitivity of ^{18}F-FDG PET/CT but in cases of malignancy, while in those with infection/inflammation no meaningful impact on the false negative results was found.

Symptoms and elevation of inflammatory parameters do not have to be presented in all of the patients with an infected vascular graft. In this study, out of 86.4% positive patients on ^{18}F-FDG PET/CT, 57.9% had leukocytosis and elevated C-reactive protein. In a study by Wassélius et al. [24], was reported normal CRP, or discretely elevated, in 13 out of 15 patients and vascular graft infection was confirmed in only one patient.

In our study, ^{18}F-FDG PET/CT helped in treatment alteration of 63.2% of the patients, which is why it is considered to be a helpful tool in avoiding unnecessary surgery and it contributes to the optimal treatment [15, 25].

CONCLUSION

According to our results, ^{18}F-FDG PET/CT is a useful diagnostic method in the detection of active vascular graft infection with high diagnostic accuracy. Because of its ability to

evaluate morphology and functional tissue using SUVmax, ^{18}F-FDG PET/CT gives an objective assessment of sights and level of the disease activity, which is why it is proved to be superior to CT. It contributes to avoiding unnecessary surgery, appropriate therapy planning and in the assessment of therapy effectiveness. However, ^{18}F-FDG PET/CT had a limited role in the detection of active vascular graft infection in the patient treated with antibiotics.

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Хибридни имиџинг инфекције васкуларног графта помоћу позитронске емисионе томографије са компјутеризованом томографијом коришћењем флуор-18-обележене флуордеоксиглукозе: искуство Националног ПЕТ центра Србије

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САЖЕТАК

Увод Позитронска емисиона томографија (ПЕТ) са комјутеризованом томографијом (КТ) уз коришћење флуор-18-обележене флуордеоксиглукозе (^{18}Ф-ФДГ ПЕТ/КТ) јесте хибридна дијагностичка метода базирана на детекцији ћелијског накупљања глукозе, који корелира са степеном активности болести. Док друге дијагностичке методе немају могућност процене функције ткива, ^{18}Ф-ФДГ ПЕТ/КТ може бити од велике помоћи у откривању активне болести код болесника са инфекцијом васкуларног графта.

Методе У овој кохортној ретроспективној студији је било укључено 22 болесника (17 мушкараца, пет жена; година старости 61,7 ± 16,1) са суспектном инфекцијом васкуларног графта. Анализе крви и КТ су урађени свим болесницима. Степен преузимања глукозе је процењен визуелно и семиквантитативно коришћењем максималне стандардизоване вредности уноса (МСВ *max.*). Налази су сматрани позитивним уколико је фокално појачано накупљање флуородеоксиглукозе (ФДГ) било интензивније у нивоу васкуларног графта него у другим деловима крвног суда и јетри.

Резултати Активна болест је уочена код 19 болесника (86%) у нивоу уграђеног васкуларног графта (16 мушкараца, три жене): шест аортобифеморалних (27%), четири аортоилијачна (18,2%), четири абдоминална (18,2%) и два са торакалном аортом (9,1%), два феморална (9,1%) и један феморопоплитеални (4,5%) (МСВ *max.* 7,9 ± 2,4). Два болесника су сматрана стварно и један лажно негативним – услед коришћења антибиотика који смањују накупљање ФДГ. ПЕТ/КТ је допринела даљем лечењу 12 болесника. Код њих седам (31,8%) започета је медикаментна терапија, а код пет (22,7%) хируршка замена графта. Свеукупна сензитивност ове методе је 95%, специфичност 100%, позитивна предиктивна вредност 100%, негативна предиктивна вредност 66,6%, тачност 95,4%.

Закључак ^{18}Ф-ФДГ ПЕТ/КТ је корисна метода у детекцији инфекције васкуларног графта са високом дијагностичком тачношћу, што је битно за избегавање непотребних операција и планирање одговарајуће терапије.

Кључне речи: ^{18}Ф-ФДГ ПЕТ/КТ; МСВ *max.*; васкуларни графт; инфекција

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Initial respiratory specimen bacteriology and isolates susceptibility to antimicrobials in promptly intubated chronic obstructive pulmonary disease adults – single-center two-year experience

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SUMMARY

Introduction/Objective Chronic obstructive pulmonary disease (COPD) exacerbation is mostly triggered by infectious agents and seriously compromises the patient's quality of life and predicts a poor outcome of the disease as well. If the signs of the probable bacterial cause of COPD exacerbation are presented in an intubated patient, initial antimicrobial management must be launched. Depending on the results of the respiratory system sample cultures, the initial antimicrobials can be changed or continued.
The objective of this study is to present in-hospital suggestions regarding the use of the initial antimicrobial management of urgently intubated COPD adults with the probable bacterial cause of exacerbations, considering the source of bacterial acquisition (i.e. facility- or community-acquired bacteria).

Methods The cross-sectional study covered 51 patients urgently intubated on admission to the medical Intensive Care Unit of the Zemun Clinical Hospital Center during 2015/2016. The patients were divided into two groups: community-acquired (n = 26) and facility-acquired infection group (n = 25). The respiratory system samples were processed in the Microbiology Laboratory.

Results *Acinetobacter* and *Pseudomonas spp.* were the most frequently isolated bacteria in both groups, followed by *Staphylococcus aureus* and *Klebsiella spp.* as the third most frequent bacteria in the community- and facility-acquired group, respectively. The parallel use of tigecycline and aminoglycosides proved to cover a sensitive microbial spectrum in 52% of examinees of the community-acquired and 32% of examinees of the facility-acquired group.

Conclusion The present study suggests the initial management of intubated adults with probable bacterial infection-induced COPD exacerbation by the parallel use of tigecycline and aminoglycosides.

Keywords: COPD; mechanical ventilation; anti-bacterial agents

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive respiratory disease, frequently presented with different respiratory complaints, caused by airflow obstruction. Such an obstruction results from a damage to the airways, mainly due to an exposure to some harmful gasses and materials, infectious agents, etc. [1]. The stable course of COPD can be acutely disturbed (i.e. exacerbated), which requires additional management. The exacerbations that induce acute respiratory failure are considered serious. These serious exacerbations often require going to the emergency or chest medicine departments, or even to the medical intensive care units (mICUs). When they persist, they occasionally require intubation and subsequent mechanical ventilation, described as invasive, which additionally aggravate patients' quality of life and predicts a poor outcome [2–5]. The most frequent causes of COPD exacerbations include mainly bacterial respiratory system infections [6].

A facility-acquired infection (FAI) is defined as a disease, which occurs up to 48 hours following hospital admission, but has not presented either during the incubation period or at the time of admission [7–10]. As far as COPD exacerbation is concerned, the 48-hour period is clinically very short for it to be defined as FAI for the purpose of this study, in order to distinguish it from bacterial colonization.

The management of the patient who experienced a highly suspicious COPD exacerbation of bacterial origin (according to the clinical and laboratory parameters) with antimicrobials is unequivocal. This is particularly true in cases requiring urgent intubation and mechanical ventilation. Initial antimicrobial management

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after proper and sometimes repeated sampling of respiratory system specimens is crucial for the outcome [11].

The purpose of this study is to determine the most frequent bacterial causes of serious COPD exacerbations and the susceptibility of facility- and community-acquired bacteria to the antimicrobial agents in patients admitted to mICU over the two-year period.

METHODS

This cross-sectional study included 51 patients, urgently intubated on admission to the mICU of the Zemun Clinical Hospital Center during 2015/2016. This study was done in accordance with standards of the institutional Committee on Ethics. The inclusion criteria were a medical record with the diagnosis of COPD, and an emergency indication for invasive mechanical ventilation (IMV). The exclusion criteria were the absence of the clinical and/or laboratory infection syndrome, negative bacterial findings of the respiratory system specimen cultures, COPD patients already covered by antimicrobial agents and a chest X-ray finding suggestive of pneumonia. The positive respiratory specimen (RS) culture conjoined with the presence of the clinical signs of infection (fever, an increase in the respiratory rate, progressive dyspnoea, purulent or changed sputum) and positive inflammatory markers (C-reactive protein, presepsin, procalcitonin, leucocytosis) were suggestive of infection. The colonization was defined as a positive RS culture with no clinical signs of infection and positive inflammatory markers [12]. The RS sampling procedures were conducted by experienced and well-trained mICU staff. After sampling, the material was forwarded to and duly managed by the Microbiology Laboratory staff. After detecting colony-forming units, the germs were identified, and, thereafter, the susceptibility to antimicrobials was tested. The examination of the germs' susceptibility to antimicrobial agents relies on the automated broth microdilution method and was conducted using the VITEK® 2 Compact (BioMerieux, France) device. The result is the precise measurement of the minimal inhibitory concentration (MIC) of the antimicrobial agents tested in the study. Using professional software, the device classified the results into sensitive, intermediate, and resistant (SIR) categories for the tested antimicrobial agents that are presented on the card for every bacterial isolate. In the present study, the RS was initially examined after direct Gram staining using a microscope, then cultured on a proper growth medium (sheep blood agar plate, Mac Conkey agar plate, chocolate agar plate and Sabouraud agar plate) and incubated (24–48 hours at 37°C) in aerobic conditions, and in the presence of 5% CO_2 for the Chocolate agar plate. For the purpose of rapid identification of bacterial isolates, Gram-positive (GP) and Gram negative (GN) device cards were used. As regards the antimicrobial susceptibility of the isolates, the device cards Antimicrobial Susceptibility Testing (AST) 76 and AST 240, and AST 580 and 592 were used in the cases of GN and GP isolates, respectively. Having determined MIC values, the device provided interpretation according to the standards of the Clinical and Laboratory Standards Institute and their recommendations for *cut-off* MIC values regularly updated by the relevant professional software.

The patients were divided into two groups depending on the incubation period (the time interval expressed in hours or days from the previous treatment episode in a Health/Care Facility to the current hospitalization). Group 1 – community-acquired infection (CAI Group) included 26 patients hospitalized for a COPD exacerbation probably caused by community-acquired bacteria, currently hospitalized from home, but beyond the incubation period. Group 2 included 25 patients hospitalized for a COPD exacerbation probably caused by facility-acquired bacteria (FAI Group), currently hospitalized from a healthcare facility or from home, but inside the incubation period.

For the purpose of this study, an arbitrary incubation period of two weeks was considered, despite the fact that it usually spanned 48 hours in literature [8]. The reason for extending the incubation period was to make a clear clinical distinction between colonization and FAI. This is of particular interest, because acutely deteriorated COPD patients are very frequently hospitalized and almost never fully recovered due to the natural history of COPD and the presence of numerous co-morbidities. Thus, when satisfactory clinical improvement is achieved after in-hospital treatment, stabilized COPD patients are discharged home or referred to some other care facility outside the hospital.

Statistics

The data obtained was analyzed applying the methods of descriptive (relative numbers, arithmetic mean, standard deviation) and analytical statistics (t-test, χ^2 and Mann–Whitney test) by SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The level of statistical significance was 0.05.

RESULTS

The average study population age was 71 ± 10 (the 39–89 range) years. Of the 51 patients, 35 (69%) were males. There was no difference between groups in terms of age ($U = 246$; $p > 0.05$) and sex ($\chi^2 = 0.488$; $DF = 1$; $p > 0.05$). Table 1 shows the RS culture findings and Table 2 features the overall susceptibility of isolates to antimicrobial agents.

There was no difference in the bacteriology cultures findings ($\chi^2 = 10.295$; $DF = 8$; $p > 0.05$), and the overall isolates' susceptibility to antimicrobial agents between the groups ($\chi^2 = 13.729$; $DF = 9$; $p > 0.05$). Table 3 shows data classified per group. Table 4 shows the most frequent bacterial isolates in the groups, and antimicrobial agents, which they are susceptible to. The combination of tigecycline and aminoglycosides (i.e. amikacin) covered the microbial spectrum in 11 (52%) and seven (33%) patients in Groups 1 and 2, respectively.

The mortality rates were 61% in CAI and 48% in the FAI group. The overall mortality rate of the study population

was 55%. No difference was identified in the outcome of the COPD exacerbation episode between the groups ($\chi^2 = 0.943$; DF = 1; $p > 0.05$).

Table 1. Study population respiratory specimen isolates

Bacteria	n (%)
Acinetobacter	20 (39)
Coagulase negative *Staphylococci*	9 (18)
Staphylococcus aureus	6 (12)
Pseudomonas spp.	6 (12)
Klebsiella spp.	4 (8)
Escherichia coli	3 (6)
Enterococcus spp.	1 (2)
Staphylococcus sciuri	1 (2)
Citrobacter spp.	1 (2)

Table 2. An overview of isolates-susceptible antimicrobial agents

Antimicrobials	n (%)
Tigecycline	13 (25.5)
Meropenem	12 (23.5)
Amikacin	8 (16)
Colistin	5 (10)
Vancomycin	4 (8)
3rd/4th gen. of Cephalosporins	3 (6)
Levofloxacin	3 (6)
Piperacillin + tazobactam	1 (2)
Sensitive to more antimicrobials	1 (2)
Resistant to more antimicrobial agents	1 (2)

DISCUSSION

Our study revealed that the management with tigecycline and aminoglycosides (i.e. amikacin) covers the broadest possible microbial spectrum isolated from the RS of urgently intubated adults with an exacerbated COPD, regardless of the current habitat the patients are coming from. As these antimicrobial agents cover *Pseudomonas spp.*, they seem to be the appropriate initial antimicrobial combination, until the definite findings of RS culture are available to continue antimicrobial de-escalation. By repeated RS sampling (tracheobronchial aspirate and lavage), the findings of "negative" and sterile cultures, as well contaminated and colonizing germs, would be significantly reduced. That is why we have excluded all the patients with *Coagulase negative Staphylococci* with no signs of the infective/inflammation syndrome and no finding of *Coagulase negative Staphylococci* in repeated RS cultures.

Rapid methods for microbial identification, such as Polymerase Chain Reaction for *Pseudomonas spp.*, can largely contribute to the rational use of antimicrobial agents. Apart from that, the unnecessary expenses and the occurrence of hospital germ resistance might also be reduced. These methods ensure that clinicians must be swiftly informed of the presence of important isolates in the respiratory secretion of exacerbated COPD adults, such as *Pseudomonas spp.* [3, 7, 12–16]. Using such rapid *Pseudomonas spp.* identification, clinicians could additionally administer antipseudomonal cephalosporin to tigecycline and/or aminoglycosides [17–21], or meropenem in our study.

Table 4. The group summary of the most frequent respiratory specimen isolates and susceptible antimicrobial agents

Isolates (n CAI/n FAI)	Group 1 – CAI	Group 2 – FAI
Acinetobacter (9/11)	Tigecycline – 7	Tigecycline – 5
	Amikacin – 1	Colistin – 5
	Piperacillin + tazobactam – 1	Levofloxacin – 1
Pseudomonas spp. (3/3)	Meropenem – 3	Meropenem – 2
		3rd/4th gen. of Cephalosporins – 1
Staphylococcus aureus (5/-)	Amikacin – 3	
	Vancomycin – 2	
Klebsiella spp. (-/4)		Meropenem – 2
		Tigecycline – 1
		Amikacin – 1

CAI – community-acquired infection; FAI – facility-acquired infection

Table 3. An overview of the overall study population data

Variable	**Group 1 – CAI (n = 26)**	**Group 2 – FAI (n = 25)**
Age [Mean ± SD (min.–max.)]	71 ± 11 (39–89)	69 ± 9 (56–85)
Sex [♂ (%)]	19 (73)	16 (64)
Bacteria [n (%)]	*Acinetobacter* – 9 (35)	*Acinetobacter* – 11 (44)
	Staphylococcus aureus – 5 (19)	*Klebsiella spp.* – 4 (16)
	Coagulase-negative Staphylococci – 5 (19)	*Coagulase-negative Staphylococci* – 4 (16)
	Pseudomonas spp. – 3 (11)	*Pseudomonas spp.* – 4 (16)
	Escherichia coli – 2 (8)	*Escherichia coli* – 1 (4)
	Staphylococcus sciuri – 1 (4)	*Staphylococcus aureus* – 1 (4)
	Citrobacter spp. – 1 (4)	*Enterococcus* – 1 (4)
Antimicrobial agents [n (%)]	Tigecycline – 7 (27)	Tigecycline – 6 (24)
	Meropenem – 7 (27)	Meropenem – 5 (20)
	Amikacin – 6 (23)	Colistin – 5 (20)
	Vancomycin – 2 (8)	Levofloxacin – 3 (12)
	Others – 4 (15)	Amikacin – 2 (8)
		Others – 4 (16)

CAI – community-acquired infection; FAI – facility-acquired infection

COPD exacerbations, especially those classified as frequent (≥ 2 exacerbations annually) or serious, significantly, compromise patients' quality of life and increase the hospitalization rate and are considered a bad omen [6, 11]. Therefore, the mainstay of COPD exacerbation management is to minimize the effects of the current exacerbation and to prevent future ones [12]. In cases of the clinical and laboratory infection syndrome and an increased production of sputum, especially if it is purulent, the clinician must suspect a bacterial cause of the COPD exacerbation [6]. An inadequate gas exchange is the parameter that determines whether mechanical ventilation is to be added to symptomatic, supportive, and causative COPD exacerbation management. Non-invasive mechanical ventilation (NIMV) is usually the initial mode of mechanical ventilation, with a positive response in respiratory failure management in 80–85% of patients. Additionally, NIMV has an important role in reducing the intubation and mortality rate of COPD patients [4, 13]. However, when NIMV is unsuccessful in the management of respiratory failure, IMV must be applied. It is worth mentioning that IMV extends the length of hospital stay and may contribute to a progressive COPD course [14]. The COPD guidelines recommend antimicrobial management with the most sensitive antibiotic/s after the RS culture is found in patients with frequent and serious COPD exacerbations, especially when mechanical ventilation is obligatory [7, 16, 17, 18, 20, 21]. Therefore, initial antimicrobial management should be conducted in accordance with the local COPD guideline [19].

In comparison with other studies, the *Acinetobacter* frequency in RS of an acutely exacerbated COPD patient is significantly low, despite the fact that the frequency of *Acinetobacter* increases with the number of hospital admissions due to acute exacerbations of COPD, the duration of COPD and its treatment [22, 23]. A probable explanation for this lies in a different methodological approach. Nevertheless, the largest increase in the number of participants with the *Acinetobacter*-induced exacerbation of COPD was registered in critically ill patients. In this patient population, a serious resistance to antimicrobials and a significant increase in mortality rates [22, 23, 24] were detected. In addition, such an increased frequency of *Acinetobacter* in RS reveals the inadequate use of empirical antimicrobials, especially in the "out-patient" environment, the insufficient treatment of previous COPD exacerbations, colonization with a new germ, irrational antimicrobial, and entire epidemiological management of hospital isolates. Many studies have shown a growing trend of *Acinetobacter* resistance to antimicrobials increase, including the culture of the "pan-drug-resistant" *Acinetobacter* strains or strains sensitive only to polymyxin [25–28]. In our study, we did not cover the cases of *Acinetobacter* resistance to tigecyclin, colistin, and carbapenems.

CONCLUSION

The results of our study point to the administration of tigecycline and aminoglycosides (i.e. amikacin) as the initial antimicrobial combination in urgently intubated adults with COPD exacerbations, irrespective of the incubation period of COPD exacerbation. It is of great importance to improve the quality of RS sampling, repeat tracheobronchial aspirate sampling, or perform parallel tracheobronchial aspirate and lavage samplings. In this manner, the findings of "negative" cultures, contaminates or colonizing germs could be reduced. The significant prevalence of *Acinetobacter* in RS of COPD adults is a serious cause for concern. Its RS detection is a bad omen concerning patient treatment, antimicrobials resistance and the outcome of COPD.

In view of the significance of *Pseudomonas spp.* as the frequent causative germ of serious COPD exacerbations, and the fact that the concurrent use of tigecycline and aminoglycosides (i.e. amikacin) do not cover *Pseudomonas spp.*, the application of rapid methods for microbial identification, such as the polymerase chain reaction, is strongly recommended. Moreover, this will contribute to the rational use of antimicrobial agents and lower drug resistance in healthcare facilities. After the definitive RS culture findings are available, the clinician should correct or adjust COPD exacerbation management. Close cooperation between clinicians, microbiologists, and clinical pharmacologists is the key to successful antimicrobial management of urgently intubated COPD exacerbation adults on the IMV. We hope that the general recommendations for the introduction of reserve antimicrobials will favor positive results in keeping bacterial resistance to antimicrobials under control.

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Приказ иницијалне бактериологије узорака респираторног тракта и осетљивости бактеријских изолата према антимикробној терапији код ургентно интубираних одраслих особа са хроничном опструктивном болешћу плућа – двогодишње искуство једног центра

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САЖЕТАК

Увод/Циљ Погоршање хроничне опструктивне болести плућа (ХОБП) најчешће је узроковано инфективним агенсима, значајно компромитује квалитет живота оболелих и претказује лош исход болести. Када постоје клиничко-лабораторијски знаци вероватне бактеријске инфекције као узрока погоршања, неопходно је код интубираног болесника одмах започети иницијални антимикробни третман. У зависности од резултата култура респираторних узорака, иницијални антибиотски третман може бити промењен или настављен.

Циљ овог рада је представљање локалног водича за примену иницијалног антимикробног третмана хитно интубираног болесника са погоршањем ХОБП која је вероватно бактеријског порекла, узимајући у обзир болничко или ванболничко окружење.

Методе Студија пресека обухватила је 51 испитаника, који су по пријему у Јединицу интернистичке интензивне неге КБЦ Земун током 2015. и 2016. године одмах интубирани и механички вентилирани. Испитаници су подељени у две групе: групу 1 (26 испитаника), који су имали вероватну бактеријску егзацербацију из ванболничког окружења, и групу 2 (25 испитаника) – из болничког/домског окружења. Узорци респираторних течности (спутум, аспират) обрађени су у Микробиолошкој лабораторији.

Резултати У обе групе испитаника најчешће изоловане бактерије су *Acinetobacter* и *Pseudomonas spp.*, док се као трећа најчешћа изолована бактерија у групи 1 издваја *Staphylococcus aureus*, а у групи 2 *Klebsiella spp*. Комбинација тигециклина и аминогликозида покрива микробни спектар код 52% испитаника у групи 1, односно код 32% испитаника у групи 2.

Закључак На основу спроведене студије, препоручује се иницијална антимикробна терапија истовременом применом тигециклина и аминогликозида код интубираних одраслих особа са вероватном бактеријском инфекцијом као узроком егзацербације ХОБП.

Кључне речи: ХОБП; механичка вентилација; антибактеријски агенси

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Assessment of cardiovascular risk factors in persons with impaired glucose tolerance

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SUMMARY

Introduction/Objective The aim of the study was to determine the profile of cardiovascular risk factors in patients with impaired glucose tolerance (IGT) in comparison to patients with impaired fasting glucose (IFG).

Methods The study consisted of 222 adult participants with established fasting blood glucose values within the 5.6–6.9 mmol/L range. IGT was defined as blood glucose of 7.8–11.1 mmol/L in the second hour after the administration of 75 g during oral glucose tolerance test. IFG is the metabolic state between normal and impaired glucose tolerance, where fasting glucose levels are 5.6–6.9 mmol/L, and normal oral glucose tolerance test values. IGT was confirmed in 142 of these individuals (107 females and 35 males; aged 54 ± 13 years). The remaining 80 participants (56 females and 24 males, p = 0.329; aged 53 ± 13 years, p = 0.76) were considered the IFG group. The following parameters were analyzed in both groups: body mass index, waist circumference, blood pressure, fasting glucose, fasting insulin levels, HOMA-IR (homeostasis model assessment – insulin resistance), C-reactive protein, fibrinogen concentrations and lipid profile.

Results Participants in the IGT group were more obese than those in the IFG group (body mass index 30.8 ± 5.5 kg/m^2 *vs.* 26.7 ± 3.8 kg/m^2, p < 0.001), and with greater waist circumference (111 ± 12 cm *vs.* 101 ± 6 cm; p < 0.001). Glucose levels (6.02 ± 0.75 mmol/L *vs.* 5.80 ± 0.62 mmol/L; p < 0.001), and blood insulin levels (21.61 ± 3.46 *vs.* 6.00 ± 2.8 mIU/L; p < 0.001), as well as HOMA-IR (5.78 ± 2.68 mIU/L *vs.* 1.54 ± 1.46 mIU/L; p < 0.001) were also higher in the IGT group. Median levels of HbA1c in IGT subjects were higher compared with those in the IFG group, but the difference was not statistically significant (6.21 ± 0.75% *vs.* 5.92 ± 0.43%; p = 0.105). Median hs-CRP levels in the IGT subjects (6.7 ± 4.88 mg/L) were higher than in the IFG subjects (5.83 ± 6.47 mg/L), but without statistical significance (p = 0.76).

Conclusion Our study indicates the presence of a large number of cardiovascular risk factors in both groups. Still, obesity, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, higher diastolic blood pressure, as well as sedentary lifestyle, were statistically significantly more prevalent in patients with IGT.

Keywords: impaired glucose tolerance; impaired fasting glucose; cardiovascular risk factors; diabetes mellitus

INTRODUCTION

Prediabetes is defined as a condition in which blood glucose levels are higher than normal but lower than the established thresholds for diagnosing diabetes [1]. Prediabetes includes impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or glycated hemoglobin levels (HbA1c) in the range of 5.7–6.4% [1, 2]. Patients with isolated IFG can be distinguished from those with isolated IGT by their fasting and two-hour postload glucose values, as well as the shape of their glucose concentration curves obtained during the oral glucose tolerance test (OGTT). By definition, IGT is a condition in which blood glucose reaches levels of 7.8–11.1 mmol/L in the second hour after the administration of 75 g of glucose during the OGTT, with the basal fasting glucose levels < 7 mmol/L. IFG, on the other hand, is defined as an intermediate metabolic state between normal and impaired glucose tolerance, where fasting glucose levels are 5.6–6.9 mmol/L with normal levels of glucose during two hours in OGTT [1, 2, 3].

Prediabetes has started to receive considerable attention recently because individuals with impaired glucose regulation have been shown to be four to six times more likely to develop diabetes than those with normal glucose regulation [4].

Previous studies have shown that IGT when accompanied by other risk factors, such as age, sex, smoking, hypertension, obesity, and dyslipidemia, increases the risk of developing a cardiovascular disease (CVD) [5, 6]. While both IFG and IGT involve insulin resistance, these conditions are distinguished by the site of insulin resistance [5]. High hepatic insulin resistance is a typical finding in patients with IFG, with almost normal values in skeletal muscle. In patients with IGT, the main site of insulin resistance is muscle, with only small changes in liver insulin sensitivity [5]. IGT can easily progress to overt diabetes, whereby macrovascular changes are more pronounced. Thus, there is a

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relevant correlation with the metabolic syndrome (MetS) and, consequently, a higher risk of developing CVD [6].

As individuals with IGT have slightly elevated blood glucose levels, which is a relatively weak risk factor for developing CVD, it is highly likely that other cardiovascular factors are also responsible for increased incidence of macrovascular diseases among individuals with IGT [7, 8, 9].

The aim of the present study was to determine which cardiovascular risk factors, other than elevated blood glucose levels, are present in individuals with IGT in comparison to patients with IFG.

METHODS

This prospective study was conducted with the approval from the Ethics Committee of the Faculty of Medicine, University of Priština, located in Kosovska Mitrovica. Written informed consent was obtained from all subjects involved in the study. The research was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects (WMA Declaration of Helsinki, 2013) [10].

Study participants

This prospective study included participants that were screened in the period from March 2016 to January 2017 at the Department of Endocrinology of the Clinical Hospital Centre in Priština – Gračanica. Criteria for the inclusion into the study were established fasting glucose values in the range of 5.6–6.9 mmol/L based on two measurements and the OGTT findings. The exclusion criteria were as follows: age < 40 years, overt diabetes, and history or presence of clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, neurological, or infectious disorders capable of altering glucose metabolism. The study sample consisted of 222 patients, 142 (107 females and 35 males, mean age 54 ± 13 years) classified to the IGT group, as they met the aforementioned criteria suggested by the American Diabetes Association in 2016 [1]. The remaining 80 subjects (56 females and 24 males, mean age 53 ± 13 years) were classified to the IFG group, as they had isolated IFG and normal OGTT. Medical histories, family histories of CVD, diabetes and obesity, reports on smoking status, and information about current diseases were obtained from all the subjects. Alcohol intake was assessed using the CAGE questionnaire [11]. Physical activity was measured based on the World Health Organization recommendations for healthy adults, and physically inactive participants (exercise < 300 minutes per week) were considered sedentary [12].

Anthropometric, clinical, and biochemical measurements

Nutritional status was determined based on the body mass index (BMI) [13]. The specific distribution of adipose tissue, or the size of abdominal fat pad, was estimated by waist circumference, while the size of abdominal fat depots was determined in relation to the reference values provided by the World Health Organization [14]. Blood pressure was measured using the Riva-Rocci sphygmomanometer. Hypertension was diagnosed if systolic and diastolic blood pressure was ≥ 140/90 mmHg [15]. MetS was diagnosed according to the American Heart Association, National Heart, Lung and Blood Institute – modified Adult Treatment Panel III (ATP III) – criteria [16]. MetS was defined as the presence of at least three of the following conditions: abdominal obesity presented as large waist circumference (men: ≥ 102 cm; women: ≥ 88 cm), elevated triglyceride levels (≥ 1.7 mmol/L), low HDL cholesterol levels (men: < 1.0 mmol/L; women: < 1.2 mmol/L), hypertension (≥ 130/85 mmHg or use of anti-hypertensive medication) or elevated fasting blood glucose level (≥ 5.6 mmol/L or use of glucose-lowering drugs).

All the subjects were on normal diet prior to the biochemical assessments. On the day of testing, venous blood was collected after overnight fasting and was stored in vials with or without anticoagulant. Thereafter, a standardized OGTT was performed in all the subjects following the intake of 75 g of anhydrous glucose. Biochemical measurements, including concentrations of serum glucose, total cholesterol (TC), LDL-cholesterol (LDL), HDL-cholesterol (HDL), and triglycerides (TG), were performed by Olympus AU400 Chemistry Analyzer (Olympus, Tokyo, Japan) using commercial test reagent kits, according to the manufacturer's recommendations [15, 16]. The quality of glycemic control was assessed in terms of HbA1c levels, determined from anticoagulated blood samples by turbidimetric inhibition immunoassay method [17]. Fasting plasma insulin levels were measured by a radioimmunoassay, with a sensitivity of 2 mIU/L (normal range: 0.5–25 mIU/L) [18]. The insulin resistance index (homeostasis model assessment-insulin resistance – HOMA-IR) was calculated using the HOMA model: (fasting insulin × fasting glucose)/22.5 [19]. High sensitivity C-reactive protein (hs-CRP) was measured by a high-sensitivity immunoturbidimetry method (latex) on a Hitachi 902 analyzer (Hitachi, Ltd., Tokyo, Japan) using Roche diagnostic reagents (normal range: 0–5 mg/L). The fibrinogen was measured by the turbidimetric method (normal range: 2–4 g/L). The latest recommendations were adopted as target values [20].

Statistical analysis

The obtained data were analyzed using SPSS Statistics, Version 19.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as prevalence, in percentages, while continuous variables were expressed as mean values and standard deviations (SD) with a confidence interval (95% CI). To analyze the differences between the groups, the χ^2 test or Fisher's exact test was adopted for testing the probability of the null hypothesis (when some of the expected frequencies were lower than five), while conducting the Student's t-test for the independent samples. Pearson correlation coefficient was used to investigate the association between the variables. The level of statistical significance was set at $p < 0.05$.

RESULTS

The study sample included 222 patients, 142 (107 females and 35 males) of whom fulfilled the criteria for IGT diagnosis. The average age of the subjects assigned to the IGT group was 54 ± 13 years. The remaining 80 subjects (56 females and 24 males; mean age 53 ± 13 years, p = 0.76) were assigned to the IFG group, as the OGTT test indicated the isolated IFG diagnosis. Basic demographic, anthropometric and clinical data pertaining to these subjects are shown in Table 1.

The age, sex distribution, fasting blood glucose, HbA1c concentration, and systolic blood pressure levels of the two groups were not statistically significantly different. In addition, no statistically significant differences in the hs-CRP levels and plasma fibrinogen were noted between the individuals with IGT and those diagnosed with IFG. However, the BMI, waist circumference, serum TC, LDL, TG, fasting insulin levels, HOMA-IR, and diastolic blood pressure were significantly higher, whereas HDL cholesterol concentration was significantly lower in the IGT group compared to the IFG group (Table 1). Also, there were more obese subjects (BMI ≥ 30 kg/m^2) in the IGT group than in the group with IFG, and the difference was statistically significant (Table 2).

In addition, we have found that central obesity, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, higher diastolic blood pressure, as well as sedentary lifestyle, were statistical significantly more prevalent in patients with IGT, and report family history of type 2 diabetes mellitus (T2DM) (Table 3).

The correlation analysis showed a statistically significant positive correlation between BMI, as well as waist circumference, and the current plasma insulin concentration, while the ratio between these nutritional status values and the current blood glucose levels was not statistically significant (Table 4).

Table 1. Anthropometric, clinical, and laboratory data of studied participants; data are presented either as frequencies (n) or arithmetic mean ± SD; differences between the groups were tested by Student's t-test.

Parameters	IGT group (n = 142)	IFG group (n = 80)	p-value
Male/ Female (n)	35/107	24/56	0.329
Age (years)	54 ± 13	53 ± 13	0.7591
BMI (kg/m^2)	30.8 ± 5.5	26.7 ± 3.8	< 0.001
Waist circumference (cm) Men Women	 111 ± 12 97.6 ± 21.7	 101 ± 6 86 ± 11.3	 0.007 0.019
Total cholesterol (mmol/L)	6.34 ± 0.93	4.52 ± 1.21	< 0.001
HDL-cholesterol (mmol/L)	1.31 ± 0.28	1.42 ± 0.17	0.032
LDL-cholesterol (mmol/L)	4.3 ± 0.92	2.85 ± 1.08	< 0.001
Triglycerides (mmol/L)	2.12 ± 1.25	1.25 ± 0.63	< 0.001
Fasting blood glucose (mmol/L)	6.02 ± 1.26	5.8 ± 0.62	0.852
HbA1c (%)	6.21 ± 0.75	5.92 ± 0.43	0.105
Fasting blood insulin (mIU/L)	21.61 ± 3,46	6 ± 2.8	< 0.001
HOMA-IR	5.78 ± 2.68	1.54 ± 1.46	0.001
Blood pressure (mmHg) Systolic Diastolic hs-CRP (mg/L) Fibrinogen (g/L)	 134.7 ± 17.6 89.7 ± 10 6.7 ± 4.88 3.67 ± 4.88	 129.8 ± 14.4 82.9 ± 9 5.83 ± 6.47 3.36 ± 0.95	 0.159 < 0.001 0.760 0.900

BMI – body mass index; HOMA-IR – homeostasis model assessment insulin resistance; HbA1c – glycated hemoglobin A1c; hs-CRP – high-sensitivity C-reactive protein; IGT – impaired glucose tolerance; IFG – impaired glucose fasting

Table 2. Distribution of anthropometric nutrition measures in studied groups; the differences between the groups in anthropometric measures, body mass index (BMI), and waist circumference, were tested by the χ^2 test

Parameters	IGT group (n = 142)	IFG group (n = 80)	p-value
BMI (kg/m^2)			
18.5–24.9 (%)	4.22	30	< 0.001
25–29.9 (%)	57.75	60	0.835
≥ 30 (%)	38.03	10	< 0.001
Waist circumference – women			
≤ 80 cm (%)	18.69	42.85	0.002
80.1–87.9 cm (%)	39.25	30.36	0.286
≥ 88 cm (%)	42.06	26.79	0.065
Waist circumference – men			
≤ 94 cm (%)	2.86	4.17	0.62
94.1–101.9 cm (%)	57.14	58.33	0.912
≥ 102 cm (%)	40	37.5	0.775

DISCUSSION

The results obtained in the present study have shown a higher incidence of obesity, insulin resistance, dyslipidemias, lower physical activity, positive history of smoking, and positive family history of obesity and T2DM among the subjects with IGT compared with the IFG group. These results confirm the existence of added risk factors for the development of micro- and macrovascular complications in individuals with IGT. In a Danish population-based study of patients with IGT or IFG, the results of fasting laboratory measures and OGTT showed that hypertension, higher BMI, serum TG, and plasma glucose levels predicted the development of T2DM during the 3.5-year follow-up period [21].

Most of the risk factors that were more common in the IGT group are considered modifiable, since they largely depend on the subject's lifestyle and habits. However, several risk factors cannot be modified, especially aging, which is an inevitable biological process associated with overexpression of some and under-expression of other genes. These changes lead to an unstable metabolic control and increased sensitivity to the effects of external factors, such as, for example, poor nutrition and other lifestyle habits [22, 23]. Consistent with previous studies, a strong association of cardiometabolic risk with increasing age in the IGT group was observed in our study. Our subjects were older than 50 years, which, according to some authors, significantly increases the likelihood of developing IGT and CVD risk [21, 22]. The mean age of our subjects with IGT was 53 ± 13.32 years, which is consistent with the findings of other authors [21], while the participants in the Garcia-Alcala's study were somewhat younger [24]. Our results suggest a slightly higher incidence of IGT in

Table 3. Distribution of cardiovascular risk factors in the studied groups; the presence of metabolic syndrome, alcohol intake, physical activity, smoking status, and family history of diabetes were assessed as described in the Methods section; the differences between the groups were tested by the χ^2 test

Risk factors	IGT group (n = 142)	IFG group (n = 80)	p-value
Metabolic syndrome (%)	39.1	11	0.001
Alcohol intake (%)	12.8	13	0.964
Low physical activity (%)	45.3	51.2	0.001
Current smoker (%)	23.1	15	0.001
Family history of diabetes (%)	22.7	15.1	0.001
Hypertension (%)	23.1	20	0.63
LDL cholesterol > 3 mmol/L (%)	32.1	15	0.01
Triglycerides > 1.7 mmol/L (%) hs-CRP 5 mg/L (%) Fibrinogen > 4.0 g/L (%)	31 16 12	12 15 10	0.001 0.85 0.66

LDL – low density cholesterol, hs-CRP – high sensitivity C-reactive protein; IGT – impaired glucose tolerance; IFG – impaired glucose fasting

Table 4. Correlations between body mass index (BMI), waist circumference, and concentrations of glucose, insulin in the group with IGT

	Fasting blood insulin (mIU/L)		Fasting plasma glucose (mmol/L)	
	Pearson's r	p-value	Pearson's r	p-value
BMI (kg/m^2)	0.365	0.010	-0.059	0.102
Waist circumference (cm)	0.402	0.005	-0.260	0.072

women, which is consistent with the data reported by other authors, who also found that its incidence continues to increase with age [5, 6].

Prediabetes carries some predictive power for macrovascular disease, but most of this association appears to be mediated through the MetS [9]. Elevated glucose levels are one component of the current consensus definition of the MetS [16]. IGT and HbA1c appear to correlate more with the CVD risk than the IFG diagnosis [6, 25]. In the present study, patients with IGT (mean glucose 6.02 mmol/L and the HbA1c of 6.2%) had higher glucose levels than the IFG group did (mean glucose 5.8 mmol/L, HbA1c 5.9%), but the difference was not statistically significant.

Our findings further demonstrated that insulin resistance was significantly present in the IGT group, while it was absent in the group with IFG. The patients with IGT had significantly higher levels of fasting insulin, as well as the HOMA index of insulin resistance. An interesting post mortem analysis conducted by Butler et al. [26] revealed that individuals with IGT have 50% fewer β-cells, indicating that there is a significant loss of β-cell mass in individuals with IGT, which occurs long before the onset of T2DM. Accordingly, for the first time, the latest AACE recommendations put emphasis on obesity, stressing that reduction of body weight, not hyperglycemia, should be the primary objective of prediabetes prevention and treatment [27]. In fact, individuals with IGT, in addition to changing their lifestyles, have other options to achieve weight loss including drug therapy and surgical procedures, and consequently reduce insulin resistance and hyperglycemia, as well as successfully prevent progression to T2DM, while improving lipid status and blood pressure levels [28].

Our results not only revealed a high incidence of obesity in the IGT group, but also demonstrated that 38.03% of the subjects had a BMI ≥ 30 kg/m^2, which was statistically significant in comparison to patients with IFG. Obesity plays an important part in the pathogenesis of insulin resistance, which is commonly seen in IGT patients [5]. In addition, our results show that people with IGT tend to exhibit central obesity, which is associated with higher insulin resistance. The risk for prediabetes increases with increasing BMI levels and is particularly significant in individuals with BMI values above 30 kg/m^2 [5, 28]. Importantly, a higher BMI level at baseline, but not BMI change, is associated with IFG/IGT to T2DM transition, as confirmed by the present study [28].

In addition, abdominal obesity is a clinical sign of excessive accumulation of visceral fat and is usually associated with a cluster of cardiovascular risk factors defined by the National Cholesterol Education Program IV Adult Treatment Panel III as the MetS [16]. We noted in the IGT group a significant presence of a cluster of cardiovascular risk factors similar to those associated with the MetS.

Insulin resistance and visceral obesity are associated with high blood pressure. Both cause an increase in blood pressure by activating the sympathetic nervous system and the renin-angiotensin system, with the consequent retention of sodium and water, volume overload, endothelial dysfunction and impaired renal function [29]. Other than an increase in the number of individuals with IGT, the population-based, cross-sectional study of the prevalence of prediabetes in England that was conducted from 2003 to 2011 also revealed an upward trend in the blood pressure in this population [30].

Regarding serum lipid abnormalities in patients with IGT, in most extant studies, statistically significantly increased levels of TC, LDH, and/or TG, and a decrease in HDL were found compared to the group with IFG [31,32]. These findings further confirm atherogenic potential in our patients with IGT.

Some authors have reported that increased levels inflammatory cytokines, such as high-sensitivity C-reactive protein and tumor necrosis factor-alpha, are associated with an increased risk of progression from normoglycemia to prediabetes [33]. In obese individuals, an increase in adipose tissue and abnormal protein with hormone characteristics is common, causing infection of the systemic inflammation type and affecting the metabolic pathway in several processes, resulting in dysglycemia, IFG or IGT, and abnormal blood pressure [34]. The median levels of hs-CRP were increased in both groups, but there was no statistically significant difference between them (p = 0.76). Also, we did not find statistically significant difference in increased CRP prevalence between the groups.

Finally, the impact of smoking and exposure to tobacco smoke on the development of prediabetes must be highlighted, even though it remains insufficiently explored. In fact, one of the few studies that have addressed the influence of smoking on the development of T2DM is the Multi-Ethnic Study of Atherosclerosis (MESA) [35].

This study has certain limitations, one of which is a relatively small sample size. In addition, no control group was

included in the analyses, and the conclusions pertaining to the CV risks are largely based on extant empirical evidence rather than solely on the study results. Moreover, no information was available on whether the patients have taken some measures to prevent CV risk factors. Patients with IGT have a significantly higher number of risk factors for the development of CVD. Their association increases this risk.

CONCLUSION

Our results have shown that, beyond impaired glucose metabolism, individuals with IGT also exhibited obesity, lipoprotein imbalance, hyperinsulinemia, and higher diastolic blood pressure, as well as reported sedentary lifestyle, cigarette smoking, and family history of diabetes, more frequently than patients with IFG, which may be implicated in the development of a cardiovascular disease. Thus, there is an evident need for thorough and systematic application of all preventive measures, including lifestyle changes in the first place, followed by drugs and other treatment modalities, in reducing the risk for the development of type 2 diabetes mellitus and cardiovascular diseases.

Conflict of interest: None declared.

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Процена кардиоваскуларних фактора ризика код особа са смањеном толеранцијом на глукозу

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САЖЕТАК

Увод/Циљ Циљ студије је био да се утврди који су кардиоваскуларни фактори ризика присутни код особа са смањеном толеранцијом на глукозу (СТГ) у поређењу са особама са повишеном гликемијом наште (ПГН).

Методе У студију је било укључено укупно 222 одрасла испитаника са константним налазом концентрације глукозе у распону 5,6–6,9 *mmol/L*. СТГ је стање у којем глукоза у крви достиже ниво 7,8–11,1 *mmol/L* у другом сату после примене 75 *g* у оралном тесту толеранције на глукозу. ПГН је метаболичко стање између нормалне и оштећене толеранције на глукозу, при чему нивои глукозе наште износе 5,6–6,9 *mmol/L*, и са нормалним вредностима оралног теста толеранције на глукозу. Групу са СТГ су чинила 142 испитаника (107 жена и 35 мушкараца; просечне старости 54 ± 13 година) код којих је оралним тестом толеранције на глукозу утврђена СТГ. Осталих 80 испитаника (56 жена и 24 мушкарца, $p = 0,329$; просечне старости 53 ± 13 година, $p = 0,76$) чинило је групу са ПГН. Код свих испитаника анализирани су следећи параметри: индекс телесне масе (ИТМ), обим струка, вредности крвног притиска, гликемије наште, базална инсулинемија, *HOMA-IR* (хомеостазни модел процене инсулинске резистенције), Ц-реактивни протеин (ЦРП), фибриноген и липидни статус.

Резултати Испитаници у групи са СТГ били су гојазнији него они у групи са ПГН (ИТМ: 30,8 ± 5,5 kg/m^2 према 26,72 ± 3,83 kg/m^2; $p < 0,001$), са већим обимом струка (111 ± 12 *cm* према 101 ± 6 *cm*; $p < 0,001$). Концентрације глукозе (6,02 ± 0,75 *mmol/L* према 5,80 ± 0,62 *mmol/L*; $p < 0,001$) и инсулина у крви (21,61 ± 3,46 према 6,00 ± 2,80 *mIU/L*; $p < 0,001$), као и вредности *HOMA-IR* (5,78 ± 2,68 према 1,54 ± 1,46; $p < 0,001$), такође су биле више у групи са СТГ. Средње вредности *HbA1c* код испитаника са СТГ биле су веће у поређењу са особама са ПГН, али није било статистички значајне разлике (6,21 ± 0,75 према 5,92 ± 0,43%, $p = 0,105$). Средњи нивои високо осетљивог ЦРП у групи са СТГ били су већи у поређењу са групом са ПГН (6,70 ± 4,88 *mg/L* према 5,83 ± 6,47 *mg/L*), али без статистички значајне разлике ($p = 0,76$).

Закључак Наша студија указује на присуство великог броја кардиоваскуларних фактора ризика у обе групе. Додатно, потврђено је да су гојазност, хиперинсулинемија, хиперхолестеролемија, хипертриглицеридемија, виши дијастолни крвни притисак, као и седентарни начин живота, статистички значајно чешће заступљени код болесника са СТГ.

Кључне речи: смањена толеранција на глукозу; повишена глукоза наште; кардиоваскуларни фактори ризика; дијабетес мелитус

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Management of major bile duct injuries following laparoscopic and open cholecystectomy – a single center experience

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SUMMARY

Introduction/**Objective** Bile duct injuries represent a devastating and potentially life-threatening consequence of cholecystectomy. Although most cholecystectomies are currently performed laparoscopically, some complex cases require an open approach.
The aim of this report is to present and analyze a single center experience regarding the management of these injuries.

Methods A retrospective study was conducted in a tertiary referral institution. During a 13-year period, we identified a total of 64 patients. Only patients requiring surgical reconstruction to repair bile duct injuries were included in the study. Patients were grouped according to the type of surgical approach, i.e. laparoscopic or open cholecystectomy.

Results Out of 64 patients with bile duct injuries, 38 (59.4%) incurred the injuries during open and 26 (40.6%) during laparoscopic cholecystectomy. No differences between the groups were observed concerning the time of bile duct injury diagnosis, type of injury, incidence of concomitant vascular and bile duct injuries, type of reconstruction procedure or complication rates after the primary intervention. The latency of bile duct injury management was found to differ between the study groups. In the open cholecystectomy group, bile duct injuries were managed significantly later than in the laparoscopic one.

Conclusion The results suggest that bile duct injuries occur with equal frequency after laparoscopic as well as open cholecystectomy. However, injuries are managed later after open than after laparoscopic cholecystectomy. Tertiary centers have satisfactory outcomes of major bile duct injury reconstruction, with low rates of both morbidity and mortality.

Keywords: bile duct injuries; laparoscopic cholecystectomy; open cholecystectomy; biliary reconstruction

INTRODUCTION

According to recent studies, the incidence of bile duct injuries (BDIs) during cholecystectomy ranges 0.4–0.9% [1, 2]. Although the rate of BDIs might be considered low in the era before laparoscopic cholecystectomy (LC), its incidence was even lower, and it ranged 0.1–0.2% [3, 4]. On the other hand, since cholecystectomy represents one of the most commonly performed surgical procedures worldwide, BDIs are an important and potentially life-threatening surgical complication.

The vast majority of cholecystectomies are now done laparoscopically, but still some complex cases require the surgeon to perform an open cholecystectomy (OC) [5]. Nowadays, LC is the method of choice for uncomplicated gallstone disease and early acute cholecystitis. Depending on their degree and clinical significance, BDIs may be classified from minor to major. Approximately 20% of BDIs are neglected during cholecystectomy [6, 7]. They are diagnosed at various times postoperatively and may lead to serious consequences such as postoperative fluid collection, biliary peritonitis, sepsis, hepatic or multiple organ failure, and even death. The objective of this study was to present and analyze a single center experience.

METHODS

A retrospective study was conducted in a single tertiary referral institution during a 13-year period between January 1, 2002 and December 31, 2014. We identified a total of 77 patients due to post-cholecystectomy BDIs and only those requiring surgical reconstruction to repair the BDIs were included in the study. The patients were grouped according to the type of surgical approach, LC or OC. Out of 77 identified patients, 13 were excluded from the study: four patients were excluded due to minor BDIs, two due to contrast allergy, two due to kidney failure, four patients who were not surgically treated, and one patient that was lost to follow-up.

Surgical bile duct repair was performed in the remaining 64 patients. Patients' medical records were retrospectively reviewed. The review included demographic and clinical characteristics, type of injury, complications due to the primary procedure, type of reconstruction and

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the outcome. Variables extracted from the recorded data were compared between the LC and OC groups.

Preoperative preparation for surgical repair of BDIs in all the patients included complete biochemical and hematological evaluations, the assessment of inflammatory parameters, and detailed physical examinations. BDI characterization was performed by abdominal ultrasound, percutaneous transhepatic cholangiography, endoscopic retrograde pancreatocholangiography, magnetic resonance imaging of bile ducts, and computed tomography angiography. BDIs were graded according to the Strasberg classification system. Biliary tree reconstruction was performed using the Hepp–Couinaud technique, Roux-en-Y hepaticojejunostomy, primary suture and T-drainage or hepatectomy. At the end of every procedure transjejunal drainage was placed and the drain was removed on the 10th postoperative day.

The success of biliary tree reconstruction was defined by the lack of post-surgical complications, including the need for further surgical treatment and biliary stricture with recurrent cholangitis. Patient follow-ups were performed one, three, six, and 12 months after BDI reconstruction, and annually after that.

Statistical analyses were performed using SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA). Numerical variables are shown as mean ± SD, while categorical variables are presented as absolute numbers and percentages. The Student's t-test was used to compare parametric variables, Mann–Whitney test to compare non-parametric variables, and Pearson's χ^2 test and Fisher's exact test to compare the differences in the frequency of categorical variables. The value of $p < 0.05$ was considered statistically significant.

RESULTS

BDIs occurred in 38 (59.4%) patients who underwent OC and in 26 (40.6%) patients who underwent LC. Out of 64 patients, 28 (43.8%) were male and 36 (56.2%) were female. The youngest patient was 23 and the oldest one 77, with the mean age of 54 ± 12.2 (see Table 1). The two groups did not statistically significantly differ with respect to age ($p = 0.112$).

Table 1. Distribution of patients according to age and sex

Parameter	LC	OC	Total	p
n	26 (40.6%)	38 (59.4%)	64	
Age (years)	51.2 ± 12.6	56.1 ± 11.7	54.1 ± 12.2	0.112
Sex				
Male	8 (28.6%)	20 (71.4%)	28 (56.2%)	0.08
Female	18 (50%)	18 (50%)	36 (43.8%)	

LC – laparoscopic cholecystectomy; OC – open cholecystectomy

BDIs were intraoperatively diagnosed in four (15.4%) patients operated by LC and in 11 (28.9%) patients during OC. This difference was not statistically significant ($p = 0.208$; see Table 2). Moreover, no statistical difference in the type of BDIs (Strasberg classification) was found between patients operated by LC or OC ($p = 0.744$; Table 2). Additionally, there was no difference in the incidence of concomitant vascular injuries and BDIs between the two groups ($p = 0.204$). The overall incidence of vascular injury was 29.6% (see Table 2).

Table 2. Time of bile duct injurie diagnosis, type of injury, and concomitant vascular injury [18]

Intraoperatively diagnosed	LC n = 26	OC n = 38	Total	p
	4 (15.4%)	11 (28.9%)	15 (23.4%)	0.208
Strasberg classification				
C	0	1 (2.6%)	1 (1.6%)	0.744
D	4 (15.4%)	5 (13.2%)	9 (14.1%)	
E1	3 (11.5%)	6 (15.8%)	9 (14.1%)	
E2	9 (34.6%)	16 (42.1%)	25 (39.1%)	
E3	6 (23.1%)	4 (10.5%)	10 (15.6%)	
E4	4 (15.4%)	6 (15.8%)	10 (15.6%)	
Concomitant vascular injury	10 (38.5%)	9 (23.7%)	19 (29.6%)	0.204

LC – laparoscopic cholecystectomy; OC – open cholecystectomy

A comparison of the latency of post-cholecystectomy BDI management revealed a statistically significant difference. OC patients were managed significantly later, with almost 58% of them being treated more than 40 days after the primary surgery ($p = 0.004$; Table 3). The most commonly performed bile duct reconstruction procedure in both groups was Roux–Hepp (see Table 3). There was no statistical significance regarding the frequency of the reconstruction type between the groups ($p = 0.724$). The incidence of complications (sepsis, thrombo-emboly, infections, etc.), abscess, biliary fistula, bile collection and hepatic necrosis were not statistically significantly different between the groups (Table 4; $p = 0.672$).

Table 3. Time of bile duct injurie management and reconstruction types

Time of BDI management	LC n = 26	OC n = 38	Total	p
Within 24 hours	6 (23.1%)	7 (18.4%)	13 (20.3%)	0.004
1–5 days	4 (15.4%)	0	4 (6.3%)	
6–40 days	12 (46.2%)	9 (23.7%)	21 (32.8%)	
Late reconstruction	4 (15.4%)	22 (57.9%)	26 (40.6%)	
Type of reconstruction				
Primary suture and T drainage	3 (11.5%)	5 (13.2%)	8 (12.5%)	0.724
Roux-en-Y HJA	9 (34.6%)	12 (31.6%)	21 (32.8%)	
Roux–Hepp	13 (50%)	16 (42.1%)	29 (45.3%)	
Hepatectomy	1 (3.8%)	5 (13.2%)	6 (9.34%)	

LC – laparoscopic cholecystectomy; OC – open cholecystectomy; BDI – bile duct injuries

Table 4. Types of complication after primary surgery and mortality rate

Complications	LC n = 26	OC n = 38	Total	p
General complications	5 (19.2%)	9 (23.7%)	14 (21.9%)	0.672
Abscess	3 (11.5%)	8 (21.1%)	11 (17.2%)	0.322
Biliary fistula	12 (46.2%)	17 (44.7%)	29 (45.3%)	0.911
Biloma	11 (42.3%)	11 (28.9%)	22 (34.4%)	0.269
Liver necrosis	6 (23.1%)	4 (10.5%)	10 (15.6%)	0.174
Mortality	0	1 (2.6%)	1 (1.6%)	

LC – laparoscopic cholecystectomy; OC – open cholecystectomy

The median patient follow-up time was 117.6 months, with a range of 12–168 months. During the follow-up period, satisfactory results were achieved after the primary reconstruction in 57 (89%) patients. Benign stenosis, as a late complication of the reconstruction, occurred in six (9.4%) patients. In those six patients, a secondary reconstruction was performed due to biliary stenosis. In two of the patients, the secondary reconstruction was performed two years after T tube placement. In the other four patients, the secondary reconstruction was performed two to seven years following the primary reconstruction, which was done within 24 hours of the injury. One lethal outcome was observed (mortality rate 1.6%), which was due to the consequences of purulent cholangitis, subhepatic abscess, and biliary peritonitis. Actually, the patient developed signs of severe septic shock, liver, and multiorgan failure 10 days after the primary reconstruction in the primary referring institution.

DISCUSSION

Regardless of the relatively low incidence rate, BDIs still represent a significant source of perioperative morbidity and mortality in patients that have undergone cholecystectomy. This type of iatrogenic surgical complication can have serious consequences, and in the worst case may lead to the lethal outcome. BDIs usually include bile duct laceration, thermal injury, occlusion, division and dissection of the bile tree and arise due to misinterpreted anatomical variations, pathological findings or surgical error [8]. The skill of the surgeon, emergency procedures, the type of surgical approach, operative field factors (inflammation, hemorrhage and field depth) and patient characteristics have been identified as factors that play an important role in the occurrence of BDIs [9].

In cases of complete bile duct transection, surgical treatment is the only option. Depending on the type of injury, several reconstruction methods are available. These included end-to-end anastomosis with the T tube, Roux-en-Y hepaticojejunostomy, and several types of hepatic resections. Roux-en-Y hepaticojejunostomy is the most frequently performed biliary duct reconstruction procedure [10, 11].

Biliary duct reconstructions should be performed by experienced surgical teams in tertiary referral centers. Our institution represents one of few specialized high-volume centers for hepaticobiliary surgery in the Republic of Serbia. During the 13-year study period, data were collected concerning 77 patients referred to our institution. When 13 patients were excluded from the study (due to exclusion criteria), the final study group consisted of 64 patients.

The results of several recent studies suggest that patients aged 40 to 50 are most likely to undergo biliary tract reconstruction procedures [12, 13, 14]. In this study, the overall mean patient age was 54 ± 12.2 years and no age differences were observed between the study groups. The results of this study suggest that older patients are more likely to require post-cholecystectomy biliary reconstruction, which confirms the previous results [2, 15, 16].

In this study, no sex differences were observed with respect to the incidence of BDIs. This is in contrast to previous findings, which suggested that these lesions are more frequently encountered in men and that sex represents an independent predictor of BDIs [16]. It is possible that the small available sample size obscured sex differences in this study.

In the LC group, 15.4% of BDIs were diagnosed during the initial surgery, while 28.9% were recognized during OC. Our data are supported by the results of previously published studies which showed that BDIs were intraoperatively diagnosed in only one quarter of patients [11]. However, the incidence of intraoperatively diagnosed BDIs is still a matter of debate as it was reported that the majority of BDIs were recognized during the primary surgery [6, 7].

When it comes to the type of surgical reconstruction, we did not find any significant differences between our groups of patients. Roux-en-Y hepaticojejunostomy was the most commonly performed type of reconstruction in both groups. It was performed in 50% of cases in the LC group and in 42.1% of cases in the OC group (see Table 3). This is in agreement with the generally accepted opinion that this procedure is the method of choice for the surgical treatment of major BDIs [10].

In our study, the time from injury to reconstruction was significantly different between the observed groups. The majority of patients in the LC group underwent the reconstruction less than 40 days after the initial surgery. On the other hand, the majority of reconstructions in the OC group were performed later than 40 days after the initial surgery. It was suggested that later reconstruction is more suitable since acute inflammation, infection, and ischemia should be resolved prior to BDI repair or before fibrosis was established [17, 18]. Furthermore, Stilling et al. [19] found that an early reconstruction increases the risk of stricture rate by 30% and negatively affects both short- and long-term mortality rate. The immediate repair of injuries that are recognized during the primary surgery should only be performed by an experienced surgeon. The success rate of reconstruction performed by an experienced surgeon is estimated to be 90%, while the success rate of reconstruction done by surgeons not specialized in hepato-biliary pathology is 70% [20, 21]. If an experienced surgeon or surgeon specialized for this kind of procedure is not available, drainage should be placed and the patient should be transferred to a tertiary institution as soon as possible.

In this study, the time between the primary surgery and BDI reconstruction was shorter after LC than after OC. This might be explained by the fact that patients recover faster after LC and, therefore, the symptoms of complications become clinically apparent sooner than after OC. Additionally, certain postoperative complications such as sepsis, abscess, and thromboembolism dictate the timing of reconstruction. Also, abdominal cavity drainage after LC is specified by the laparoscopic ports – therefore, the drains may not be placed as ideally as during OC. Furthermore, one of the main conditions of successful reconstruction is the usage of intraoperative cholangiography (IOH). BDI reconstruction without the use of IOH was shown

to have a failure rate of 29%, while with the use of IOH, the failure rate is only 4% [22]. In the present study, IOH was performed in all 64 cases, thus explaining the high reconstruction success rate.

Our study groups did not statistically significantly differ in terms of incidence of concomitant vascular injuries and BDIs. The overall incidence of joint vascular injury was 29.6%. Literature data reported that the incidence of joint lesions was 12–32% in patients that underwent LC, and 14–42% in patients who underwent OC [23, 24, 25]. Although the exact incidence of these injuries is still unknown, the incidence in the present study is in the range of previously published results. As in the study by Alves et al., in this study, the vasculobiliary injuries did not affect mortality rate – concomitant injuries did not lead to any lethal outcome of our patients [23]. On the contrary, some authors found that concomitant injuries resulted in a higher mortality rate [24, 26]. The mortality rate in the present study was 1.6%. This is in concordance with the published literature, where it was shown that the mortality rate ranged 0–4.2% [7, 21, 27, 28, 29]. Although BDIs represent a serious health problem, they generally have a very good outcome, even in major BDIs, when Roux-en-Y hepaticojejunostomy reconstruction needs to be performed. In our study, only six patients required secondary reconstruction. Also, one large study by de Reuver et al. [30] found that patient survival after BDI reconstruction in a referral institution was similar to that of the general population.

CONCLUSION

In conclusion, special attention should be paid to BDIs, which, although uncommon, can have serious or life-threatening consequences. BDIs should be managed in tertiary institutions by experienced surgical teams familiar with hepato-biliary pathology. IOH represents *conditione sine qua non* in the prevention and intraoperative management of BDIs. Based on the results of this study, these injuries occur with equal frequency after laparoscopic and open cholecystectomy. Furthermore, with laparoscopic cholecystectomy there may be a tendency for reconstruction to be performed sooner after the primary surgery than after open cholecystectomy. Regardless of the approach or the timing of reconstruction, adequate reconstruction results in satisfactory outcomes with low rates of morbidity and mortality.

Conflict of interest: None declared.

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Збрињавање компликованих повреда жучних путева после лапароскопске и отворене холецистектомије – искуство једног центра

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САЖЕТАК

Увод/Циљ Повреде жучних путева представљају разарајућу и могућу смртоносну последицу холецистектомије. Иако се већина холецистектомија обавља лапароскопски, неки сложенији случајеви захтевају отворени приступ.
Циљ овог рада је да представи и анализира искуство једног центра у вези са збрињавањем ових повреда.

Методе Спроведена је ретроспективна студија у терцијарној институцији. Током тринаестогодишњег периода идентификовали смо укупно 64 болесника. У студију су били укључени само болесници којима је била потребна хируршка реконструкција жучних путева. Болесници су били груписани према врсти хируршког приступа, тј. лапароскопској или отвореној холецистектомији.

Резултати Од 64 болесника са повредама жучних путева, 38 (59,4%) њих је било са повредама током отворене и 26 (40,6%) током лапароскопске холецистектомије. Нису примећене разлике између група у погледу времена дијагнозе повреда жучних путева, врсте повреде, инциденције истовремених повреда васкуларних и жучних путева, врсте поступка реконструкције или стопа компликација након примарне интервенције. Утврђено је да се време реконструкције повреда жучних путева разликује између студијских група. У групи са отвореном холецистектомијом повреде жучних путева су знатно касније збрињаване него у групи са лапароскопском холецистектомијом.

Закључак Резултати показују да до повреда жучних путева долази подједнако после лапароскопске као и отворене холецистектомије. Међутим, повреде се збрињавају касније после отворене него после лапароскопске холецистектомије. Терцијарни центри имају задовољавајући исход реконструкције великих повреда жучних канала, са ниским стопама морбидитета и морталитета.

Кључне речи: повреде жучних путева; лапароскопска холецистектомија; отворена холецистектомија; реконструкција жучних путева

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

High-energy tibial plateau fractures treated with Ilizarov fixator

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SUMMARY
Introduction/Objective Tibial plateau fractures constitute a significant group of injuries to a major weight-bearing joint. High-energy fractures are difficult to treat, as they entail articular depression, condylar displacement, dissociation of comminuted metaphysis, and closed degloving injuries. The principles of the treatment are anatomical reconstruction of the articular surface, restoration of the anatomical axis, fixation spanning the metaphyseal comminution, and further minimization of soft tissue injury. The aim of this study is to evaluate the clinical outcome of using Ilizarov external fixator in the treatment of high-energy Schatzker IV, V, and VI tibial plateau fractures.
Methods This retrospective study was conducted from 2013–2016 on 35 patients (36 fractures) with high-energy tibial plateau fractures classified as Schatzker type IV, V, and VI. The mechanisms of injury were road traffic accident, fall from a height and direct trauma. The fractures were closed in 26 cases and open in 10 cases. All patients were treated with ligamentotaxis and percutaneous fixation using Ilizarov fixator. Functional outcome was determined using the Knee Society Score.
Results The mean follow-up period was 20 months. All fractures healed in an average time of 14 weeks. The range of knee flexion after one-year follow-up averaged at 100°. Average Knee Society Score in our study was 77.
Conclusion Ilizarov external fixation is a safe and efficient treatment modality for high-energy tibial plateau fractures. It allows reconstruction of the articular surface, stable fixation, early rehabilitation, and care of soft tissue injuries.
Keywords: Ilizarov method; tibial plateau; fracture

INTRODUCTION

Tibial plateau fractures constitute a significant group of major weight-bearing joint injuries and are often associated with functional impairment [1]. High-energy plateau fractures are difficult to treat, as they are followed by articular depression, condylar displacement, comminuted of metaphysis, and extensive soft tissue injuries. The outcome is usually poor with a high rate of complications that directly affect surgical treatment and long-term outcomes [2]. Complications include severe soft tissue coverage problems, lower extremity compartment syndrome, peroneal nerve and vascular injury, and eventual osteoarthritis of the knee. These accompanying complications directly influence surgical decision-making and prognosis [3].

The treatment principles are an anatomical reconstruction of the joint surface, spanning the metaphyseal comminution, restoration of the anatomical axis and further minimization of secondary insult to an already traumatized soft tissue envelope [4]. These goals can be achieved through various methods such as: internal fixation, bridge plating, and percutaneous screws with casting, external fixator with or without limited open and bone grafting or a combination of these methods [3].

Over the years, many treatment modalities have been proposed for these complex fractures [2]. The most popular treatment option has been open reduction and internal fixation with double plating but research data showed that this method is associated with many complications that include joint stiffness, non-union, mal-union, skin defects, osteomyelitis, which could lead to amputation and even death [5]. The complication rate appeared to be as high as 50% in some studies and the rate of postoperative skin infection and osteomyelitis has been reported to be up to 33% [6]. In order to reduce the occurrence of these problems, closed reduction and percutaneous external fixation was proposed by Ilizarov [6, 7].

With an extensive contusion or soft-tissue injury, a joint-bridging external fixator is useful to provide a sufficient stability needed for soft tissue recovery. The concept of "spanning" the knee joint was introduced in the 1990s. This concept evolved as proponents of indirect fracture reduction and external fixation reported increased full recovery rates [6].

The aim of this study is to evaluate the clinical outcome of using Ilizarov external fixator in the treatment of high-energy Schatzker IV, V, and VI tibial plateau fractures.

METHODS

This retrospective study was conducted at the Banjica Institute for Orthopaedic Surgery on

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35 patients (36 fractures) with high-energy tibial plateau injuries classified as Schatzker type IV, V, and VI [8]. Patients were treated from 2013–2016 using Ilizarov external fixation method. Age ranged from 43 to 72 years with an average of 56 years, 16 patients were females and 19 were males. The mechanism of injury was a road traffic accident in 21 patients, a fall from a height in ten patients, and direct trauma in four patients. The right limb was affected in 19 and the left limb in 17 cases with one patient had bilateral Schatzker type IV fracture. The fractures were closed in 26 cases and open in 10 cases. The open fractures were Gustilo–Anderson type I in six cases and type II in four cases [9]. Eight out of 26 closed fractures had closed soft tissue injuries grade II according to the classification of Tscherne and Gotzen [10]. Eight fractures were Schatzker type IV, 13 cases Schatzker type V and 15 cases type VI (Table 1). Fracture classification was performed by the coauthors retrospectively based on preoperative radiographs.

Soft tissue condition had a crucial role in planning the time of the operation. All patients with open fractures (n = 10) were operated within two days after injury with Ilizarov technique after wound debridement, irrigation, and intravenous antibiotics (first generation cephalosporin and aminoglycoside); others were treated within an average period of five days after injury (range: three to nine days) in order to allow soft tissue oedema to subside.

The operation was performed under spinal or general anesthesia. Prophylactic first generation cephalosporin antibiotics were administered intravenously in all cases until third postoperative day. All operations were performed by the lead author. The fragments were reduced by ligamentotaxis, applying distraction force on a traction table. After satisfactory radiographic confirmation of reduction, axial and rotational alignment, counter opposed olive wires through the fragments were used to achieve interfragmentary compression. The number and direction of wires used on the fracture site was defined by fracture pattern and reduction stability. The wires were placed below joint surface to prevent synovial contact and to avoid septic arthritis. After the first ring was fixed to the proximal wires, it was then connected to two rings distally with four interconnecting rods. The middle ring was positioned just distal to any shaft fracture component. The distal ring was placed proximally and parallel to the ankle joint surface. Special care was taken to restore the mechanical axis in relationship to the condyles. Based on intraoperative assessment and surgeons experience in cases of extremely complex and unstable fractures (n = 9), frame was extended onto the distal femur with two levels of fixation. Thromboprophylaxis with low-molecular-weight heparin were carried out for three weeks or until femoral part of the frame was removed.

Postoperative care consisted of daily-performed thorough pin care, from the first postoperative day. Ankle equinus deformity was prevented by active joint mobilization. From the second postoperative day passive range of knee motion, isometric quadriceps exercises and hip raising exercises were began. All patients were allowed to bear weight as tolerated from the second postoperative day. The external fixator was removed once radiographic and clinical evidence of union were established. Clinically, healing was defined as the ability to bear full weight without pain. Physiotherapy was continued after removal of the fixator to improve range of knee motion. Functional outcome was determined using the knee society score (KSS) [11]. For data description, we use measure of central tendency (arithmetic mean) and measures of variability (minimum and maximum value). This study was done in accord with standards of the institutional Committee on Ethics.

Table 1. Preoperative parameters and surgery outcome.

Case	Age/ Sex	Injury	Type	Schatzker class.	Fixator time (weeks)		Knee ROM Flex./ Ext.	Knee Society Score
					Tibia	Femur		
1	63♀	Fall	Closed	V	15		120/-15	78
2	71♂	Fall	Closed	VI	17	4	105/-5	84
3	63♀	TA	Closed	V	14		110/-15	76
4	55♀	TA	Open	IV	15		80/0	87
5	49♂	TA	Open	VI	14		85/-5	74
6	62♂	TA	Closed	VI	14	4	120/-15	83
7	54♀	Fall	Open	V	12		130/-10	91
8	43♀	TA	Closed	IV	15		80/-15	68
9	53♂	TA	Closed	V	13		115/-15	87
10	43♂	TA	Open	VI	18	5	95/-15	61
11	60♀	Fall	Open	VI	16	4	85/-10	65
12	63♂	TA	Closed	V	14		85/-15	64
13	62♀	TA	Closed	VI	13		85/-10	69
14	44♂	DT	Open	V	16		130/-15	82
15	60♂	Fall	Closed	IV	12		100/-10	86
16	44♀	TA	Closed	VI	12		105/-5	81
17	53♂	TA	Closed	VI	16	4	100/-10	77
18	57♀	DT	Closed	V	14		80/-15	69
19	61♀	TA	Open	VI	18		125/0	88
20	61♂	TA	Closed	IV	12		115/-5	83
21	55♂	TA	Open	V	16	4	80/-10	57
22	46♂	TA	Closed	V	13		120/-10	85
23	54♀	TA	Closed	VI	13		115/-5	84
24	50♀	DT	Open	V	17		115/-15	78
25	51♂	Fall	Closed	IV	13		120/0	90
26	65♂	TA	Closed	VI	12		85/-10	67
27	57♂	TA	Closed	VI	14		105/-5	79
28	49♂	TA	Closed	V	15		80/-10	72
29	63♀	Fall	Closed	V	16		80/-15	70
30	56♂	DT	Open	VI	17	5	80/-15	66
31	59♀	Fall	Closed	VI	13		80/0	71
32	43♀	TA	Closed	V	13		125/0	89
33	47♂	TA	Closed	IV	14		130/-15	85
34	63♂	Fall	Closed	VI	15		100/-5	76
35	72♀	Fall	Closed	IV	16	6	120/0	84
			Closed	IV	16	6	120/0	

DT – direct trauma; TA – traffic accident; ROM – range of motion

RESULTS

The mean follow-up period was 20 months (ranging from 16 to 28). All patients were monitored by the lead author. The mean interval between injury and surgery was four

(range: 1–9) days. All fractures united in an average time of 14 (range: 12–18 weeks). Patients did not require blood transfusion, nor had any nonunion, septic arthritis, myositis ossificans, pulmonary embolism, deep venous thrombosis, soft tissue necrosis, or peroneal nerve palsy.

After removal of the frame, an extension lag was a common finding. It was observed in 19 cases, most of them improved with physiotherapy with mean lack of extension of 10° (range: 0–15°) after 1 year (Table 1). In nine cases, there were extremely complex and unstable fractures with extensive soft tissue injury. Therefore, knee was spanned using additional femoral ring as frame extension. The femoral frame was removed in average 5 weeks postoperatively (range: 4–6 weeks), and then patients were encouraged to fully bear weight (Table 1).

The range of knee flexion after one-year follow-up averaged at 100° (range: 80–130°) (Table 1). Four patients had a positive anterior drawer test, but they did not show functional instability. There were no cases of mediolateral instability. Complications included pin tract infection in five cases; all were improved with local treatment and a short course of systemic antibiotics. Malunion was established on standing radiographs in the form of varus deformity 10° in two cases and valgus deformity 10° in two cases. All the patients were allowed to go back to work and their daily activities within five months of their injury and were able to carry out their job requirements and daily activities as before. According to the KSS, the results were evaluated as excellent in 16 patients, good in ten patients, fair in eight patient, and poor in one. Average KSS in our study was 77 (Table 1).

DISCUSSION

Tibial plateau fractures, caused by high-energy trauma, inflict extensive damage to the bone and additional injury to the soft tissue. Early problems in treatment include fracture instability and inability to adequately reduce and fixate the bone fragments [12].

An open wound is present in one third of the Schatzker type-IV, V, and VI fractures that correspond to our sample in which open fractures occurred in 29% of patients. Careful management of the soft-tissue injury is crucial and the use of the Ilizarov method allows its undisturbed healing [13]. Patients with closed and open fractures were analyzed in a same sample group. The reason for this is that the objective was not to compare these two types in terms of treatment methods and outcomes, which is one of the drawbacks of the study.

The presence of fracture blisters or extensive subcutaneous hemorrhage and bruising does not limit the placement of the percutaneous wires that avoids additional devitalization of the bone since the periosteal and endosteal blood supply are not damaged any further. Small tensioned wires allow capture of small bone fragments with olives that compress the condylar fractures in the same way lag screws would. Maintenance of the desired mechanical axis can be continually monitored by frame adjustment [6].

In our study, the fractures were most common for patients in their fifties, with an average of 56 years. The other series show a higher incidence of fractures in younger age groups [14]. The most common cause of proximal tibia fractures in our study was traffic accident (TA). This corresponds to the study of Ngim et al. [15] who described 60% of patients with fractures of the tibia following road traffic accidents. In our case, fracture union time was 14 weeks in average (range: 12–18 weeks). Other studies also show similar healing time [16].

Ilizarov circular fixation allows both early movement and early weight bearing. The value of early movement has been well established but early loading of fractures of the tibial plateau has generally been avoided because of the concern that the reduction may be lost, resulting in depression of the articular surface [6]. Studies show that early weight bearing, however, stimulates bone healing, increases the formation of new woven bone, and allows retention of muscular strength [17]. In our study, partial weight bearing was allowed from second postoperative day, while full weight bearing was allowed at four weeks.

The mean range of motion (ROM) reported by Guadinez et al. [18] was 85° and by Morandi and Pearse [13] was 113°. All patients reported by Zecher et al. [19] achieved at least 90°. The average knee ROM in our study was 100° of flexion and lack of extension was 10°, which is in the spectrum of other studies.

Opponents of this technique may argue that congruous reduction can only be confirmed by open reduction, but even with open reduction, one requires imaging to confirm congruous reduction. Internal fixation of these highly complex injuries has led to some disastrous results. Moore [20] reported that 23% of cases treated with open reduction with internal fixation (ORIF) became infected. The rate of infection with ORIF in other studies ranged from 30% to 40% [12]. Pearse and Morandi [13] reported an advantage of external fixation of complex tibial plateau fractures with decreasing rates of complications.

In our case, we saw that the average optimal femoral fixation time for the intra-articular fractures to form soft callus and soft tissues to complete healing was five weeks. Spanning the knee with the external fixator also allows adequate initial weight bearing (Figure 1, 2).

When applying the KSS, the average knee score in our study was 77. The observed results were 16 (46%) excellent, 10 (28%) good, eight (23%) fair, and one (3%) poor. Our findings were similar to the results of Mikulak et al. [21], who reported a mean score of 78.5, and Kumar and Whittle [22], who described a mean KSS of 83.

Complications included pin tract infection in five cases; all were successfully cured with local treatment and a short period of systemic antibiotics. Four patients had axial deformities established on standing radiographs in the form of varus deviation of 10° in two cases, valgus deviation of 10° in two cases. However all the patients were allowed to go back to work within five months of their injury and were able to perform their job requirements and daily activities as before the injuries. Limitation of this study is the relatively short follow up period to make assessment about

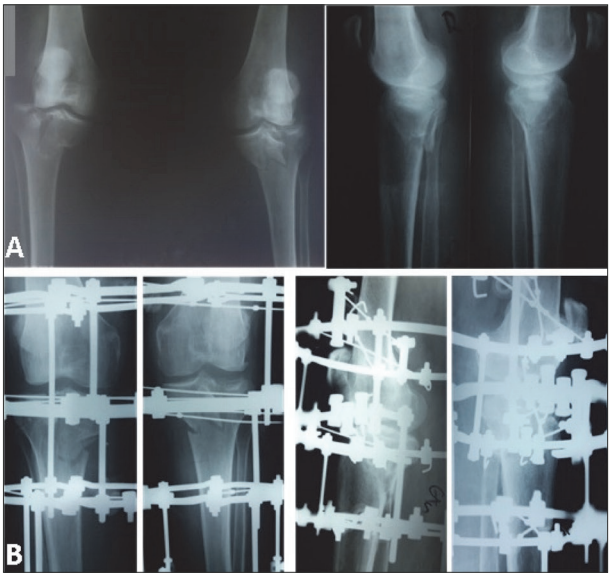

Figure 1. A – Radiographs of closed bilateral Schatzker IV type fracture in a 72 year old female patient; B – postoperative radiographs after fracture reduction and fixation using Ilizarov external fixator with femoral frame extension

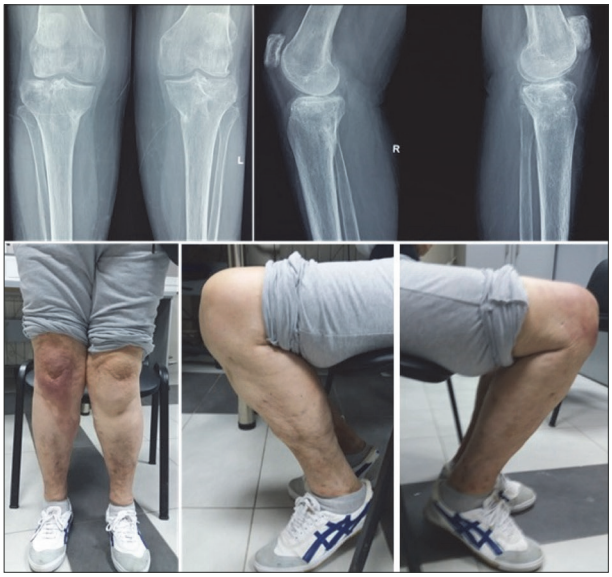

Figure 2. Same patient two years after surgery; postoperative radiological and functional outcome

degenerative arthritis as one of the late complications after tibial plateau injury. The other limitation is reliance on radiographs alone in lack of much superior computerized tomography imaging.

CONCLUSION

Ilizarov external fixation is a safe and efficient treatment modality for high-energy tibial plateau fractures. It provides reconstruction of the articular surface, stable fixation of fracture fragments, early rehabilitation of the joint, and care of associated soft tissue injuries.

The functional outcomes of this treatment method are more predictable with the high rate of union. Decreased incidence of soft tissue complications, early range of motion, early weight bearing, and good functional recovery all compare favorably with other reported results and serve as recommendation that Ilizarov external fixator should be the treatment of choice for such injuries.

Conflict of interest: None declared.

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Високоенергетски преломи тибијалног платоа лечени фиксатором по Илизарову

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САЖЕТАК

Увод/Циљ Преломи платоа тибије представљају значајну групу повреда једног од главних носећих зглобова. Високоенергетски преломи су захтевни и тешки за лечење услед артикуларне депресије, размицања кондила, коминуције метафизног региона, као и оштећења мекоткивног покривача. Циљеви лечења су анатомска реконструкција зглобне површине, успостављање анатомске осовине ноге, стабилна фиксација фрагмената и што мање додатно оштећење меких ткива.

Циљ овог рада је процена успешности лечења применом фиксатора по Илизарову код високоенергетских прелома тибијалног платоа који обухватају тип IV, V и VI класификације по Шацкеру.

Методе Ретроспективно су у периоду 2013–2016. године анализирани подаци о 35 болесника (36 прелома) са високоенергетским преломима платоа тибије класификованим као Шацкеров тип IV, V и IV. Механизам повређивања обухватао је саобраћајне несреће, пад са висине и директну трауму. Затворени преломи констатовани су у 26 случајева, док је отворене имало 10 болесника. Сви преломи су репонирани принципима лигаментотаксе и фиксирани перкутано апаратом по Илизарову. Функционални опоравак болесника праћен је коришћењем резултата Удружења за колено.

Резултати Просечан период праћења износио је 20 месеци. Сви преломи су зарасли у просеку за 14 недеља после ношења апарата по Илизарову. Средња вредност флексије у колену после годину дана праћења износила је 100°. Просечан резултат Удружења за колено био је 77.

Закључак Апарат по Илизарову представља безбедан и ефиксан начин лечења високоенергетских прелома платоа тибије. Њиме се постижу реконструкција зглоба, стабилна фиксација уз минимално оштећење меких ткива и спровођење ране рехабилитације.

Кључне речи: Илизаровљева метода; плато тибије; прелом

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Dexasone and metoclopramide vs. granisetron in the prevention of postoperative nausea and vomiting

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SUMMARY

Introduction Postoperative nausea and vomiting (PONV) is one of the most common postoperative complications. The incidence in adult population is 20–30%, and it can be up to 80% in high-risk population such as gynecological and laparoscopic surgeries.

The objective of this study is to compare the efficiency of the combination therapy in comparison with monotherapy in the prevention of PONV in gynecological and laparoscopic surgeries.

Methods An observational prospective cohort study was conducted on a sample of 64 patients (32 patients per group) treated postoperatively at the Gynecology and Obstetrics Ward of GH Subotica, in the period from January–March 2017. The anesthesiologist in charge administered the combination of dexasone and metoclopramide or granisetron in monotherapy according to protocol to patients for prevention of PONV.

Results The demographic characteristics of patients are homogenous and show a statistically significant difference only in the characteristics of length of smoker status and maximum intra-abdominal pressure during surgery. The total incidence of postoperative nausea in the fifth, 15th and 60th minute was 15.6%, 17.2% and 18.7% respectively, and in the fourth, eighth, 12th, and 24th postoperative hour it was 12.5%, 7.8%, 10.9%, and 6.2%, respectively. The incidence of postoperative vomiting in the fifth, 15th, and 60th minute was 1.6%, 4.7%, and 4.7%, respectively, and in the fourth, eighth, 12th, and 24th postoperative hour it was 1.6%, 3.2%, 1.6%, and 1.6%, respectively.

Conclusion The study proved that the combination effect of dexasone and metoclopramide is not inferior compared to monotherapy with granisetron.

Keywords: postoperative; nausea; vomiting

INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most frequent postoperative complications, occurring after surgery under general, regional, or local anesthesia. Previous studies have shown that patients regard vomiting as the most undesirable complication of anesthesia and qualify it as a more unpleasant sensation than pain [1, 2]. The incidence of PONV in adult population is 30% [3], and in high-risk population such as gynecologic and laparoscopic surgery, it can be up to 80% [4, 5].

The potential risk factors for PONV can be classified into four groups:

1. patient related factors (female sex, age, positive anamnesis for PONV, kinetosis, non-smoker status, the patient's American Society of Anesthesiologists (ASA) status, positive anamnesis for migraine, menstrual cycle phase);
2. surgery related factors (length of surgery, type of surgery);
3. anesthesia related factors (inhalation anesthetics, intravenous anesthetics, opioids, muscle block reversal, anesthetic technique and N_2O);
4. early postoperative period related factor (pain, opioid administration, postoperative movement of patients, early fluid and food ingestion and hypotension) [6].

The most used antiemetic drugs used in PONV prevention and therapy include dopamine receptor antagonists, serotonin 5-HT_3 receptor antagonists, and corticosteroids [7, 8].

In the therapy and prevention of PONV, anesthesiologists have the most experience in the application of dopamine antagonist metoclopramide. Due to its short-term action, it should always be administered towards the end of the surgery. At the dosage of 0.1–0.2 mg/kg, it very rarely causes adverse effects in adult patients [7, 8].

From the group of corticosteroids, antiemetic effect has been shown in the administration of dexasone. Its exact mechanism of action is unknown, but it is assumed to be based on inhibition of prostaglandin synthesis, decrease of serotonin levels in the brain, local anti-inflammatory action, and reduction of brain-blood barrier permeability [7, 8]. Dexasone potentiates the action of other antiemetics through the stabilization of receptors on which they act [9]. The recommended dose of 2.5–5 mg is administered at the beginning of the surgery.

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One of the most potent selective 5-HT_3 antagonists is granisetron, which can provide a 24-hour antiemetic effect at the dose of 1 mg after anesthesia induction. The main factor limiting the clinical use of granisetron is its price, rendering the routine prophylaxis with this drug being extremely costly [7, 8].

There are over 60 randomized controlled studies comparing the effects of antiemetics in comparison with monotherapy, and most showed better results when using two or more agents with different location of receptor action, which is also in compliance with the multifactorial origin of PONV [10, 11]. A rational approach when combining antiemetics implies that combined administration of drugs potentiates their positive sides, and reduces adverse effects.

A prospective randomised study by Wallenborn et al. [12] proved dosage dependent antiemetic effect of metoclopramide, as well as the efficiency of combination of metoclopramide and dexasone in the prevention of PONV.

The objective of this study is to compare the efficiency of the combination of metoclopramide and dexasone in comparison with monotherapy with granisetron in the prevention of PONV in gynecological laparoscopic surgeries. In case of proving the non-inferiority of the combination compared to monotherapy, the clinical use of the combination of metoclopramide and dexasone in comparison with monotherapy would be justified for economic reasons.

METHODS

An observational prospective cohort study was conducted on a sample of 64 patients (32 patients per group) treated postoperatively at the Gynecology and Obstetrics Ward of Subotica General Hospital, in the period from January to March 2017.

The conduct of this study was approved by the Ethical Committee of Subotica General Hospital, and the patients were introduced into studies after giving written consent to participation.

The study included patients over 18 years of age, who had undergone laparoscopic gynecological surgery, with ASA classification of physical health condition I – III (the latest approved classification dated October 15, 2014, available at https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system).

The study excluded:

1. Patients with ASA classification > III;
2. Patients with BMI of 35.3;
3. Patients allergic to medication planned for the study;
4. Patients with acute surgical disease and urgent surgery;
5. Patients with conversion during surgery;
6. Patients with liver central nervous system diseases;
7. Pregnant and nursing women;
8. Patients on antiemetic and opioid therapy;
9. Patients with kidney failure, expressed creatinine clearance rate lower than 30 ml/min;
10. Patients suffering from malignant diseases and receiving chemotherapy.

In accordance with the normal procedure, all patients were examined by anesthesiologists in the preoperative outpatient examination units one day prior to the surgery. Special attention was paid to risk factors (kinetosis, anamnesis for prior PONV, migraine, menstrual cycle period and smoker status length). The following data were taken for each patient: body mass (BM), height (H), body mass index (BMI), blood pressure (BP), heart rate (HR).

Apfel's postoperative nausea (PON) prediction model (available at https://www.ncbi.nlm.nih.gov/pubmed/10485781) will be used at the end of the examination (Tables 1 and 2).

Table 1. Simplified Apfel score for postoperative nausea with four predictors

Predictors	Points
Female sex	1
Prior PONV or kinetosis	1
Non-smoker status	1
Postoperative opioid analgesics	1
Score	0, 1, 2, 3, 4

PONV – postoperative nausea and vomiting

Table 2. Approximate probability of occurrence of postoperative nausea according to Apfel

Risk	Number of predictors	Expected incidence (%)
Very low	0	10
Low	1	21
Moderate	2	39
High	3	61
Very high	4	79

Ingestion of solid food is discontinued eight hours prior to the scheduled beginning of surgery, and ingestion of clear liquids is discontinued two hours prior to surgery.

Before entering the operating theatre, the patient is admitted for induction, where the vein route is opened and the patient is rehydrated with 10 ml/kg of Hartmann's solution. The patients receive premedication amp. dormicum 5 mg IM. To prevent stress peptic ulcer, proton pump inhibitors (PPIs) were administered to all the patients. 20 minutes before premedication, the patient is admitted into the operating theatre and preoxygenated with 100% oxygen for three minutes. Monitoring is continued in the meantime (Electrocardiography, non-invasive measurement of blood pressure, hemoglobin saturation, capnography).

At induction to general endotracheal anesthesia, the patients receive IM amp. atropine as needed, amp. midazolam 2 mg IV, amp. propofol 2 mg/kg, amp. succinylcholine 1 mg/kg. Upon orotracheal intubation, the patient receives amp. rocuronium at the dose of 0.15 mg/kg. Volatile anesthetic sevoflurane is used for maintaining anesthesia. The patients are ventilated during anesthesia with a mixture of oxygen and nitrogen oxide 1:1, and analgesia is provided with opioid analgesic fentanyl and alfentanil as needed. During the surgery, the patients are laid in the Trendelenburg position.

The anesthesia chart records the beginning and the end of the surgical intervention, the start and the end of

anesthesia, the duration of pneumoperitoneum, as well as the maximum reached intra-abdominal pressure, blood pressure, pulse, values of exhaled carbon monoxide in the fifth, 30th and 60th minute, and every subsequent hour of anesthesia, 0.5–1 mg atropine and 1.5–2.5 mg Prostigmin are used for reversal of muscular relaxation.

After extubation and oxygenation, the patients are placed in a recovery room or an inpatient room, depending on the type of surgical intervention. Over the first 24 hours after surgery, vital signs are monitored postoperatively: blood pressure, heart rate, respiratory rate. Ketorolac is given every six hours (for pain on the visual analogue scale [VAS] up to 5), tramadol 50–100 mg (for pain VAS over 5), or combination of ketorolac and tramadol is used for postoperative analgesia. The anesthesiologist assessed PONV in the fifth minute, 15th minute, first hour, fourth hour, hour, 12th hour, and 24th hour. To assess nausea, which is a subjective category, VAS was used, on which each postoperative patient assessed individually the intensity of nausea on a scale of 0–100, where 0 stands for total absence of nausea, and 100 the most intensive possible nausea. The seriousness of postoperative vomiting, expressed as the number of emetic episodes was evaluated as follows: 0 – without vomiting; 1 – medium serious (up to four episodes) and 2 serious (more than four episodes).

According to the anesthesiologist's personal decision, for PONV prevention, the combination dexasone and metoclopramide was administered to patients. The patients received dexamethasone intravenously at the dose of 4 mg after induction to general anesthesia, and a 10 mg ampoule of metoclopramide 15 minutes before the end of the surgical intervention, or 1 mg IV granisetron in monotherapy 15 minutes before the end of the surgical intervention.

The sample size was calculated based on data obtained from earlier studies [13]. The study sample was calculated taking alpha as 0.05 and power of the study of 0.8 for Student's t-test (two independent samples), comparing the groups, according to statistical program G*Power 3 (Heinrich Heine University, Düsseldorf, Germany). Based on the assumption requiring the largest sample, that is, the expected least difference in examined parameters between the two groups of patients, the total number of 32 patients per group was determined, or a total of 64 patients. Such a study sample assumes establishing a statistically significant difference (Student's t-test for two independent samples or Mann–Whitney test) between the two groups of patients with power of the study ≥ 80%.

Variables

1. Independent variables: administration of dexamethasone and metoclopramide, or granisetron.
2. Dependent variables: PONV.
3. Confounding variables: the patient's age, ASA score, the patient's nutritive status, simultaneous administration of medications potentiating the effects of antiemetics, smoker status, migraine.

Statistical analysis

Statistical data analysis encompassed methods of descriptive statistics. Absolute and relative numbers (%) were used, as well as central tendency measures (arithmetic mean, median) and dispersion measures (standard deviation, interquartile range). Parametric Student's t-test for two independent samples or its non-parametric alternative – Mann–Whitney test, was used for determining significance of difference in continuous variables, and difference between category features was examined by χ^2 test or Fisher's test of exact probability in situations where the frequency of individual categories is a linear trend. The probability level lower than 0.05 will be used for rejecting the null hypothesis. Commercial program package SPSS version 20 (IBM, Armonk, NY, USA) was used for processing the obtained results.

RESULTS

Three patients were excluded during the study due to conversion. The mean value of patients' age with combined therapy and monotherapy does not show statistically significant difference. All the other patient's demographic characteristics are shown in Table 3. Both groups of patients are homogenous and show statistically significant difference only in the characteristics length of smoker status and maximum intra-abdominal pressure during the surgical intervention.

The total incidence of postoperative nausea in the fifth, 15th, and 60th postoperative minute was 15.6%, 18.7%, and 18.7%, respectively, and in the fourth, eighth, 12th, and 24th postoperative hour it was 12.5%, 7.8%, 10.9%, and 6.2%. Incidence of postoperative nausea across groups is shown in Table 4. The incidence of postoperative vomiting in the fifth, 15th, and 60th postoperative minute was 1.6%, 4.7%, and 4.7% and in the fourth, eighth, 12th, and 24th postoperative hour it was 1.6%, 3.2%, 1.6 and 1.6%. The incidence of postoperative vomiting across groups is shown in Table 5.

We found difference in the occurrence and degree of PON between two groups of patients, but it is not statistically significant (Figure 1). The degree of postoperative nausea has maximum value in the first hour, followed by a decline in the degree of postoperative nausea until the fourth hour, when recurring slight increase is observed (Figure 2). The patients who had had kinetosis in earlier anamnesis show statistical difference in the occurrence of PON in the first eight hours after the surgery (Figure 3).

The degree of postoperative analgesia was monitored by visual analogue scale (VAS). The strongest pain occurred in the 30th minute, and then the VAS value declined as the time passed (Figure 4).

When three groups of patients (non-steroidal anti-inflammatory drugs [NSAID], opioids, and NSAID with opioids) are compared depending on which type of analgesia they received postoperatively, there is a statistically significant difference in PON in the fourth hour after surgery. (Table 6) (Showing the degree of PON assessed

Table 3. Demographic characteristics of patients

Parameters		n [%]	n [%]	p
Number of patients		32 [50]	32 [50]	
Age structure		39.50 ± 12.1	36.38 ± 8.9	0.514
ASA I		15 [46.9]	18 [56.2]	0.617
ASA II		17 [53.19]	14 [43.8]	0.617
BM [kg]		66.78 ± 9.78	63.13 ± 10.51	0.076
BH [cm]		166.96 ± 4.64	166.53 ± 8.00	0.79
BMI [kg/m^2]		23.9 ± 3.24	22.7 ± 3.41	0.131
Kinetosis	Yes	6 [18.8]	7 [21.9]	> 0.05
	No	26 [81.2]	25 [78.1]	
Migraine	Yes	8 [25]	5 [15.6]	> 0.05
	No	24 [75]	27 [84.4]	
Earlier PONV	Yes	4 [12.5]	6 [18.8]	> 0.05
	No	28 [87.5]	26 [81.3]	
Smoker status	Yes	9 [28.1]	18 [56.3]	**0.043**
	No	23 [71.9]	14 [43.8]	
Earlier HT	Yes	5 [15.6]	3 [9.4]	0.708
	No	27 [84.4]	29 [90.6]	
Thyroid gland disease	Yes	4 [12.5]	2 [6.3]	0.668
	No	28 [87.5]	30 [93.8]	
Apfel score		1.97 ± 0.822	2.25 ± 0.88	0.184
The last dose of opioids		26.78 ± 12.8	26.63 ± 13.61	0.908
Total amount of fentanyl [μg]		226 ± 70.6	225 ± 71.1	0.908
Total amount of esmeron		39.5 ± 13.0	39.72 ± 15.76	0.902
Duration of pneumoperitoneum		36.7 ± 24.5	36.9 ± 26.0	0.861
Maximum IAP (mmHG)		13.25 ± 1.6	14.03 ± 1.6	**0.049**
Postoperative analgesia	NSAID	21 [65.6]	23 [71.9]	0.565
	Opioids	1 [3.1]	0 [0]	0.465
	NSAID + opioids	10 [31.3]	9 [28.1]	0.683

n – number of patients; ASA – asa classification for assessment of risk of surgical intervention; BM – body mass; BH – height; BMI – body mass index; PONV – postoperative nausea and vomiting; HT – hypertension; Apfel score – score for preoperative assessment of risk of PON; IAP – intra abdominal pressure; NSAID – non-steroidal anti-inflammatory drugs; OPIOIDS – opioid analgesics

Table 4. Incidence of nausea across groups

Groups	PON 5	PON 15	PON 60	PON 4	PON 8	PON 12	PON 24
Combination	12.5%	15.7%	12.5%	9.4%	6.3%	9.4%	9.4%
Monotherapy	18.75%	18.75%	25%	15.7%	9.4%	12.5%	3.2%

PON – postoperative nausea

Table 5. Incidence of vomiting across groups

Groups	POV 5	POV 15	POV 60	POV 4	POV 8	POV 12	POV 24
Combination	3.2%	6.3%	0%	0%	3.2%	3.2%	3.2%
Combination	0%	3.2%	9.4%	3.2%	3.2%	0%	0%

POV – postoperative vomiting

Table 6. Presentation of the mean value of postoperative nausea in the fourth hour in relation to the administered analgesic postoperative therapy

Mean value of postoperative nausea in the fourth hour	NSAID	Opioids	NSAID and opioids	p
	1.36	40	5.26	0.002

NSAID – non-steroidal anti-inflammatory drugs

by VAS scale 1–100 in patients in terms of analgesia that they received regardless of which group of patients they belonged to).

In our study, there is a statistically significant correlation between the intensity of postoperative pain and degree of postoperative nausea (Table 7).

DISCUSSION

Contemporary literature points to the fact that female sex possesses a strong predictive factor for the occurrence of PONV [14], and a high incidence of PON and POV is expected. In addition to sex, the type of surgical intervention in terms of gynecological laparoscopic surgery also influences the highly expected incidence of PONV, up to 80% [3]. For ethical reasons, this study did not include a control group that would receive a placebo, and the total incidence of PON and POV remains only at prediction level. The total expected incidence of PON calculated by a simplified Apfel score was about 40% [6]. In our study, the total incidence of PON amounts to 12.7%, incidence of PON in the group receiving combined therapy was 10.74%, and in the group receiving monotherapy, it was 14.75%. As in can be concluded, therapy administered to both groups was effective in terms of reduced PON in comparison to the expected levels. Although the incidence was 4% lower in the group of patients receiving combined therapy, there

Table 7. Correlation of PON depending on pain intensity

		VAS 5 minutes	VAS 30 minutes	VAS 60 minutes	VAS 6 hours	VAS 24 hours
PON 5 minutes	Pearson correlation	**0.412****	**0.391****	0.190	0.088	0.053
	Sig. (2-tailed)	**0.001**	**0.001**	0.133	0.490	0.676
	n	**64**	**64**	64	64	64
PON 15 minutes	Pearson correlation	**0.421****	**0.443****	0.085	**0.302***	**0.281***
	Sig. (2-tailed)	**0.001**	**0.000**	0.506	**0.015**	**0.025**
	n	**64**	**64**	64	**64**	**64**
PON 60 minutes	Pearson correlation	-0.045	-0.043	**0.346****	0.223	**0.280***
	Sig. (2-tailed)	0.726	0.739	**0.005**	0.076	**0.025**
	n	64	64	**64**	64	**64**
PON 4 hours	Pearson correlation	0.097	0.207	0.095	-0.015	0.058
	Sig. (2-tailed)	0.444	0.101	0.454	0.908	0.647
	n	64	64	64	64	64
PON 8 hours	Pearson correlation	0.141	0.200	0.125	-0.003	-0.008
	Sig. (2-tailed)	0.265	0.113	0.324	0.980	0.949
	n	64	64	64	64	64
PON 12 hours	Pearson correlation	-0.058	0.067	0.013	0.232	0.226
	Sig. (2-tailed)	0.648	0.601	0.919	0.065	0.072
	n	64	64	64	64	64
PON 24 hours	Pearson correlation	-0.049	0.017	0.063	**0.286***	**0.282***
	Sig. (2-tailed)	0.701	0.891	0.621	**0.022**	**0.024**
	n	64	64	64	**64**	**64**

VAS – visual analogue scale; PON – postoperative nausea;
**correlation is significant at the 0.01 level (2-tailed);
*correlation is significant at the 0.05 level (2-tailed)

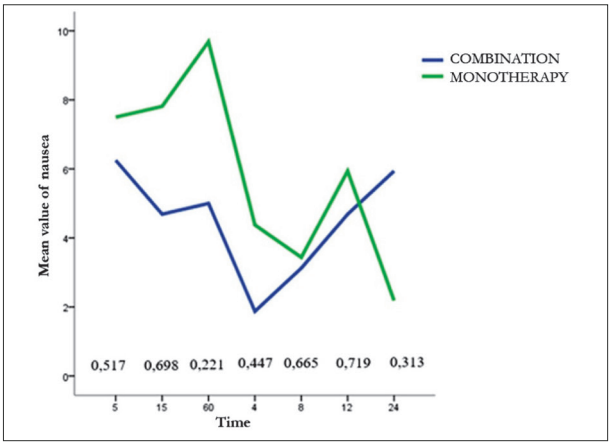

Figure 1. Difference in the degree of postoperative nausea

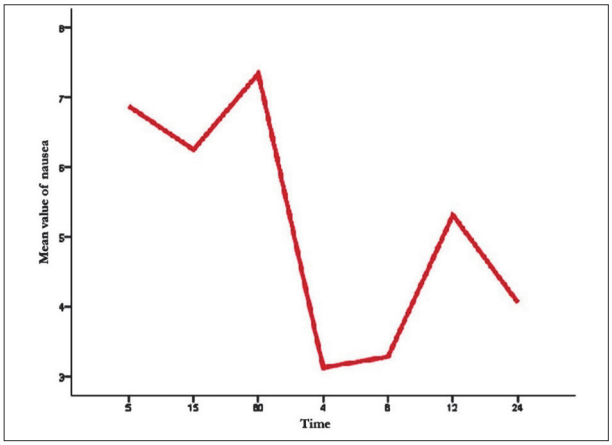

Figure 2. Postoperative nausea as a subjective category was measured by visual analogue scale

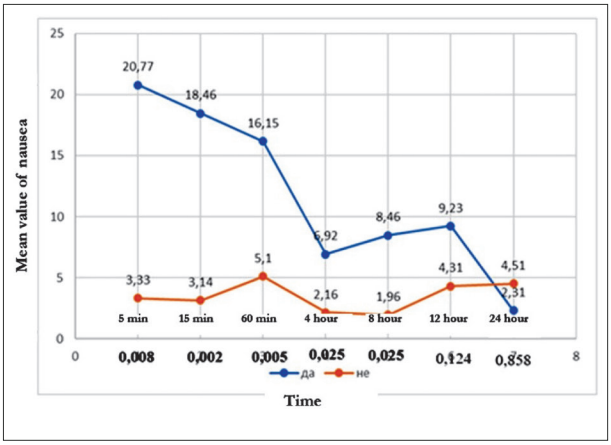

Figure 3. Presentation of the degree of nausea in patients who had had kinetosis

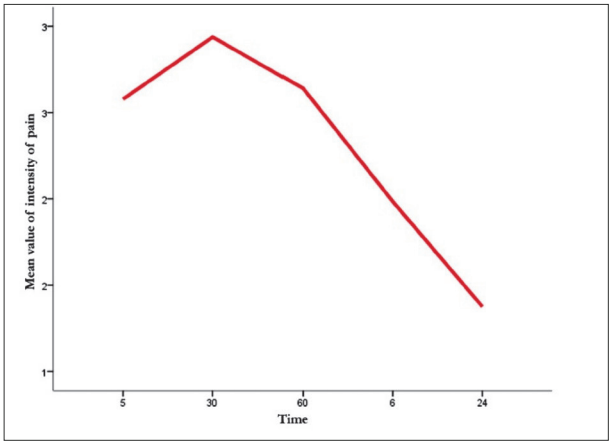

Figure 4. Postoperative pain was measured by visual analogue scale

is no statistical significance either in the incidence or in the level of nausea between patients of the two groups.

In terms of demographic characteristics, preoperative and intraoperative anesthesiological intervention was homogenous without statistically significant difference, except for the smoker status length before surgery and intra-abdominal pressure value during the creation of pneumoperitoneum. This is significant information, because both of these characteristics are listed in literature as predictive factors in the occurrence of PONV. Non-smoker status is known in literature as an independent predictor of occurrence of PONV [6]. Over the past 15 years, research has proven that non-smoker status reduces the likelihood of PONV by 34%. One of the possible explanations for protective action of smoking is the induction of enzyme CyP450, facilitating faster breakdown of medications used in anesthesia [15]. In our study, a statistically significantly higher number of smokers was in the group receiving monotherapy – 56.3%, compared to the group receiving combined therapy – 28.1%, so that non-smoking status did not feature as a predictive factor of PONV. Explanation for this result should perhaps be sought in the fact that, in our study, we regarded former smokers as non-smokers, or in the efficiency of combined therapy that might be even more superior if the groups of patients in this segment had been homogenous.

The intra-abdominal pressure values during laparoscopic surgery were statistically significantly higher in the monotherapy group, which corresponds to the fact that the incidence of vomiting was higher in this group of patients. Cohen et al. [16] proved that, in addition to ophthalmological, gynecological, and laparoscopic interventions, surgical interventions also have a high incidence of PONV. Two observational studies point to the fact that intra-abdominal surgery has a higher incidence of PONV than other surgeries. In their study, identified the pathophysiological and pharmacological role of visceral innervation on the emetic reflex [17, 18].

The positive anamnesis in terms of anamnestic data about prior kinetosis is one of the most commonly listed risk factors for PONV. Kinetosis is a relatively common disorder affecting about 33% of population transported by various means of transport [19].

In our study, the patient who had had the anamnestic data about prior kinetosis had significantly higher values of PONV in the first eight hours after the surgical intervention compared to the patients who had not had anamnestic data about prior kinetosis.

PONV is normally monitored during the first 24 hours; PON and POV in the first four hours are defined as the so-called early PONV, and in the later period of 4–24 hours as late or delayed PONV [21]. In our study, the mean value of PONV during the first four hours after surgery was significantly higher than in the later period. After the 8th hour, up to the 12th hour there was a slight increase in the mean value of PON.

The highest incidence of PON was in the 60th minute in patients treated by monotherapy, as high as 25%, whereas the highest incidence in the group in combined therapy occurs in the 15th postoperative minute, amounting to 15.7%. As regards POV, the highest incidence corresponds to PONV, so that in the group, receiving monotherapy it was in the 60th postoperative minute and amounted to 9.4%, and in the group in combined therapy, the incidence of POV was the highest in the 15th minute and was 6.3%.

Our study clearly showed a correlation between pain and PON, especially in early postoperative period. Data analysis produced results showing a statistically significant difference in the mean value of PON in the fourth hour in patients who received NSAID and opioids, as well as combination of these ($p = 0.002$) , for postoperative analgesia (Table 6). Earlier studies had proved that the administration of opioids in postoperative analgesia, regardless of administration route, in the first 24 hours have nausea and vomiting as adverse effects [22]. Only descriptive statistical analysis was used in the study.

CONCLUSION

As a common complication in patients undergoing gynecological laparoscopic surgical interventions, PONV requires administration of antiemetics for prevention of complications that can be associated with the occurrence of PONV in postoperative period. Our study has proved that the effect of combination of dexasone and metoclopramide is not inferior compared to the effect of monotherapy with granisetron. From the clinical aspect, this information is significant because the cost of combined therapy is significantly lower than the cost of monotherapy.

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Conflict of interest: None declared.

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Поређење ефикасности комбинације дексазона и метоклопрамида са монотерапијом гранисетроном у превенцији постоперативне мучнине и повраћања

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САЖЕТАК

Увод/Циљ Постоперативна мучнина и повраћање (ПОМП) једна је од најчешћих постоперативних компликација. Инциденција ПОМП код одрасле популације је 20–30%, а може да буде и до 80% у популацији са повишеним ризиком, као што су гинеколошке и лапароскопске операције.
Циљ ове студије је поређење ефикасности комбиноване у односу на монотерапију у превенцији ПОМП код гинеколошких и лапароскопских операција.

Методе Спроведена је опсервациона проспективна кохортна студија на узорку од 64 болеснице (32 болеснице по групи) оперативно лечене у Служби за гинекологију и акушерство Опште болнице у Суботици, у периоду јануар–март 2017. Надлежни анестезиолог је за превенцију ПОМП у складу са протоколом давао болесницама комбинацију дексазона и метоклопрамида или гранисетрон у монотерапији. За статистичку обраду добијених резултата коришћен је комерцијални програмски пакет *SPSS*, верзија 20.

Резултати Демографске карактеристике болесница су хомогене и статистички значајну разлику показују само у карактеристикама дужина пушачког статуса и максималном интраабдоминалном притиску током оперативног захвата. Укупна инциденција постоперативне мучнине у петом, 15. и 60. минуту после операције била је 15,6%, 17,2% и 18,7%, а у четвртом, осмом, 12. и 24. сату после операције била је 12,5%, 7,8%, 10,9% и 6,2%. Инциденција постоперативног повраћања у петом, 15. и 60. минуту после операције била је 1,6%, 4,7% и 4,7%, а у четвртом, осмом, 12. и 24. сату после операције била је 1,6%, 3,2%, 1,6% и 1,6%.

Закључак У истраживању смо доказали да ефекат комбинације дексазона и метоклопрамида није слабији у односу на ефекат монотерапије гранисетроном.

Кључне речи: постоперативна; мучнина; повраћање

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Determination of follicular direction and preparation of micrograft holes for hair transplantation

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SUMMARY

Introduction/Objective Hair transplantation is one of the fastest evolving procedures in aesthetic surgery and is accompanied by continuous improvement of new techniques. Hairline planning is one of the most important steps in hair transplantation. The shape of the hair also varies depending on the variation of facial shape so it is very important when determining hair direction and making holes for future grafts.

Methods We used ordinary 18 gauge injection needles whose number was the same as the number of micrographs we planned for transplantation.

Needles are administered in pile growth direction and angle, starting from the first row, and then proceeding to the second one and so on, until we insert all prepared needles. We insert them one in front of the other with a precision ease for future follicles.

Results In all 56 patients, we obtained natural hair growth. Inserting the needles reduced bleeding and the average time of the operation was three hours. The success of grafting was 95%. We only had one infection in one patient. Hair growth corresponded to the needle insertion. After a year of transplantation at the last control, the patient's satisfaction was 100%.

Conclusion By using the same number of needles as the number of grafts we reduced operating time, we had a better determination of the direction of hair growth, we can prevent follicular extraction that can be caused by new needle insertion, and this technique achieved a good aesthetic result.

Keywords: hair transplantation; follicular unit extraction; follicular unit transplantation

INTRODUCTION

Hair transplantation has been one of the fastest evolving procedures in aesthetic surgery in the last 20 years, and has been accompanied by continuous improvement of new techniques. Recent advances in technology and the concept of the use of follicles of individual grafts have made this procedure reach a new height [1, 2]. Not surprisingly, the ability to get very natural results by these techniques has encouraged a large number of bald men and sometimes women to opt for this surgical solution [3, 4].

Hair loss is usually accompanied by various psychological problems, such as lack of confidence, depression etc. Hair loss and baldness in men usually begins between the age of 20 and 40. Genetics is the most important factor causing baldness. It is the most common cause of hair loss and it is autosomal dominant inheritance. Like most tissues, hair is subject to constant renewal through life. Follicles are periodically replaced by new ones.

The total number of scalp hair in human beings is usually 100,000. Approximately 40–100 hairs per day drop; this rate increases at the end of summer and in early autumn, and is reduced at the end of winter and in early spring, due to the effects of temperature change. We used the seven phases of Norwood baldness classification [5, 6, 7]. Hair transplantation depends on the hair density and the dominance of the hair follicles of the donor region in androgenic alopecia.

Individual hair grafts are used to create natural hair. Two techniques are most commonly used today: follicular unit extraction (FUE) is a hair transplantation technique that uses small pinches (0.8–1 mm in diameter) to extract the follicular units and follicular unit transplantation (FUT) is a technique based on harvesting the follicular unit from a strip of tissue [2, 8–13].

During the last ten years, many authors have dealt with these two techniques and the way of harvesting follicular units from the donor region. However, a small number of authors have dealt with the method of making holes in the recipient region and determining the direction of future hair [2, 4, 14–17].

Hairline planning is one of the most important steps in hair transplantation [7, 8, 18]. The shape of hair also varies depending on the variation of facial shape so that determining hair direction and making holes for future grafts is very important [19, 20].

Hair transplantation can be accomplished by making holes for micrografts in the recipient region with incisional devices: punch graft instrument, 64 blade on a round beaver handle, 15 blade on a conventional scalpel han-

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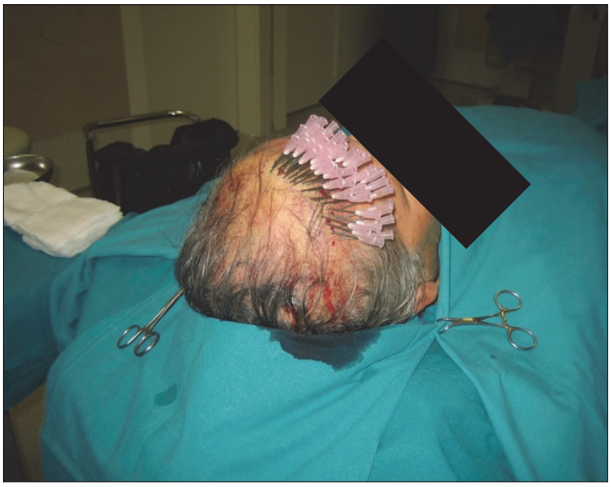

Figure 1. Needles are inserted in the direction of hair growth.

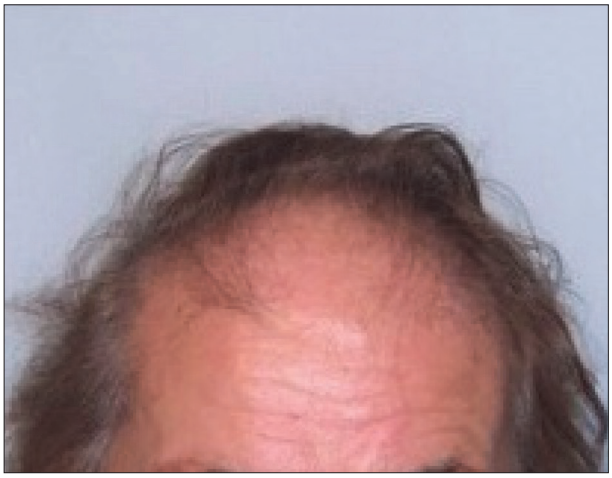

Figure 2. Patient before surgery with scaly hair in the frontal region

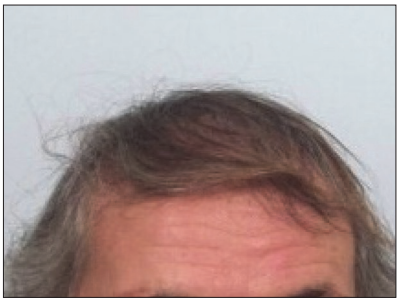

Figure 3. The same patient 10 months after transplantation

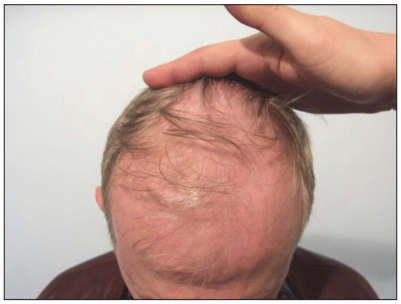

Figure 4. Patient before surgery

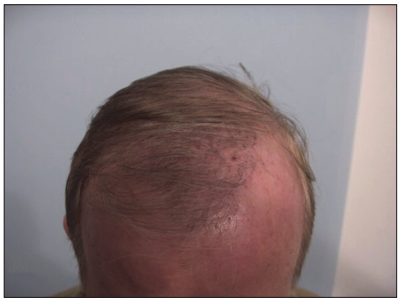

Figure 5. The same patient seven months after surgery

dle, laser or Chois single-hair implantation [7, 21, 22, 23] needle and so on. There are two problems associated with these methods: one is bleeding, and the other is wrong determination of the direction of future hair growth.

We have solved this problem by using ordinary 18 gauge injection needles whose number was the same as the number of hair micrographs we planned for transplantation.

METHODS

The transplantation was performed in 56 patients (of which 49 male and seven female). The patient was asked to shampoo his head with Betadine the day before and the morning before surgery. After removing donor strip with number 10 blade from occipital donor area, we prepared mini and micrografts. It is very important that during the excision of the donor skin area that the scalpel blades stay parallel with the hair direction so that the hair of the root is not damaged [12, 13, 22].

The recipient area was injected with prepared solution (160 ml Ringer lactate, 1 ml epinephrine, and 40 ml 2% xylocaine). Fifteen minutes after injecting the solution and making a plan for the distribution of grafts, we inserted needles (18 gauge), the number of which is the same as the planned number of hair micrografts, covering the whole recipient region (Figure 1).

Needles are administered in pile's growth direction and angle, starting from the first row, and then proceeding to the second one and so on, until we inserted all prepared needles. We inserted them one in front of the other with a precision ease for future follicles.

When all the needles are inserted, we started with transplantation working backwards, removing needles and placing mini and micrografts into every slit.

This study was done in accord with standards of the institutional Committee on Ethics.

RESULTS

In all 56 patients, we obtained natural hair growth (Figure 2 and Figure 3). Inserting the needles reduced bleeding and the average operation time took three hours. The success of grafting was 95%. We only had one case of infection in one patient. Hair growth corresponded to the direction of needle insertion (Figure 4 and Figure 5). A year after transplantation at the follow-up, the patient's satisfaction was 100%.

DISCUSSION

By injecting donor and recipient areas with prepared solution, we prevented bleeding. If it does happen in some slits, it can be stopped with a simple finger pressure for 1–2 minutes.

By using the same number of needles as the number of grafts, we can easily determine and control the direction of hair growth. With this method, there is no dropping of hair grafts caused by hematoma and pressure caused by needle insertion [24, 25, 26].

We think that this method is better than the use of lasers for making holes because CO_2 laser causes micro necrosis. In other methods, punch methods for example, it is more difficult to control the bleeding [12, 13, 16].

CONCLUSION

By using the same number of needles as the number of grafts, we reduce operating time, we have a better determination of the direction of hair growth, we can prevent follicular extraction that can be caused by new needle insertion, and this technique achieves a good aesthetic result.

Conflict of interest: None declared.

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Одређивање правца фоликула и припремање рупа за микрографтовање код трансплантације косе

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САЖЕТАК

Увод/Циљ Трансплантација косе је једна од најбрже еволуирајућих процедура у естетској хирургији и праћена је сталним побољшањем нових техника. Планирање линије косе је један од најважнијих корака у трансплантацији косе. Облик косе такође варира у зависности од варијације облика лица, тако да је одређивање правца косе и прављење рупа за будуће графтове врло важно.

Методе Користили смо обичне инјекционе игле промила 18 *gauge*, чији је број био исти са бројем микрографтова косе који смо планирали за трансплантацију. Игле смо убадали тако да прате правац и угао раста длаке у датој реципијентној регији, полазећи од првог реда, ка другом, трећем и тако даље, док нисмо пласирали све припремљене игле. Пласирали смо их једну испред друге са прецизном лакћом за будуће фоликуле.

Резултати Код свих 56 пацијената смо добили природан раст косе. Убадањем игала смањили смо крварење и просечно време саме операције за три сата. Успешност примања графтова је био 95%. Инфекцију смо имали само код једног пацијента. Раст косе одговарао је правцу убадања игала. На последњој контроли, после годину дана од трансплантације, задовољство пацијената је било 100%.

Закључак Коришћењем истог броја игала са бројем графтова косе смањујемо операционо време, боље одређујемо правац раста косе, можемо спречити фоликуларну екстракцију која може бити изазвана неким новим убодом игле и овом техником постижемо добар естетски резултат и смањујемо операционо време.

Кључне речи: трансплантација косе; екстракција фоликуларне јединице; трансплантација фоликуларне јединице

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Evaluation of the diagnostic utility of the new clinical case definition of pertussis – experience from sentinel and hospital-based pertussis surveillance

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SUMMARY

Introduction/Objective Global surveillance systems use different clinical case definitions of pertussis. The aim of this study was to identify sign and symptom combinations with best relation with laboratory-confirmed pertussis.

Methods A one-year prospective observational study, proposed by the Global Pertussis Initiative (GPI) for three age groups (0–3 months, four months to nine years, and ≥ 10 years) was performed in Novi Sad to evaluate the performance of the clinical case definition of pertussis. Laboratory confirmation of *B. pertussis* infection was obtained using the DNA polymerase chain reaction (PCR) or ELISA serology tests.

Results From October 1, 2013 to September 30, 2014, 103 (32.3%) out of 319 participants with suspected pertussis had laboratory-confirmed pertussis. Combined whooping, post-tussive emesis, and worsening of symptoms at night was the best predictor of pertussis in outpatients aged four months to nine years (positive likelihood ratio (LR+) 11.6), while among inpatients of the same age group it was apnoea (LR+ 13.5). The LR+ in outpatients aged ≥10 years for combinations of apnoea and post-tussive emesis, or a combination of whooping and sweating episodes between paroxysms and post-tussive emesis was 16.8, while among in-patients LR+ was < 2.3 for all combinations in the same age group.

Conclusions The GPI case definitions for pertussis are good predictors for laboratory-confirmed pertussis and are useful for the purpose of pertussis surveillance.

Keywords: pertussis (whooping cough); Global Pertussis Initiative; case definition; surveillance

INTRODUCTION

Pertussis remains an important cause of morbidity and mortality among infants and children, even in countries with high vaccination coverage rates. The World Health Organization (WHO) estimates that 50 million cases and 300,000 deaths occur every year because of pertussis, and case-fatality rates of pertussis in developing countries are estimated to be as high as 4% in infants [1]. Consequently, establishing a reliable diagnosis of pertussis has become increasingly important [2, 3].

Because of the heterogeneity in clinical manifestations of pertussis, lack of general availability of laboratory confirmation of the disease, mixed infections, and a low index of suspicion among many physicians, pertussis is under-recognized worldwide. In addition, the absence of a sensitive clinical case definition of pertussis has contributed to missed or misdiagnosed pertussis cases [4, 5, 6].

Existing clinical case definitions of pertussis are based on clinical presentation in infants and children, but they are also used for adolescents and adults who may manifest distinct signs and symptoms. Therefore, in an effort to improve the diagnosis of pertussis, the Global Pertussis Initiative (GPI) proposed an algorithm based on the most common signs and symptoms of pertussis for three age groups, i.e. 0–3 months, four months to nine years, and ≥ 10 years old [7].

Until 2012, the epidemiology of pertussis in Novi Sad has not been described well, when an improved surveillance method for pertussis was introduced following the GPI recommendations [7]. We then determined that pertussis was widespread in our population, affecting patients of any age [8, 9].

The aim of this study was to determine the most predictive signs and symptoms of pertussis, and to evaluate the diagnostic performance of certain combinations of signs and symptoms based on the case definitions of pertussis proposed by the GPI.

METHODS

Study design, specimen collection, and laboratory testing

The recruitment period was from October 1, 2013 to September 30, 2014 (52 weeks). According to the GPI, methods have previously been described in detail [7, 9]. Briefly, we

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simultaneously conducted prospective surveillance at both primary (outpatients) and tertiary (inpatients) health care levels in the city of Novi Sad. Participants were identified and sampled by the physicians in the two health care levels as a part of their daily routine. Hospital surveillance for the entire Novi Sad area (341,624 inhabitants) was conducted in two inpatient facilities: pulmonology clinic of the Institute of Child and Youth Health Care of Vojvodina (pediatric inpatient facility) and the Institute of Pulmonary Diseases of Vojvodina (adult inpatient facility). We only included patients who fulfilled one or more criteria of clinical case definitions for three age groups (0–3 months, four months to nine years, and ≥ 10 years old) [7].

Patient data collection, sampling, and transport of patient material, as well as the laboratory testing of samples and interpretation of results was performed according to the previously used methodology [7, 9].

We classified participants as "fully vaccinated" according to their age, "partly vaccinated" (cases who had received ≥ 1 but not all the vaccinations required for their age), and "unvaccinated." Due to waning immunity after vaccination against pertussis, only vaccination status for participants < 18 years was recorded. All participants aged ≥ 18 years were considered as participants with an unknown vaccination status.

Verbal informed consent was obtained from patients before swab taking in accordance with national regulations and written consent from parents or guardians was obtained.

Statistical analysis

Because we registered only five laboratory-confirmed pertussis cases in infants aged 0–3 months, we did not perform a validation of certain sings and symptoms in this age group. A two-tailed P value $p < 0.05$ was considered to indicate statistical significance for all statistical tests. Data analysis was performed using the SPSS for Windows, version 22.0 software (IBM Corp. NY, USA) and MedCalc for Windows, version 12.3.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

During the study period, 319 participants with suspected pertussis were enrolled, and 103 (32.3%) had laboratory-confirmed pertussis by PCR or serology. Among the laboratory-confirmed cases, 29, 71, and three patients were positive by PCR and the enzyme-linked immunosorbent assay (ELISA) respectively. *B. parapertussis* or *B. bronchiseptica* infections were not detected. No participant with suspected pertussis had been vaccinated against pertussis during the 12 months before inclusion into the study, and there were no deaths. Patients with laboratory-confirmed pertussis were younger than those without laboratory confirmation ($p = 0.030$), and the proportion of pertussis was higher among hospitalized patients compared to outpatients ($p < 0.001$), and higher among "unvaccinated" and "partly vaccinated" children compared to those where "fully vaccinated," although the difference was not significant (OR 1.87, 95% CI 0.97–3.60, $p = 0.062$) (data not shown).

Pertussis was confirmed in 31.3% (5/16), 27.4% (34/124) and 35.8% (64/179) in individuals 0–3 months, four months to nine years, and ≥ 10 years old, respectively.

In infants 0–3 months of age, the mandatory signs and symptoms (MSS) in combination with pneumonia (OR 6.75, 95% CI 0.64–71.18) and close exposure to a person with a prolonged afebrile cough illness (contact) (OR 2.50, CI 0.12–50.45) had a strong association with pertussis, but due to a limited number of participants, differences between positive and negative cases were not statistically significant ($p > 0.05$).

In the four months to nine years and ≥ 10 years age groups, the MSS accompanied by whoop or apnoea or post-tussive emesis or worsening of the symptoms at night were significantly associated with having a laboratory-confirmed pertussis ($p < 0.05$). Among the participants aged four months – nine years, only combination of MSS and pneumonia was not associated with pertussis, and in the ≥ 10 years age group, only MSS accompanied by sweating episodes between paroxysms was not a predictor of laboratory-confirmed pertussis ($p > 0.05$) (Table 1).

The diagnostic performance of the selected sign and symptom combinations for pertussis in the participants aged four months to nine years is shown in Table 2 and for those ≥ 10 years in Table 3.

Among the outpatients, the MSS of pertussis in the age group from four months–nine years accompanied by whoop, post-tussive emesis and worsening symptoms at night had the highest diagnostic value of laboratory-confirmed pertussis (LR+ 11.6, 95% CI 2.6–51.8). A combination of the MSS and apnoea was the strongest predictor of pertussis among inpatients (LR+ 13.5, 95% CI 1.8–99.6). When stratified by the surveillance sites, the MSS along with apnoea was significantly more sensitive in the hospital than in the sentinel sites (42.1% *vs.* 6.7%, $p = 0.022$). The MSS in combination with post-tussive emesis or accompanied by post-tussive emesis and contact were significantly more specific among the outpatients than in the inpatients (77.6% *vs.* 43.8%, $p = 0.001$ and 100% *vs.* 90.6%, $p = 0.018$, respectively).

According to the values of LR+ for participants aged ≥ 10 years, among the inpatients there was no combination with LR+ greater than 2.3. In the outpatients, including the MSS in combination with one or more signs and symptoms through sentinel surveillance, we have determined that five different combinations from the proposed case definition were the strongest predictors of pertussis in the ≥ 10 years age group (LR+ above 10).

Compared to the values of sensitivities and specificities among the participants aged ≥ 10 years in the two surveillance systems, including the MSS of pertussis, post-tussive emesis was significantly more sensitive among the out-patients than in the in-patients (61.3% *vs.* 27.3%, $p = 0.007$, respectively). The combination of MSS along with worsening of symptoms at night was significantly more sensitive (84.9% *vs.* 61.3%, $p = 0.034$, respectively), and the combination of MSS accompanied by whoop and post-tussive emesis was

Table 1. Signs and symptoms associated with laboratory confirmed pertussis infections in the sentinel and hospital surveillance of pertussis by age group

Age group with mandatory and other signs and symptoms of pertussis	Total (n = 319)	Positive (n = 103)	Negative (n = 216)	crude OR (95% CI)	p	adjusted OR[a, b] (95% CI)	p
1) 0–3 months Cough and coryza with no or minimal fever plus:	(n = 16) n (%)	(n = 5) n (%)	(n = 11) n (%)	Ref.			
Whoop	7 (43.8)	2 (40)	5 (45.5)	0.80 (0.09–6.85)	0.839	-	-
Apnoea	3 (18.8)	3 (60)	0 (-)	NA	ND	-	-
Post-tussive emesis	7 (43.8)	1 (20)	6 (54.5)	0.21 (0.02–2.52)	0.217	-	-
Cyanosis	5 (31.3)	1 (20)	4 (36.4)	0.44 (0.04–5.40)	0.519	-	-
Seizure	1 (6.3)	1 (20)	0 (-)	NA	ND	-	-
Pneumonia	5 (31.3)	3 (60)	2 (18.2)	6.75 (0.64–71.18)	0.112	-	-
Contact[c]	2 (12.5)	1 (20)	1 (9.1)	2.50 (0.12–50.45)	0.550	-	-
2) four months to nine years Paroxysmal cough with no or minimal fever plus:	(n = 124) n (%)	(n = 34) n (%)	(n = 90) n (%)	Ref.			
Whoop	55 (44.4)	23 (67.6)	32 (35.6)	3.79 (1.64–8.76)	**0.002**	3.63 (1.48–8.90)	**0.005**
Apnoea	13 (10.5)	9 (26.5)	4 (4.4)	7.74 (2.20–27.26)	**0.001**	10.11 (2.40–42.63)	**0.002**
Post-tussive emesis	52 (41.9)	21 (61.8)	31 (34.4)	3.07 (1.36–6.96)	**0.007**	3.51 (1.44–8.57)	**0.006**
Worsening of symptoms at night	58 (46.8)	21 (61.8)	37 (41.1)	2.31 (1.03–5.20)	**0.042**	3.29 (1.31–8.25)	**0.011**
Pneumonia	8 (6.5)	1 (2.9)	7 (7.8)	0.36 (0.04–3.04)	0.347	-	-
Seizure	0 (-)	0 (-)	0 (-)	NA	ND	NA	ND
Contact[c]	20 (16.1)	10 (29.4)	10 (11.1)	3.33 (1.24–8.95)	**0.017**	5.68 (1.76–18.35)	**0.004**
3) ≥ 10 years Non-productive, paroxysmal cough of ≥ 2 weeks duration without fever plus:	(n = 179) n (%)	(n = 64) n (%)	(n = 115) n (%)	Ref.			
Whoop	76 (42.5)	44 (68.8)	32 (27.8)	5.71 (2.93–11.12)	**< 0.001**	4.64 (2.29–9.41)	**< 0.001**
Apnoea	17 (9.5)	14 (21.9)	3 (2.6)	10.45 (2.88–38)	**< 0.001**	10.68 (2.74–41.54)	**0.001**
Sweating episodes between paroxysms	79 (44.1)	24 (37.5)	55 (47.8)	0.65 (0.35–1.22)	0.184	-	-
Post-tussive emesis	51 (28.5)	28 (43.8)	23 (20)	3.11 (1.59–6.10)	**0.001**	2.73 (1.32–5.67)	**0.007**
Worsening of symptoms at night	105 (58.7)	47 (73.4)	58 (50.4)	2.72 (1.40–5.28)	**0.003**	3.66 (1.74–7.69)	**0.001**

Values that differ significantly between positive and negative pertussis cases are marked in bold;
NA – not applicable; ND – not determined;

[a]adjusted for the following variables: age, gender, duration of cough and vaccination status (fully vaccinated persons compared with unvaccinated, partly vaccinated, and persons with unknown vaccination status together) for characteristics with significance difference according to univariate analysis;
[b]not calculable and omitted in logistic regression analyses in the 0–3 months age group;
[c]close exposure to an adolescent or adult (usually a family member) with a prolonged afebrile cough illness

significantly less specific (81.8% *vs.* 97.1%, p = 0.019, respectively) in hospitalized than in outpatient cases.

DISCUSSION

The main aim of the study was to validate the pertussis case definitions of the GPI. A very important aspect of our study was the estimation of the sensitivity and specificity of various combinations of signs and symptoms of the clinical case definitions proposed by the GPI.

One of the first published studies, in which certain signs and symptoms of pertussis case definition were evaluated, was conducted during two community outbreak years in Wisconsin and Delaware (in 1985 and 1986) [10]. In this study, participants were enrolled in the outbreak settings with wide inclusion criteria (one or more symptoms of acute respiratory illness, regardless of the age of participants), and a total of 50% of patients had laboratory evidence of pertussis, while the prevalence of laboratory-confirmed pertussis in our study was 32.3%. Except for the pertussis outbreak in the families, there were no registered

Table 2. Diagnostic accuracy of signs and symptoms and their combinations of proposed case definitions of patients aged four months to nine years with suspected pertussis infection

Surveillance system	Mandatory signs and symptoms plus:	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR- (95% CI)
Sentinel surveillance (outpatients)	Whoop	73.3 (44.9–92.1)	63.8 (50.1–76)	34.4 (18.6–53.2)	90.2 (76.9–97.2)	2 (1.3–3.2)	0.4 (0.2–0.9)
	Apnoea	6.7 (1.1–32)[a]	94.8 (85.6–98.9)	25 (4.1–79.7)	79.7 (68.3–88.4)	1.3 (0.1–11.5)	1 (0.9–1.1)
	Post-tussive emesis	60 (32.3–83.6)	77.6 (64.7–87.5)[b]	40.9 (20.8–63.6)	88.2 (76.1–95.5)	2.7 (1.4–5)	0.5 (0.3–0.9)
	Worsening of symptoms at night	66.7 (38.4–88.1)	55.2 (41.5–68.3)	27.8 (14.2–45.2)	86.5 (71.2–95.4)	1.5 (0.9–2.4)	0.6 (0.3–1.3)
	Pneumonia	0 (-)	91.4 (81–97.1)	NA	77.9 (66.2–87.1)	NA	1.1 (1–1.2)
	Contact[c]	40 (16.4–67.7)	89.7 (78.8–96.1)	50 (21.2–78.8)	85.3 (73.8–93)	3.9 (1.5–10.3)	0.7 (0.4–1)
	Whoop + apnoea	6.7 (1.1–32)	94.8 (85.6–98.9)	25 (4.1–79.7)	79.7 (68.3–88.4)	1.3 (0.1–11.5)	1 (0.9–1.1)
	Whoop + post-tussive emesis	46.7 (21.3–73.4)	93.1 (83.3–98.1)	63.6 (30.9–88.9)	87.1 (76.1–94.2)	6.8 (2.3–20.1)	0.6 (0.4–0.9)
	Whoop + worsening of symptoms at night	40 (16.4–67.7)	82.8 (70.6–91.4)	37.5 (15.3–64.5)	84.2 (72.1–92.5)	2.3 (1–5.4)	0.7 (0.5–1.1)
	Whoop + contact[c]	33.3 (12–61.6)	96.6 (88.1–99.5)	71.4 (29.3–95.5)	84.9 (73.9–92.5)	9.7 (2.1–45)	0.7 (0.5–1)
	Post-tussive emesis + worsening of symptoms at night	53.3 (26.7–78.7)	89.7 (78.8–96.1)	57.1 (28.9–82.2)	88.1 (77.1–95.1)	5.2 (2.1–12.6)	0.5 (0.3–0.9)
	Post-tussive emesis + contact[c]	20 (4.6–48.1)	100 (-)[b]	100 (-)	82.9 (72–90.8)	NA	0.8 (0.6–1)
	Worsening of symptoms at night + contact	20 (4.6–48.1)	96.6 (88.1–99.5)	60 (15.4–93.5)	82.4 (71.2–90.5)	5.8 (1.1–31.7)	0.8 (0.6–1.1)
	Whoop + post-tussive emesis + worsening of symptoms at night	40 (16.4–67.7)	96.6 (88.1–99.5)	75 (35.1–96.1)	86.2 (75.3–93.5)	11.6 (2.6–51.8)	0.6 (0.4–0.9)
	Whoop + post-tussive emesis + worsening of symptoms at night + contact[c]	13.3 (2.1–40.5)	98.3 (90.7–99.7)	66.7 (11.6–94.5)	81.4 (70.3–89.7)	7.7 (0.6–79.7)	0.9 (0.7–1.1)
Hospital surveillance (inpatients)	Whoop	63.2 (38.4–83.7)	65.6 (46.8–81.4)	52.2 (30.6–73.2)	75 (55.1–89.3)	1.8 (1–3.3)	0.6 (0.3–1.1)
	Apnoea	42.1 (20.3–66.5)[a]	96.9 (83.7–99.5)	88.9 (51.7–98.2)	73.8 (57.9–86.1)	13.5 (1.8–99.6)	0.6 (0.4–0.9)
	Post-tussive emesis	63.2 (38.4–83.7)	43.8 (26.4–62.3)[b]	40 (22.7–59.4)	66.7 (43–85.4)	1.1 (0.7–1.8)	0.8 (0.4–1.7)
	Worsening of symptoms at night	57.9 (33.5–79.7)	65.6 (46.8–81.4)	50 (28.3–71.8)	72.4 (52.8–87.2)	1.7 (0.9–3.1)	0.6 (0.4–1.2)
	Pneumonia	5.3 (0.9–26.1)	93.8 (79.2–99.1)	33.3 (5.5–88.5)	62.5 (47.4–76)	0.8 (0–8.7)	1 (0.9–1.2)
	Contact[c]	21.1 (6.2–45.6)	87.5 (70.9–96.4)	50 (16–83.9)	65.1 (49.1–78.9)	1.7 (0.5–5.9)	0.9 (0.7–1.2)
	Whoop + apnoea	31.6 (12.7–56.5)	96.9 (83.7–99.5)	85.7 (42.2–97.6)	70.5 (54.8–83.2)	10.1 (1.3–77.7)	0.7 (0.5–1)
	Whoop + post-tussive emesis	36.8 (16.4–61.6)	81.3 (63.6–92.8)	53.9 (25.2–80.7)	68.4 (51.4–82.5)	2 (0.8–5)	0.8 (0.5–1.1)
	Whoop + worsening of symptoms at night	31.6 (12.7–56.5)	84.4 (67.2–94.7)	54.6 (23.5–83.1)	67.5 (50.9–81.4)	2 (0.7–5.7)	0.8 (0.6–1.1)
	Whoop + contact[c]	10.5 (1.6–33.2)	93.8 (79.2–99.1)	50 (8.3–91.7)	63.8 (48.5–77.3)	1.7 (0.3–11)	1 (0.8–1.1)
	Post-tussive emesis + worsening of symptoms at night	36.8 (16.4–61.6)	78.1 (60–90.7)	50 (23.1–76.9)	67.6 (50.2–82)	1.7 (0.7–4.1)	0.8 (0.6–1.2)
	Post-tussive emesis + contact[c]	21.1 (6.2–45.6)	90.6 (75–97.9)[b]	57.1 (18.8–89.6)	65.9 (50.1–79.5)	2.3 (0.6–9)	0.9 (0.7–1.1)
	Worsening of symptoms at night + contact[c]	15.8 (3.6–39.6)	96.9 (83.7–99.5)	75 (20.3–95.9)	66 (50.7–79.1)	5.1 (0.6–45.2)	0.9 (0.7–1)
	Whoop + post-tussive emesis + worsening of symptoms at night	21.1 (6.2–45.6)	87.5 (71–96.4)	50 (16–84)	65.1 (49.1–79)	1.7 (0.5–6.)	0.9 (0.7–1.2)
	Whoop + post-tussive emesis + worsening of symptoms at night + contact[c]	10.5 (1.6–33.2)	100 (-)	100 (-)	65.3 (50.4–78.3)	NA	0.9 (0.8–1)

NA – not applicable; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio;
[a]sensitivity significantly different between the two surveillance systems;
[b]specificity significantly different between the two surveillance systems;
[c]close exposure to an adolescent or adult (usually a family member) with a prolonged afebrile cough illness

Table 3. Diagnostic accuracy of signs and symptoms and their combinations of proposed case definitions of patients aged ≥ 10 years with suspected pertussis infection

Surveillance system	Mandatory signs and symptoms plus:	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR- (95% CI)
Sentinel surveillance (out-patients)	Whoop	71 (52–85.8)	74 (64.5–82.1)	44.9 (30.7–59.8)	89.5 (81.1–95.1)	2.7 (1.8–4.1)	0.4 (0.2–0.7)
	Apnoea	16.1 (5.5–33.7)	97.1 (91.8–99.4)	62.5 (24.7–91)	79.5 (71.5–86.2)	5.6 (1.4–22.1)	0.9 (0.7–1)
	Sweating episodes between paroxysms	35.5 (19.3–54.6)	51.9 (41.9- 61.8)	18 (9.4–30)	73 (61.4–82.6)	0.7 (0.4–1.2)	1.2 (0.9–1.7)
	Post-tussive emesis	61.3 (42.2–78.1)[a]	81.7 (73–88.6)	50 (33.4–66.6)	87.6 (79.4–93.4)	3.4 (2.1–5.5)	0.5 (0.3–0.7)
	Worsening of symptoms at night	61.3 (42.2–78.1)[a]	51 (41–60.9)	27.1 (17.2–39.1)	81.5 (70–90.1)	1.3 (0.9–1.8)	0.8 (0.5–1.2)
	Whoop + apnoea	12.9 (3.7–29.9)	99 (94.7–99.8)	80 (28.8–96.7)	79.2 (71.2–85.8)	13.4 (1.6–115.7)	0.9 (0.8–1)
	Whoop + post-tussive emesis	38.7 (22–57.8)	97.1 (91.8–99.4)[b]	80 (51.9–95.4)	84.2 (76.4–90.2)	13.4 (4–44.6)	0.6 (0.5–0.8)
	Post-tussive emesis + worsening of symptoms at night	32.3 (16.7–51.4)	90.4 (83–95.3)	50 (27.2–72.8)	81.7 (73.5–88.3)	3.4 (1.5–7.3)	0.8 (0.6–1)
	Apnoea + post-tussive emesis	16.1 (5.5–33.7)	99 (94.7–99.8)	83.3 (36.1–97.2)	79.8 (71.9–86.4)	16.8 (2–138.3)	0.9 (0.7–1)
	Whoop + sweating episodes between paroxysms + worsening of symptoms at night	9.7 (2–25.8)	95.2 (89.1–98.4)	37.5 (8.5–75.5)	78 (69.7–84.8)	2 (0.5–8)	1 (0.8–1.1)
	Whoop + sweating episodes between paroxysms + post-tussive emesis	16.1 (5.5–33.7)	99 (94.7–99.8)	83.3 (36.1–97.2)	79.8 (71.9–86.4)	16.8 (2–138.3)	0.9 (0.7–1)
	Whoop + worsening of symptoms at night + post-tussive emesis	19.4 (7.5–37.5)	98.1 (93.2–99.7)	75 (35.1–96.1)	80.3 (72.3–86.8)	10.1 (2.1–47.4)	0.8 (0.7–1)
	Apnoea + sweating episodes between paroxysms + post-tussive emesis	3.2 (0.1–16.7)	99 (94.8–99.9)	50 (1.3–98.7)	77.4 (69.4–84.2)	3.4 (0.2–52.1)	1 (0.9–1)
Hospital surveillance (in-patients)	Whoop	66.7 (48.2–82)	54.6 (23.5–83.1)	81.5 (61.9–93.6)	35.3 (14.3–61.7)	1.5 (0.7–2.9)	0.6 (0.3–1.2.7)
	Apnoea	27.3 (13.3–45.5)	100 (-)	100 (-)	31.4 (16.9–49.3)	NA	0.7 (0.6–0.9)
	Sweating episodes between paroxysms	39.4 (22.9–57.9)	54.6 (23.5–83.1)	72.2 (46.5–90.2)	23.1 (9–43.7)	0.9 (0.4–1.9)	1.1 (0.6–2)
	Post-tussive emesis	27.3 (13.3–45.5)[a]	63.6 (30.9–88.9)	69.2 (38.6–90.7)	22.6 (9.6–41.1)	0.8 (0.3–2)	1.1 (0.7–1.9)
	Worsening of symptoms at night	84.9 (68.1–94.8)[a]	36.4 (11.2–69.1)	80 (63.1–91.5)	44.4 (14–78.6)	1.3 (0.8–2.1)	0.4 (0.1–1.3)
	Whoop + apnoea	21.2 (9–38.9)	100 (-)	100 (-)	29.7 (15.9–47)	NA	0.8 (0.7–0.9)
	Whoop + post-tussive emesis	18.2 (7–35.5)	81.8 (48.2–97.2)[b]	75 (35.1–96.1)	25 (12.2–42.2)	1 (0.2–4.3)	1 (0.7–1.4)
	Post-tussive emesis + worsening of symptoms at night	24.2 (11.1–42.3)	72.7 (39.1–93.7)	72.7 (39.1–93.7)	24.2 (11.1–42.3)	0.9 (0.3–2.8)	1 (0.7–1.6)
	Apnoea + post-tussive emesis	6.1 (0.9–20.3)	100 (-)	100 (-)	26.2 (13.9–42)	NA	0.9 (0.9–1)
	Whoop + sweating episodes between paroxysms + worsening of symptoms at night	21.2 (9–38.9)	90.9 (58.7–99.8)	87.5 (47.4–99.7)	27.8 (14.2–45.2)	2.3 (0.3–16.9)	0.9 (0.7–1.1)
	Whoop + sweating episodes between paroxysms + post-tussive emesis	6.1 (0.9–20.3)	90.9 (58.7–98.5)	66.7 (11.6–94.5)	24.4 (12.4–40.3)	0.7 (0.1–6.7)	1 (0.8–1.3)
	Whoop + worsening of symptoms at night + post-tussive emesis	18.2 (7–35.5)	90.9 (58.7–98.5)	85.7 (42.2–97.6)	27 (13.8–44.1)	2 (0.3–14.8)	0.9 (0.7–1.2)
	Apnoea + sweating episodes between paroxysms + post-tussive emesis	0 (-)	100 (-)	NA	25 (13.2–40.3)	NA	NA

NA – not applicable; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio;
[a]sensitivity significantly different between the two surveillance systems;
[b]specificity significantly different between the two surveillance systems

outbreaks in the population in the city of Novi Sad during our study period [8, 9]. Because participants in our study were enrolled during an epidemic free year and because we included only those who fulfilled the required signs and symptoms for the three age groups, we are convinced that mentioned differences would have contributed to the discrepancy of the results in the cited study [10].

Surveillance of pertussis in many countries across the world is based on the clinical case definitions of pertussis recommended by the WHO, the US Centers for Disease Control Prevention, or the European Centre for Disease Prevention and Control. Unlike these commonly applied case definitions, which include cough duration of two weeks or longer for all age groups, in the clinical case definitions of pertussis proposed by the GPI, cough duration depends on the age of the patients [7]. Thus, we included all patients aged ≥ 10 years, which had a non-productive, paroxysmal cough of that lasted two weeks or longer without fever. Among the participants younger than 10 years, MSS were paroxysmal cough with no or minimal fever (patients aged four months to nine years), and cough and coryza with no or minimal fever (patients 0–3 months of age), regardless of the duration of cough. The differences between case definitions did not allow us to compare our results with the published studies by other investigators. Certain clinical criteria of the GPI case definitions helped us to detect pertussis more efficiently in patients younger than 10 years old, in whom coughing duration was shorter than two weeks.

The primary objective of our study was to estimate the highest values both of sensitivity and specificity, complimented by PPV and LR+ for a certain sign and symptom combinations from the case definitions proposed by the GPI.

We provided evidence that whoop in combination with prerequisite signs and symptoms had the highest sensitivity of pertussis in the four months to nine years age group who have visited the primary or tertiary health care levels (73% *vs*. 63%, respectively). Nonetheless, among the in-patients, post-tussive emesis had the same sensitivity as a whoop. Among the outpatients, seven different sign and symptom combinations had specificities of 95% or more, while in the in-patients four different combinations had specificities above 96%.

As is known, the significance of a high PPV is helpful for clinical case management to maximize the detection of laboratory-confirmed cases among the tested participants [11]. We found that the outpatients aged four months–nine years with a combination of different symptoms which included MSS, whoop and contact had a high number of true positive pertussis cases (PPV > 71%). On the other hand, the inpatients had a highest PPV for apnoea in combination with MSS (89%) and for MSS combined with whoop, post-tussive emesis, worsening of the symptoms at night and contact (PPV = 100%).

For the participants aged ≥ 10 years, MSS combined with whoop had the highest sensitivity and a moderate PPV (71% and 45%, respectively) in outpatients, whereas the MSS in combination with worsening of symptoms at night had the highest sensitivity and high PPV (85% and 80%, respectively) among inpatients. Apnoea in combination with MSS, or in combination with other signs and symptoms had the highest specificity among the inpatients and outpatients, and was exceeding the value of 97% in all observed combinations.

Ghanaie et al. [4] reported that cough that lasted two or more weeks, with whoop had a sensitivity of 71% and a specificity of 46%, after examining the performance of the WHO pertussis case definition (cough ≥ 14 days with either paroxysmal cough, inspiratory whoop, or post-tussive emesis without other apparent causes), among the outpatients between the ages of six and 14 years. We found that the sensitivity and specificity of MSS combined with a whoop among the outpatients were 73% *vs*. 64%, respectively (four months to nine years age group) and 71% *vs*. 74%, respectively (≥ 10 years age group).

Our results showed that MSS combined with apnoea was a better predictor of pertussis among the inpatients than in the outpatients aged four months to nine years, possibly reflecting milder disease among the outpatients registered at primary health care centers.

Although the existing GPI case definition includes minimal fever or absence of fever depending on the age, many medical conditions can still resemble pertussis [12]. The differences in awareness and subjectivity of some signs and symptoms could influence the defined differences of sensitivity and specificity between the two surveillance systems and two studied age groups.

We recognize certain limitations of our study that should be addressed in future research.

Due to the limited number of participants, we could not perform a validation of certain signs and symptoms in the 0–3 months age group. Further and more extensive prospective studies would be required to elucidate the GPI case definition for this age group.

For better evaluation of sensitivity and specificity, participants with non-infectious and infectious causes which are clinically similar to pertussis, should be excluded by applying rigorous laboratory tests for diagnosing alternative cough etiologies.

CONCLUSION

The findings of our study pointed out that multiple sign and symptom combinations of the GPI pertussis case definitions were good predictors for laboratory-confirmed pertussis. Since we have found that LR+ for many proposed signs and symptoms of the GPI case definitions was above two, it is reasonable to consider the usefulness of these signs and symptoms to predict a diagnosis of pertussis. The addition of one or more signs and symptoms from the proposed case definition reduced the sensitivity but improved the specificity. Our study supported the fact that the choice of case definition in the recognition of pertussis should take into account the patient's age.

Further studies with larger samples to assess the validation of the GPI case definition for pertussis in other regions in various epidemiologic contexts are imperative.

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Евалуација дијагностичке вредности нове дефиниције случаја великог кашља – искуства из сентинелног и хоспиталног надзора над великим кашљем

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САЖЕТАК

Увод/Циљ У надзору над пертусисом у свету се користе различите дефиниције случаја великог кашља.
Циљ рада је био да се одреде оне комбинације знакова и симптома које доприносе најбољем препознавању великог кашља.

Методе У циљу евалуације знакова и симптома из дефиниција случаја великог кашља предложених од стране Глобалне пертусисне иницијативе (ГПИ) за три узрасне групе (0–3 месеца, од четири месеца до девет година и узраст ≥ 10 година), у Новом Саду је спроведена проспективна опсервациона студија у трајању од годину дана. Лабораторијска потврда инфекције изазване бактеријом *B. pertussis* је добијена употребом метода *PCR* или серолошким (*ELISA*) тестовима.

Резултати У периоду од 1. октобра 2013. до 30. септембра 2014, од укупно 319 испитаника са сумњом на велики кашаљ, код 103 (32,3%) болесника је добијена лабораторијска потврда великог кашља. Комбинација инспираторног стридора, повраћања после кашља и погоршања симптома током ноћи је имала највећи дијагностички значај (степен вероватноће позитивног резултата (*LR*+) 11,6) у доказивању пертусиса у сентинелном надзору међу болесницима узраста од четвртог месеца до девет година, док је међу хоспитализованима истог узраста најбољи показатељ позитивног резултата била апнеа (*LR*+ 13,5). У узрасту ≥ 10 година, *LR*+ за болеснике регистроване у сентинелном надзору са апнеом удруженом са повраћањем после кашља или са комбинацијом инспираторног стридора удруженог са презнојавањем између пароксизама и повраћањем после кашља био је 16,8, док је међу хоспитализованим болесницима овог узраста *LR*+ био мањи од 2,3 за све комбинације знакова/симптома.

Закључак Дефиниције случаја ГПИ имају дијагностички значај у циљу откривања оболевања од великог кашља и зато могу бити корисне у надзору над овом болешћу.

Кључне речи: велики кашаљ; пертусис; Глобална пертусисна иницијатива; дефиниција случаја; надзор

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Isolated hypertransaminasemia in children up to two years old with classical celiac disease

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SUMMARY

Introduction/Objective Isolated hypertransaminasemia (IHTS) is a common, benign, and transient appearance in patients with celiac disease (CD).

The aim of this study is to determine the frequency of IHTS in children up to two years old with clinically classical CD, as well as its connection with the onset of the first symptoms of the disease, the age of diagnosis, the clinical and laboratory nutritional parameters, and the degree of damage of small intestinal mucosa.

Methods The study was based on a sample of 82 children, 55 female and 27 male, ages 7–24 (14.28 ± 4.41) months. The diagnosis of CD was based on the revised ESPGHAN criteria and the activity of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by standard laboratory methods.

Results IHTS was found in 39 (47.56%) patients, 27 of whom (69.23%) had elevated levels of both transaminases and 12 of only one – eight of AST and four of ALT. The increase in relation to the aforementioned reference value for ALT was 1.1–10.08 (1.67 ± 1.73), and for AST it was 1.08–7.91 (1.56 ± 1.29) times. In patients with IHTS compared to those with normal transaminasemia, the age of onset of CD was significantly lower (9.83 ± 3.69 *vs.* 12.95 ± 4.43 months, p = 0.001), as well as the age of diagnosis (12.97 ± 3.88 *vs.* 15.47 ± 4.56 months; p = 0.01), while the differences in the other observed parameters were not significant.

Conclusions IHTS occurs in almost half of children up to two years old with classical CD. Hypertransaminasemia is in most cases mild and significantly more frequent in patients with earlier clinical expression of the CD.

Keywords: isolated hypertransaminasemia; classical celiac disease; children up to 2 years old

INTRODUCTION

Transaminases (aminotransferases) represent a group of enzymes of essential importance in catabolism and amino acid biosynthesis [1, 2]. They are characterized by high specificity for amino acids from which transamination is performed, as well as the presence in all cells of the organism, mainly those that are metabolically most active, such as hepatocytes, myocytes, tubulocytes, and others [1, 2]. From the physiological and clinical point of view, the most important are alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [3, 4]. ALT is a cytoplasmic, and AST is a cytoplasmic and mitochondrial enzyme [3, 4]. The ALT activity is the greatest in hepatocytes, while AST is most active in the heart muscle, followed by the liver, kidney, and skeletal muscle cells [4, 5, 6]. Due to the limited life span of cells, and reversible damage to their membranes, a small amount of transaminases is normally registered in the serum. Physiological variations of their activities in serum depend on the age, during the generative period of the sex, on the level of physical activity, and on the type of test by which they are determined [5, 6]. In conditions following extensive cellular damage, serum transaminase activity is multiplying, which is a valuable laboratory indicator of various diseases, primarily in the liver, skeletal muscles, and the heart [1, 2, 6]. In liver damage, the elevation of the serum ALT level is usually higher than that of AST, while in muscular and hemolytic diseases, the finding is reversed [4, 7].

Celiac disease (CD) is a systemic immune-mediated disorder triggered by dietary gluten in genetically predisposed individuals [8]. In addition to gluten-sensitive enteropathy, as a basic component of the disease, it is characterized by numerous extraintestinal manifestations, including isolated hypertransaminasemia (IHTS), i.e. elevated levels of serum

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transaminases without other signs of hepatic dysfunction [8–12]. Although it was first described in 1977, the basis for IHTS in the CD is not entirely clear [13, 14]. Histological examination of liver tissue in these patients shows mild steatosis and minimal inflammatory changes, with no relation to aminotransferase levels [12, 15]. It is most common in patients with classical CD, especially in those of the youngest age [16, 17]. In a certain number of patients, both children and adults, IHTS may be the first or only sign of this disease [5, 16, 18]. Unlike other diseases that can coexist with CD, such as autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, and primary biliary cirrhosis, IHTS is a benign disorder that in most cases disappears during a one-year gluten-free diet [9–12, 16, 17, 19, 20, 21].

The objective of this study was to determine the frequency of IHTS in children up to two years old with clinically classical CD, as well as its connection with the onset of the first symptoms of the disease, the duration of the symptoms, the age of diagnosis, the clinical and laboratory nutritional parameters, and the degree of damage to the mucosa of the small intestine.

METHODS

The objectives of the study were considered on a sample of 82 children (55 female and 27 male) aged 7–24 (14.28 ± 4.41) months, with clinically classical CD, i.e. disease characterized by chronic diarrhea, poor appetite, and failure to thrive [8, 22]. The study protocol was approved by the local ethics committee. The diagnosis of CD was based on the revised criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) from 1989 and on the new ESPGHAN guidelines published in 2012 [8, 23].

In the anamnesis for each patient, exact data related to the onset, duration, and severity of the underlying disease was obtained, while in the clinical examination, each patient's body length (BL) and weight (BW) was accurately measured and the obtained values were compared to the standard for the appropriate age and sex [24].

The liver function test (bilirubinemia, total and conjugated, ALT, AST, and gamma-glutamyl transferase) and laboratory nutritional indicators (blood level of hemoglobin, iron, total proteins, albumin, total cholesterol and 3-glyceride) were determined by standard laboratory methods from the morning portion of the blood before breakfast. The obtained findings were compared with standard reference values. In patients with hypertransaminase, the serum creatine phosphokinase activity was determined, so none of them, in addition to the absence of cholestasis and hemolysis, had no elements for rhabdomyolysis. Also, none received any medication following an increase in the serum level of transaminases, nor did they have an intercurrent infection that would produce this effect. The degree of increase in the activity of ALT and AST is expressed by an absolute number of magnitudes in relation to the upper limit of the reference value.

Classification of pathohistological changes of the small intestinal mucosa was performed according to modified Marsh criteria on infiltrative (I), infiltrative-hyperplastic (II), destructive (III), and hypoplastic (IV) type [25]. According to the degree of mucosal damage, destructive enteropathy is additionally classified into partial (IIIa), subtotal (IIIb), and total (IIIc).

The association of the occurrence of hypertransaminase with the age of onset of CD began, the duration of the symptoms, the age of diagnosis, and the clinical and laboratory nutritional parameters were tested with the Student's t-test, and the degree of damage to the small intestine with the χ^2 test.

RESULTS

Of the 82 patients, mild to moderate hypertransaminasemia was found in 39 (47.56%), 27 of which (32.93%) had elevated levels of both transaminases, and 12 of only one – eight of AST and four of ALT (Figure 1). The increase in relation to the upper limit of the reference value for ALT was 1.1–10.08 (1.67 ± 1.73) times, and 1.08–7.91 (1.56 ± 1.29) times for AST.

Although there was no significant difference between patients with IHTS and those with normal serum transaminases at the age of introduction of gluten-containing food (4.76 ± 1.13 *vs.* 5.06 ± 1.23 months; p = 0.302), nor in the duration of the disease until diagnosis (3.13 ± 2.75 *vs.* 2.53 ± 1.80 months, p = 0.248), occurrence of CD symptoms in children in the first group (4–23 months, average 9.83 ± 3.69 months) was significantly earlier than in those with normal serum transaminase levels (4–21 months, average 12.95 ± 4.43 months) (t = 3.447; p = 0.001). Accordingly, the age of diagnosis of CD in children with IHTS (8.5–24 months, mean 12.97 ± 3.88 months) was significantly lower than that in children with normal serum transaminases (7–24 months, mean 15.47 ± 4.56 months) (t = 2.650; p = 0.01) (Figure 2).

No significant differences were found by comparing the differences in percentile BL, the degree of BW deviation compared to the ideal for the appropriate length, age and sex, Hb level, total proteins, total cholesterol, and 3-glyceride in the blood, as well as the severity of damage to the small intestine mucosa in patients with IHTS and patients with normal serum transaminase values (Table 1).

DISCUSSION

IHTS is a common finding in patients with active CD. It occurs in patients of all ages and all types of illness, something often in children than adults. According to systematic reviews, it is found in 39–47% of adults and in 26–57% of children at the time of diagnosis of CD [21]. It is most common in children with classical CD, especially in those of the youngest age [16, 17, 21]. Hypertransaminasemia can sometimes be the first or only sign of CD; therefore, in all cases where its presence is unrecognized, testing in

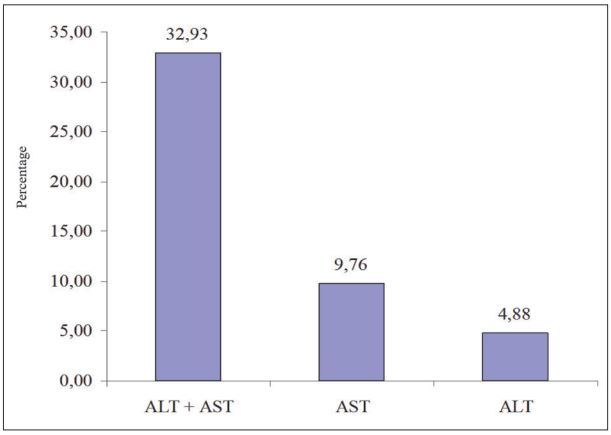

Figure 1. Frequency of isolated hypertransaminasemia in our patients with CD (No. 82)

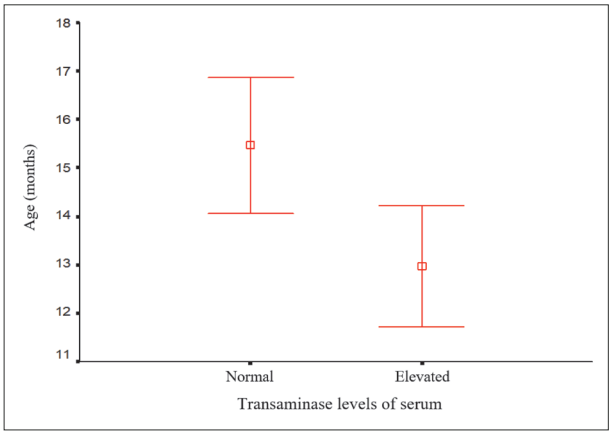

Figure 2. Age of patients with normal and elevated serum transaminase levels during the diagnosis of celiac disease

Table 1. Differences in percentile of body length, weight deficiency, laboratory nutritional parameters, and degree of small intestine mucosal damage in children with celiac disease according to the level of serum transaminases

Observed parameters	Patients without IHTS (No 43)	Patients with IHTS (No 39)	Statistical significance
BL (percentile)	44.24 ± 27.07	35.21 ± 23.29	ns
Percentage of BW deviation in relation to the ideal	-13.84 ± 943	-16.67 ± 8.58	ns
Blood tests			
Hemoglobin (g/L)	108.07 ± 14.33	102.81 ± 21.22	ns
Iron (μmol/L)	6.18 ± 3.49	6.30 ± 3.73	ns
Total protein (g/L)	58.9 ± 10	56.80 ± 8.1	ns
Cholesterol (mmol/L)	3.31 ± 0.7	2.95 ± 0.77	ns
3-glycerides (mmol/L)	1.41 ± 0.48	1.39 ± 0.55	ns
Enteropathy			
Partial (IIIa)	4 (9.3%)	1 (2.56%)	ns
Subtotal (IIIb)	19 (44.19%)	22 (56.41%)	
Total (IIIc)	20 (46.51%)	16 (41.03%)	

BL – body length; BW – body weight; ns – not significant

that sense is recommended [16, 21, 26]. Rarely, CD can be associated with severe autoimmune liver disease [12, 26, 27]. In contrast to IHTS associated with CD, which disappears on gluten-free diet, autoimmune diseases of the liver in these patients are gluten-independent [12, 26, 28].

Although the presence of IHTS in CD is long known, its pathogenetic basis has not been fully clarified. It is assumed that the possible mechanism leading to hepatic damage in patients with untreated CD is related to the entry of toxins, inflammatory molecules, and antigens in the portal circulation [9, 29]. In any case, it is generally asymptomatic, benign, and with a strict gluten-free diet transient condition [9, 21, 26]. There is, however, evidence that IHTS in patients with CD in cases of an inconsistent gluten-free child can evolve into serious liver disorders, such as chronic hepatitis and consequent liver cirrhosis [30].

In our study, based on a sample of 82 children under the age of two years with classical CD, mild to moderate IHTS was found in almost half of them. In accordance with the findings of other authors, such a high prevalence of IHTS explains the average age of our patients at the diagnosis of CD, which was less than 15 months, as well as its clinical form, which was classical in all [16, 17]. Accordingly, there was a significantly higher incidence of IHTS in younger patients compared to the older ones. However, the anticipated more frequent appearance of IHTS in patients with lower BL percentile, a more significant BW deficiency, more pronounced laboratory nutritional deficiency indicators, and a more severe degree of damage to the small intestine mucosa inflicted by enterobiasis, was not found. The same findings were also based on the child population, state, and other parameters. [17, 19]. The explanation for the absence of this link is most likely to lie in the identical type of CD and the close age of our patients.

Almost always, CD-associated IHTS disappears within one year on gluten-free diet [16, 17]. If it does not, in addition to poor adherence to the gluten-free diet, autoimmune and other liver disorders associated with CD should be considered [12, 17]. Also, because of the possibility of a later onset of autoimmune liver disease, it is recommended that all patients with CD undergo annual liver tests [17]. Normalization of transaminases in all of our patients was established after two to nine months of gluten-free diet. Normalization of liver test results was preceded by a complete clinical recovery of patients. During further ambulatory monitoring, most of them over the course of several years, none have developed any of the autoimmune liver diseases.

CONCLUSION

Isolated hypertransaminasemia is a benign, and with a strict gluten-free diet transient, occurrence found in almost half of children up to two years old with active classical type of CD. The increase in serum transaminase levels is in most cases mild and significantly more frequent in patients with earlier clinical expression of CD.

Conflict of interest: None declared.

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Изолована хипертрансаминаземија код деце до две године са класичном целијачном болешћу

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САЖЕТАК

Увод/Циљ Изолована хипертрансаминаземија (ИХТС) представља честу, бенигну и пролазну појаву код болесника са целијачном болешћу (ЦБ). Циљ ове студије је да се утврди учесталост ИХТС код деце узраста до две године са класичном ЦБ, као и повезаност њене појаве са узрастом настанка првих симптома болести, узрастом постављања дијагнозе, клиничко-лабораторијским параметрима исхрањености и степеном оштећења слузнице танког црева.

Методе Студија је базирана на узорку од 82 детета, 55 женског и 27 мушког пола, узраста 7–24 (14,28 ± 4,41) месеци. Дијагноза ЦБ је заснивана на ревидираним *ESPGHAN* критеријумима, а активност серумске аланин-аминотрансферазе (АЛТ) и аспартат-аминотрансферазе (АСТ) стандардном лабораторијском методом.

Резултати ИХТС је утврђена код 39 (47,56%) болесника, при чему код 27 (69,23%) са повишеним нивоима обе трансаминазе, а код 12 само једне од њих, код осам АСТ и код четири АЛТ. Повећање у односу на горњу референтну вредност је износило за АЛТ 1,10–10,08 (1,67 ± 1,73), а за АСТ 1,08–7,91 (1,56 ± 1,29) пута. Код болесника са ИХТС у односу на оне са нормалном трансаминаземијом узраст појаве првих симптома ЦБ је био знатно мањи (9,83 ± 3,69 месеци наспрам 12,95 ± 4,43 месеца; $p = 0,001$), као и узраст њеног дијагностиковања (12,97 ± 3,88 наспрам 15,47 ± 4,56 месеци; $p = 0,01$), док разлике у осталим посматраним параметрима нису биле значајне.

Закључак ИХТС се јавља код близу половине деце узраста до две године са класичном ЦБ. Хипертрансаминаземија је у већини случајева блага и знатно учесталија код болесника са ранијом клиничком експресијом ЦБ.

Кључне речи: изолована хипертрансаминаземија; класична целијачна болест; деца до две године

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Evaluation of independent predictors of in-hospital mortality in patients with severe trauma

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SUMMARY

Introduction/Objective The aim of this study was to determine independent predictors and the best trauma scoring system (REMS, RTS, GSC, SOFA, APPACHE II) of in-hospital mortality in patients with severe trauma at the Department of Emergency, Emergency Center, Clinical Center of Serbia, Belgrade.

Methods Longitudinal study included 208 consecutive patients with severe trauma. In order to determine independent survival contributors, univariate and multivariate Cox regression analyses were performed. The power of above-mentioned scoring systems (measured at admission to the Emergency center) to predict mortality was compared using the area under the curve (AUC).

Results There were 208 patients (159 male, 49 female), with the average age of 47.3 ± 20.7 years. Majority of patients were initially intubated (86.1%) on admission to the emergency department, and 59.6% patients were sedated before intubation. After finishing of diagnostic procedures, 17 patients were additionally intubated, and, at that time, 94.2% patients were on mechanic ventilation. The majority of patients was traumatized in a car crash (33.2%), followed by falls from height (26.4%) and as pedestrians (22.6%). Patients had an average of 24.7 ± 21.2 days spent in intensive care unit. The overall case-fatality ratio was 17/208 (8.2%). In Cox regression analysis only elevated heart rate (HR = 1.03, p = 0.012) and decreased arterial oxygen saturation (SpO_2) (HR = 0.91, p = 0.033) singled out as independent contributors to in-hospital mortality of patients with severe trauma. REMS (AUC 0.72 ± 0.64) and SOFA (AUC 0.716 ± 0.067) scores were found fair and similar predictor of in-hospital mortality, while APACHE II (AUC 0.614 ± 0.062) and RTS (0.396 ± 0.068) were poor predictors.

Conclusion Results of this study showed an important role of REMS, which appears to provide balance between the predictive ability and the practical application, and components of REMS in prediction of outcome in patients with severe trauma and that HR and SpO_2 are independent predictors of in-hospital mortality.

Keywords: injury; Rapid Emergency Medicine Score; cohort study

INTRODUCTION

Trauma remains an increasingly common entity and one of the leading causes of death among young adults, killing a million people worldwide. Therefore, trauma is significant factor of morbidity, disability, mortality and has important financial and social impact [1]. Keeping in mind the frequency and consequences of trauma, it is very important to define predictors of outcome with certain level of accuracy. However, this issue is related to measuring quality of trauma system, including feasibility, ethical considerations, risk assessment, and other type of evaluation. All these activities have the same goal, to support the concept of preventable death resulting from poor medical care [2].

In order to assess injury severity and predict prognosis, many different trauma-scoring systems are used. These measures vary widely in terms of design, complexity, and accuracy in predicting mortality after severe trauma [3, 4]. Besides that, the robustness of certain trauma scoring system depends on population under study. For example, the presence of very healthy patients who will probably survive as well as elder patients or patients with severe comorbidity who probably won't survive might significantly affect the ability of the scoring system to correctly predict the outcome [5]. Furthermore, the use of trauma scoring systems helps clinicians in management of trauma patients. Besides that, prediction of severe trauma is associated with presence of comorbidity, time interval between trauma and its care, treatment settlements [6].

Over the last decades many scoring system have been developed and used for trauma. The Revised Trauma Score (RTS) is the most commonly used physiological score. It is widely used in hospital and pre-hospital patients (pre-hospital triage). It consists of the Glasgow Coma Scale (GSC), systolic blood pressure, and respiratory rate (RR) [7]. The Rapid Emergency Medicine Score (REMS) was developed for predicting in-hospital mortality in nonsurgical emergency department (ED) patients [8]. REMS incorporates GSC, age, mean arterial pressure (MAP), RR, heart rate (HR) and arterial

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oxygen saturation (SpO_2). The most spread used scoring system is The Acute Physiology and Chronic Health Evaluation (APACHE II). This scoring system evaluates the severity of surgical, non-surgical and intensive care unit (ICU) patients. APACHE II consists of the body temperature, RR, HR, MAP, oxygenation of arterial blood, arterial pH, serum sodium and potassium levels, serum creatinine, hematocrit, white cell count and GCS [9]. The Sequential Organ Failure Assessment (SOFA) was designed in 1994 for assesses the severity of illness in patients in the ICU [10]. The score incorporates PaO_2/FiO_2 mmHg, MAP, vasopressors, serum creatinine, serum bilirubin, platelets, and GSC.

Bearing in mind all of the mentioned above, the aim of this study was to determine independent predictors and the best trauma scoring system (REMS, RTS, GSC, SOFA, APPACHE II) of in-hospital mortality in patients with severe trauma at the Department of Emergency, Emergency Center, Clinical Center of Serbia, Belgrade.

METHODS

Study design

Prospective cohort study included 208 consecutive patients with severe trauma admitted to the Emergency Center, Clinical Center of Serbia in Belgrade, from June 1, 2015 to June 1, 2016. Patients were followed until discharge or death. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade (decision no. 29/IV-19; 25-APR-2016).

Inclusion and exclusion criteria

All patients with severe trauma, aged over 18 years, were included in the study. Mechanism of injury was established as Injury Severity Score (ISS) of over 15 [10]. Exclusion criteria were unknown identity of person, absence of accompanying person, patients transferred from other emergency centers, patients intubated and reanimated at the place of injury, sedated patients.

Data collection

Data on demographic characteristics, personal history, concomitant therapy, and mechanism of injury were collected by questionnaire. Additionally, for all patients ISS, RTS, and REMS were determined at admission in the Emergency center (EC) [7, 8, 10]. Furthermore, SOFA score and APACHE II score were determined at the admission in ICU [9, 10]. Information on clinical characteristics (body temperature, systolic and diastolic blood pressure, HR, RR, SpO_2), blood sample analyses (serum sodium and potassium levels, serum creatinine, serum bilirubin, hematocrit, leucocytes count, platelets) and other analyses (PaO_2/FiO_2 mmHg, vasopressor, oxygenation of arterial blood, arterial pH) were obtained from medical records. Initial vital signs (HR, RR, systolic, diastolic blood pressure and SpO_2) and GCS recorded immediately upon arrival at ED. The assessments of noninvasive blood pressure, HR, SpO_2 (determined by peripheral pulse oximeter) done by Infinity Vista Xl Drager monitor. Normal ranges of hemodynamic and respiratory parameters are defined by Advanced Trauma Life support classification of shock [11]. For example, arterial hypotension is defined as systolic blood pressure lower than 90 mmHg, tachycardia is defined as HR faster than 100 beats per minute (BPM).

Statistical analysis

Baseline characteristics of the study sample (mean, standard deviation, percentages) are presented. Nonparametric test was used for the comparisons between groups (Mann-Whitney test for continuous variables). Moreover, the predictive factors were tested in univariate and multivariate models using Cox proportional hazard regression models for reaching clinical outcome (death). In these analyses, death was considered as dependent variable. All variables that were associated ($p < 0.100$) with the outcome in the univariate analysis were analyzed together in multivariate Cox proportionate hazard regression model in order to determine independent predictors of in-hospital mortality in patients with severe trauma. The power of scoring systems to predict mortality was compared using the area under the curve (AUC). All analyses were performed using the SPSS (SPSS Inc. Chicago, USA), version 17.0 for Windows. Probability level of < 0.05 was considered statistically significant.

RESULTS

The characteristics of 208 patients with severe trauma are shown in Table 1. There were 159 (76.4%) male and 49 (23.6%) female patients, with average age of 47.3 ± 20.7 years. Almost all patients (99.5%) came to the ED by ambulance. Average time spent in Emergency ambulance prior to hospitalization was 1.3 hours. The largest proportion of patients was traumatized in car crash (33.2%), followed by falls from the height (26.4%) and as pedestrians (22.6%) (Figure 1). The overall case-fatality ratio was 17/208 (8.2%).

Regarding clinical characteristics, values of systolic and diastolic blood pressure and number of respirations were in the normal range, while average HR was elevated (110 ± 25 beats per minute) and SpO_2 was decreased (85.4 ± 4.5%) (Table 1).

Majority of the patients were initially intubated (86.1%), at admission to ED, and 59.6% patients were sedated before intubation. After finishing of diagnostic procedures, 17 patients were additionally intubated, and, at that time, 94.2% patients were on mechanic ventilation (Table 1).

Different values of scale scores at admission to ED and ICU are shown in Table 2. Based on their values, it is obvious that included patients suffered from severe trauma, which requires hospitalization in ICU. There is a statistically significant difference between REMS and SOFA score

Table 1. Patients' characteristics

Variable	Values*
Age (years)*	47.3 ± 20.7
Sex** Male Female	 159 (76.4%) 49 (23.6%)
Arrival to the Emergency Department by:** Emergency Private car	 207 (99.5%) 1 (0.5%)
Time spent in ambulance on admission (hours)*	1.3 ± 0.5
Systolic blood pressure (mmHg)*	118.8 ± 36.1
Diastolic blood pressure (mmHg)*	71.2 ± 22.4
Heart rate (bpm)*	110 ± 25
Number of respirations*	14 ± 10
Saturation (%)*	85.4 ± 4.5
Intubation** Yes No	 179 (86.1%) 29 (13.9%)
Mechanic ventilation** Yes No	 196 (94.2%) 12 (5.8%)
Sedation** Yes No	 124 (59.6%) 84 (40.4%)
Hemodynamics** Stable Unstable	 138 (66.3%) 70 (33.7%)
Inotropic support** Yes No	 70 (33.7%) 138 (66.3%)

*Mean ± SD;
**values are presented as frequencies (%)

values between dead and alive patients (Table 3), p-value for the REMS score is 0.002 and for the SOFA score p-value is 0.003 (according to the Mann–Whitney test).

Patients had an average of 24.7 ± 21.2 days spent in ICU.

According to the results of univariate Cox proportional regression analysis, following variables entered in multivariate model ($p < 0.100$): HR ($p = 0.008$), SpO2 ($p = 0.019$), REMS ($p = 0.058$), SOFA on admission ($p = 0.077$) (Table 4). These variables were statistically significant in univariate analyses. After multivariate Cox regression model using above mentioned variables significant in univariate analysis, only elevated HR (HR = 1.03, $p = 0.012$) and decreased of SpO_2 (HR = 0.91, $p = 0.033$) at admission remained significant, i.e. singled out as independent contributors to in-hospital mortality of patients with severe trauma. In other words, an increase of HR for one unit is associated with an increase of risk of death by 3%. Additionally, a decrease of SpO_2 for one unit is associated with an increase of risk of death by 9%.

We compared RTS, REMS, APACHE II and SOFA in predicting in – hospital mortality by using Receiving Operating Curve (ROC) analysis (Figure 2). REMS (AUC 0.72 ± 0.64) and SOFA (AUC 0.716 ± 0.067) were found fair and similar predictors of in-hospital mortality. On the other hand APACHE II (AUC 0.614 ± 0.062) and RTS (0.396 ± 0.068) were found poor predictors of in-hospital mortality.

Table 2. Scores at admission

Scale	Mean ± SD
GCS	8.5 ± 4.1
ISS	33.1 ± 10.2
RTS	5.5 ± 1.5
REMS	10 ± 4.1
APACHE II	18.5 ± 8.6
SOFA	7.5 ± 3.1

GCS – Glasgow Coma Scale; ISS – Injury Severity Score; RTS – Revised Trauma Score; REMS – Rapid Emergency Medicine Score; APACHE II – Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment

Table 3. Injury scores

Scores	Dead (mean ± SD)	Alive (mean ± SD)	p-value
REMS	13.17 ± 4.36	9.73 ± 3.94	0.002
RTS	5.01 ± 1.39	5.54 ± 1.45	0.162
GSC	7.18 ± 3.14	8.58 ± 4.2	0.33
SOFA	9.59 ±3.04	7.39 ± 2.96	0.003
APACHE	21.41 ± 6.65	18.28 ± 8.61	0.126

GCS – Glasgow Coma Scale; RTS – Revised Trauma Score; REMS – Rapid Emergency Medicine Score; APACHE II – Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment

Table 4. Results of univariate Cox regression analysis

Variable	Hazard ratio	95% confidence interval	p-value
Age	0.99	0.97–1.01	0.33
Sex	0.59	0.17–2.07	0.414
Admission to the Emergency Department	0.05	0–0.75	0.856
Time spent in ambulance on admission	1.53	0.52–4.56	0.443
Systolic blood pressure	0.99	0.98–1	0.173
Diastolic blood pressure	0.98	0.96–1	0.109
Heart rate	1.03	1.01–1.05	**0.008**
Number of respirations	1.01	0.96–1.07	0.593
Saturation	0.90	0.82–0.98	**0.019**
Comorbid hypertension	1.11	0.37–3.31	0.857
Mechanism of injury	1.01	0.75–1.37	0.939
GCS	1	0.87–1.14	0.964
Breathing	20.35	0–26.05	0.856
Intubation	1.04	0.13–8.31	0.973
Mechanic ventilation	0.05	0–5.83	0.711
Sedation	1.7	0.65–4.43	0.282
Hemodynamic	1.19	0.46–3.06	0.723
Inotrop support	0.81	0.31–2.15	0.676
RTS	0.9	0.61–1.33	0.606
REMS	1.1	1–1.22	**0.058**
APACHE II on admission in ICU	0.99	0.94–1.06	0.87
SOFA on admission in ICU	1.17	0.98–1.38	**0.077**
Mechanic ventilation in ICU	0.05	0.01–5.83	0.914
Hemorrhage	1.48	0.56–3.94	0.427
Surgical intervention	0.8	0.29–2.20	0.66

Bold values denote statistical significance ($p < 0.100$)

GCS – Glasgow Coma Scale; RTS – Revised Trauma Score; REMS – Rapid Emergency Medicine Score; APACHE II – Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment; ICU – intensive care unit

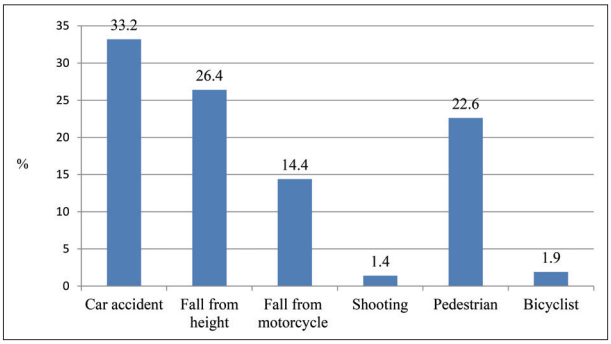

Figure 1. Mechanisms of injury

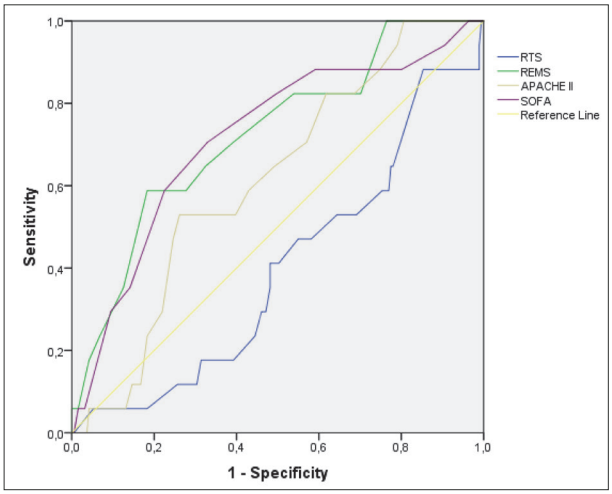

Figure 2. Area under curve for the injury scores;

RTS – Revised Trauma Score; REMS – Rapid Emergency Medicine Score; APACHE II – Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment

DISCUSSION

The assessment of outcome in severe trauma patients is a demanding task due to the diversity and variation in severity of trauma, and consequently, heterogeneity of patient population. Additional factors, which may influence the assessment of outcome in these patients, are related to the issue of appropriate assignment of severity of symptoms and presence of different comorbidities [11].

Our mortality rate is 8.2%, which is higher than in other study where, were mortality rate found to be around 5% [1]. This difference may be because in these studies, all traumatized patients were included, and one of our inclusion criteria was ISS over 15. Considering this inclusion criterion our patients had greater mortality risk.

In our study the largest proportion of patients was traumatized in car crash (33.2%), followed by falls from the height (26.4%) and as pedestrians (22.6%). Our findings were similar like in previous studies [12].

Our finding of predictive role of age in in-hospital mortality in univariate analysis was not significant, which is opposite than in the other studies [13, 14]. Miyamoto et al. [13] and Jawa et al. [14] found that older age was an indicator of in-hospital mortality. The possible reason for different findings might be a larger sample size, and different statistical approach in these studies.

In our study, regarding the trauma scoring system, REMS is similar to or better than the other system. REMS has similar results as the SOFA, the advantages of REMS is more rapid and less invasive then SOFA. APACHE II and RTS were found poor predictors of in-hospital mortality [15]. Imhoff et al. [16] and Lee et al. [17] found that the REMS scoring system, performed in the ED, was a strong predictor of in-hospital mortality. Slight differences between REMS and RTS as predictors of in-hospital mortality can be observed in both studies. REMS scoring system is easier and simpler than RTS because it is consisting of six variables (GSC, age, MAP, RR, HR, SpO_2) which are easy to obtain. Considering all this, REMS scoring system can be highly applicable at the ED and in the prehospital treatment of patients. Our findings support the growing body of literature examining the use of REMS in judgment after major injury [18, 19].

In this prospective cohort study, we demonstrated that HR and SpO_2 on admission are independent predictors of in-hospital mortality in patients with severe trauma. Using the Cox proportional hazard regression models we demonstrated that an increase of HR for one unit is associated with increase of risk of death for 3%, while a decrease of SpO_2 for one unit is associated with increase of risk of death for 9%. Both these variables are components of the REMS, which has been developed for predicting in-hospital mortality in nonsurgical ED patients [20]. Our work confirms that in the most severely injured patients, initial measurement of REMS components, especially HR and SpO_2, are reliable indicators of those who are at the greatest risk of in-hospital death. These findings are opposite then in the literature, Imhof et al. [16] found that HR do not have statistically significant contribution in mortality prediction, on the other hand age and GSC have high statistically significant contribution in mortality prediction. These opposite findings can be explained by autonomic compensation to severe trauma [21]. In our study, we had only severe traumatized patients which is different between Imhof et al. [16], regarding to the SpO_2 we have same finding like in other studies [22].

It is well known that determination of vital signs such as SpO_2 and HR upon arrival at the ED is frequently used as prognostic indicators for adverse outcome in patients with severe trauma. On the other hand, analysis of HR variability provides insight into adequacy of autonomic compensation to severe trauma in pre-hospital settings [21]. In the same study, authors stated that their findings support the fact that autonomic balance and pulse pressure are associated with mortality, and may give important diagnostic and prognostic findings in management of patients with severe trauma. Physiological response to injury with consequent reductions of central blood volume includes increased HR and peripheral vascular resistance. These autonomic compensations are mediated by decrease of parasympathetic and activation of sympathetic efferent neural way to the heart and vasculature [23, 24]. Additionally, alterations of tissue perfusion and oxygenation due to an impaired

microcirculation have been shown to contribute to the subsequent development of organ dysfunction and unfavorable outcome [25, 26]. In line with these results, low SpO_2 values at baseline have been associated with the development of multiorgan dysfunction and death [27, 28, 29].

Some limitations of our study have to be mentioned. First, 208 patients with severe trauma were enrolled in this study, and a larger sample size would have been beneficial for generalizability of the results. Second, traumatized patients who died in pre-hospital settings were not included in the analysis, which represents a type of selection bias. Third, the patient's vital parameters varied over time, so the values presented might not be representative. Finally, the lack of available data regarding the presence of comorbidities, and their management was not included and may have resulted in bias in the outcome.

CONCLUSION

Results of this study showed the important role of REMS, which appears to provide balance between the predictive ability and the practical application, and components of REMS in prediction of outcome in patients with severe trauma and that HR and SpO_2 are independent predictors of in-hospital mortality.

Conflict of interest: None declared.

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Евалуација независних предиктора интрахоспиталног морталитета код болесника са тешком траумом

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САЖЕТАК

Увод/Циљ Циљ ове студије био је одређивање најбољег бодовног система код траума (*REMS*, *RTS*, *GSC*, *SOFA*, *APPACHE* II) и независних предиктора интрахоспиталног морталитета код болесника са тешком траумом, лечених у Ургентном центру Клиничког центра Србије у Београду.

Методе Лонгитудинална студија је укључила 208 консекутивних болесника са тешком траумом, примљених у Ургентни центар. У циљу одређивања независних предиктора преживљавања, урађене су униваријантна и мултиваријантна Коксова регресиона анализа. Такође, утицај система бодовања раније поменутих резултата на пријему у Ургентни центар у предикцији морталитета поређен је коришћењем теста *Area under curve* (*AUC*).

Резултати Испитивани узорак чинило је 208 болесника (159 мушкараца, 49 жена), просечног узраста 47,3 ± 20,7 година. Већина болесника била је иницијално интубирана (86,1%), на пријему у Ургентни центар, а 59,6% болесника било је седирано пре интубације. После завршетка дијагностичких процедура, 17 болесника је додатно интубирано, тако да је на механичкој вентилацији било 94,2% болесника. Болесници су најчешће повређивани у саобраћајним несрећама (33,2%), приликом пада са висине (26,4%) и као пешаци (22,6%). Просечна дужина боравка у Јединици интензивне неге износила је 24,7 ± 21,2 дана. Леталитет је био 17/208 (8,2%). Коксовом регресионом анализом показано је да су повишена срчана фреквенца (*HR* = 1,03, *p* = 0,012) и снижена сатурација крви кисеоником (*XP* = 0,91, *p* = 0,033) независни предиктори смртног исхода болесника са тешком траумом. *REMS* (*AUC* 0,72 ± 0,64) и *SOFA* (*AUC* 0,716 ± 0,067) показали су сличну предиктивну вредност, док су *APACHE* II (*AUC* 0,614 ± 0,062) и *PTC* (0,396 ± 0,068) били лоши показатељи интрахоспиталног морталитета код болесника са тешком траумом.

Закључак Резултати студије показали су важну улогу компоненти *REMS* у предикцији исхода болесника са тешком траумом, као и да су срчана фреквенца и сатурација крви кисеоником независни предиктори интрахоспиталног морталитета.

Кључне речи: повреде; бодовни систем *REMS*; кохортна студија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The effects of auditory amplification on subjective assessments of hearing impairment and anxiety in people with presbycusis

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SUMMARY

Introduction/Objective Presbycusis, elderly hearing loss, is a progressive, bilateral sensoryneural hearing loss characterized by reduced sensitivity of hearing and understanding speech in a noisy environment, thereby impairing communication and inducing anxiety.
The objective was to examine the impact of hearing amplification on subjective hearing disability assessment and anxiety in people with presbycusis.

Method Sample consisted of 120 respondents aged 47–85 with presbycusis, 60 subjects with and 60 subjects with no auditory amplification. The standardized Hearing Handicap Inventory for the Elderly and the Spielberger State Trait Anxiety Inventory were used in the study.

Results In subjects with hearing amplification, test/retest has no statistical significance in the STAI and HHIE scales and subscales, except the HHIE-S ($p = 0.004$) with a lower score on the retest. Respondents in whom hearing amplification was performed during the year was statistically significant in HHIE ($p = 0.016$), HHIE-S ($p = 0.004$) and STAI-S ($p = 0.029$) which speaks of favorable effect of hearing amplification. In the group with no hearing amplification, statistical significance was observed in relation to the HHIE scores ($p = 0.002$), HHIE-E ($p = 0.000$), STAI ($p = 0.000$), STAI-S ($p = 0.001$) and STAI-T ($p = 0.001$) and it was noticed that anxiety, loss of emotional contacts, and more pronounced degree of hearing impairment were the result of unassisted hearing rehabilitation.

Conclusion Audiological practice should include tests for assessment of hearing disability and anxiety in order to preserve health in later life.

Keywords: presbycusis; anxiety; hearing impairment; social isolation

INTRODUCTION

Old age is a period of reduced physical and mental abilities and increased disability, and demographic aging can be seen as an increase in population dependent on economic, social and health terms [1, 2]. Presbycusis, hearing impairment in elderly, is a physiological phenomenon, which cause hearing loss in adults all over the world [3]. Presbycusis affects more than half of adults up to 75 years of age, most adults older than 80 years and is usually present in all people over 90 [4]. Presbycusis is the third most common disease besides hypertension and arthritis in the elderly [5]. The gradual hearing loss process lasts for several years, usually affecting high frequencies, and is accompanied with reduced speech understanding in a noisy environment, a slow acoustic information processing, and sound source localization disorder [6]. Hearing loss, accompanied by difficulties in speech comprehension, contributes to the reduction of concentration and memory, leads to isolation, and increases the sense of disability [7]. On the other side, the elderly have a higher prevalence of mental and emotional disorders and are more exposed to neglect of family members and caregivers [8].

The greater hearing loss, the more pronounced are anxiety reactions [9, 10]. Under the influence of external social and economic factors, loss of hearing may be a trigger for the manifestation of anxiety states [11]. Therefore, audiological attitude toward presbyacusia is important in hearing amplification [12]. Loss of hearing leads to psychological isolation can cause an identity crisis and lead to the manifestation of anxiety or reactive depression. Social support can alleviate stress and prevent the withdrawal of a person with a presbycusis from social life [13].

This research suggests the application of audiological assessments with adequate psychometric scales in persons with hearing impairment, in order to define subjective experience of hearing impairment, emotional response to hearing loss, and degree of social functioning as well as anxiety assessment. Hearing Handicap Inventory for Elderly (HHIE) questionnaire confirmed sensitivity, specificity, and reliability and allows assessment of auditory perception disability [14, 15].

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There is a high variability of functional status for any level of hearing loss [16]. Therefore, it is necessary to change the position in audiological practice so that determining the degree of hearing impairment should not be only guideline for recommending a hearing aid without the perception of communication capabilities in the context of free life activities [17]. One of the most important psychological aspects in elderly refers to human's ability to adapt and maintain activities for that age which is a major challenge for modern health care system [18, 19].

METHODS

Research sample

The study included 120 respondents with presbycusis of both sexes, 60 examinees with auditory amplification and 60 subjects with no auditory amplification. In subjects with hearing amplification, the average age is 69.4 years (SD 9.86), while in the group with no auditory amplification 67.8 years (SD 6.68). In the group of subjects with hearing amplification 31 (51.7%) respondents were male, female 29 (48.3%), while in the group without amplification 29 (48.3%) respondents were male and female 31 (51.7%).

Pearson's χ^2 test ($r = 0.71$, $df = 1$) found that there was no statistically significant difference and that both groups of subjects were uniform in terms of sex, and in relation to auditory amplification. In the period of one year in 16 subjects was conducted auditory amplification. The study defined three groups of respondents: with auditory amplification on test and retest (N = 60); without auditory amplification on test and with auditory amplification on the retest (N = 16); without auditory amplification on the test and the retest (N = 44). χ^2 analysis has confirmed the homogeneity of both groups by sex, age, and hearing amplification.

The general questionnaire enabled the collection of socio-demographic data: sex, age, marital status, place of residence, level of education, employment, general health assessment and thus are defined independent variables in the research. Applied instruments in research (Hearing Handicap Inventory for the Elderly – HHIE and Spielberg State Anxiety Inventory – STAI) enabled the monitoring of dependent variables: subjective assessment of hearing disability and anxiety in people with presbycusis.

By analyzing the average age of 67.8 years (SD 6.68), Pearson correlation coefficient found that there was no statistically significant correlation between the scores HHIE, STAI and the age of the respondents (statistical significance $p > 0.01$) HHIE ($r = 0.13$, $p = 0.15$), HHIE-S ($r = 0.1$, $p = 0.26$), HHIE-E ($r = 0.14$, $p = 0.11$), STAI ($r = 0.09$, $p = 0.31$), STAI-S ($r = 0.1$, $p = 0.26$), STAI-T ($r = 0.06$, $p = 0.45$).

According to marital status of respondents are married 79 (65.8%), 26 (21.8%) are widowed, eight (6.7%) divorced, five (4%) unmarried, while two (1.7%) live in an extramarital community. The single-factor analysis of the variance (ANOVA) found that the independent variable – marital status was not statistically significant interaction ($p > 0.05$) with a score on the HHIE and STAI scales: HHIE ($F = 0{,}339$, $df1 = 4$, $df = 115$, $p = 0.85$, $\eta^2 = 0.01$) HHIE-S ($F = 0{,}362$, $df1 = 1$, $df = 115$, $p = 0.83$, $\eta^2 = 0.01$) HHIE-E ($F = 0{,}675$, $df1 = 4$, $df = 115$, $p = 0.61$, $\eta^2 = 0.02$); STAI ($F = 0{,}699$, $df1 = 4$, $df = 115$, $p = 0.59$, $\eta^2 = 0.02$), STAI-S ($F = 0{,}847$, $df1 = 4$, $df = 115$, $p = 0.49$, $\eta^2 = 0.02$), STAI-T ($F = 0{,}478$, $df1 = 4$, $df = 115$, $p = 0.75$, $\eta^2 = 0.01$).

The respondents of both groups compared to the level of education: three (2.5%) without education, primary education has nine (7.5%), secondary 67 (55.8%), high 14 (11.7%), faculty education (20.0%) and master's degree 3 (2.5%). Using the Cheffé post hoc test, it was noticed statistical significance on the STAI scale in subjects without education and magister ($p = 0.041$ for $p < 0.05$), and descriptive statistics showed a more pronounced degree of anxiety in respondents without education (M 107.33; SD 12.34) compared to respondents with a master's degree (M 68.33; SD 4.04). The single-factor analysis of variance does not determined statistically significant association (for $p < 0.05$) level of education and HHIE scores.

The highest number of respondents are in status of retiree 74 (61.6%), the permanent job has 22 (18.3%), the occasional work has 16 (13.3%), three (2.5%) were unemployed, while 4.3% of respondents did not answer this question. A single-factor analysis of variance did not establish a statistical significance at the level of $p < 0.05$ of the working status and scores on the scales: HHIE ($F = 0.67$, $df1 = 5$, $df = 114$, $p = 0.64$, $\eta^2 = 0.02$), HHIE-S ($F = 0.38$, $df1 = 5$, $df = 114$, $p = 0.86$, $\eta^2 = 0.01$), HHIE-E ($F = 0.9$, $df1 = 5$, $df = 114$, $p = 0.48$, $\eta^2 = 0.38$), STAI ($F = 1.500$, $df1 = 5$, $df = 114$, $p = 0.19$, $\eta^2 = 0.06$), STAI-S ($F = 0.95$, $df1 = 5$, $df = 114$, $p = 0.45$, $\eta^2 = 0.04$) and STAI-T ($F = 2.112$, $df1 = 5$, $df = 114$, $p = 0.07$, $\eta^2 = 0.08$).

The largest number of respondents 108 (90%) live in their home / flat, as tenants live 10 (8.3%), while 2 (1.7%) respondents have no answer. The results of a single-factor analysis of variance do not confirm statistical significance for different housing conditions (resolved housing issues) in relation to the scores HHIE and STAI ($p > 0.05$): HHIE ($F = 0.016$, $df1 = 2$, $df = 117$, $p = 0.98$, $\eta 2 = 0.00$) HHIE-S ($F = 0.773$, $df1 = 2$, $df = 117$, $p = 0.46$, $\eta^2 = 0.01$) HHIE-E ($F = 0.444$, $df1 = 2$, $df = 117$, $p = 0.64$, $\eta^2 = 0.00$), STAI ($F = 1.089$, $df1 = 2$, $df = 117$, $p = 0.34$, $\eta^2 = 0.01$), STAI-S ($F = 2.661$, $df^1 = 2$, $df = 117$, $p = 0.74$, $\eta^2 = 0.04$), STAI-T ($F = 0.489$, $df^1 = 2$, $df = 117$, $p = 0.61$, $\eta^2 = 0.00$).

Distribution of subjects by grade of hearing impairment (mild, moderate, severe, severe to profound) in the group of subjects with hearing amplification: mild hearing loss six (46.2%), moderate 38 (44.2%), severe 14 (73.7%), and severe to profound two (100.0%) subjects. In the group of subjects without amplification: seven (53.8%) subjects had mild hearing impairment, moderate 48 (55.8%), severe five (26.3%); there were no subjects with very severe hearing impairment (0%) (Table 1).

Study design

The clinical, prospective cross section study, was conducted from April 2016 to April 2017 at the Department

Table 1. Distribution according to degree of hearing impairment and amplification

Hearing Loss	Hearing amplification					
	Yes		No		Total	
	N	%	N	%	N	%
Mild	6	10	7	11.7	13	10.8
Moderate	38	63.3	48	80.0	86	71.7
Severe	14	23.3	5	8.3	19	15.8
Severe-to-Profound	2	3.3	0	0.0	2	1.7
Total	60	100	60	100	120	100

of audiology and vestibulology of KBC Zemun, with the approval of the Ethics Committee of this institution in accordance with legal standards.

In all subjects with presbycusis, with and without hearing amplification, at the beginning of the study (test) and after a period of one year (retest), conducted tests of subjective assessment of hearing impairment (HHIE) and anxiety (STAI) in order to evaluate the effects of auditory amplification.

Instruments

The Hearing Handicap Inventory for the Elderly (HHIE) is a standardized questionnaire that enables the assessment of hearing impairment perceptions and is an objective measure in the planning of rehabilitation interventions [20, 15]. HHIE is a self-assessment hearing impairment tool and is designed to evaluate the effects of hearing loss on the emotional and social adjustment of older people.

State Trait Anxiety Inventory (STAI) is an instrument that quantifies the anxiety of adults by focusing on areas that include: caring, tension, fear and nervousness. It is designed to assess anxiety as both emotional state (STAI-S) and personality trait (STAI-T) [21, 22]. HHIE and STAI were performed at the beginning of the study and after a year.

Statistical analysis of the data

For the analysis of sex, education, marital status and life situations a χ^2 test was used and t-test for age analysis. The reliability of the applied scale (HHIE and STAI) as well as the subscales was determined by the Kronbach ά coefficient. Reliability for the HHIE scale is 0.886 (test) and 0.868 (retest), which is good reliability. The reliability of the STAI scale is 0.922 (test) and 0.907 (retest), which is high reliability. Kolmogorov–Smirnov test, nonparametric methods for comparing two samples, enabled the testing of the distribution normality in the research. Mann–Whitney was used to illustrate the results of the HHIE and STAI scale as well as the multivariate logistic regression in order to explore the influence of various factors on the socio-emotional status in people with presbycusis. The level of statistical significance was taken as $p < 0.05$ for all analysis. The data collected were processed using a software package for data processing in social sciences (Statistical Package for the Social Sciences – SPSS, version 22.0).

RESULTS

According to the method of purchasing auditory devices of the group with hearing amplification and correlation with the HHIE and STAI scale scores (as well as their subscales), the statistical significance of the difference was not determined.

Descriptive statistical analysis of the HHIE-S subscale in all subjects indicated that 11.7% of respondents do not have social and situational consequences of hearing disability, 81.6% mild to moderate, while significant social disability is in 6.7% of respondents (Figure 1).

The HHIE-E subscale suggests that without the emotional effects of hearing impairment are in 47.5% of subjects, mild to moderate in 50.8%, while the significant emotional component of hearing impairment is observed in 1.7% of respondents (Figure 2). Low anxiety 1.7% is

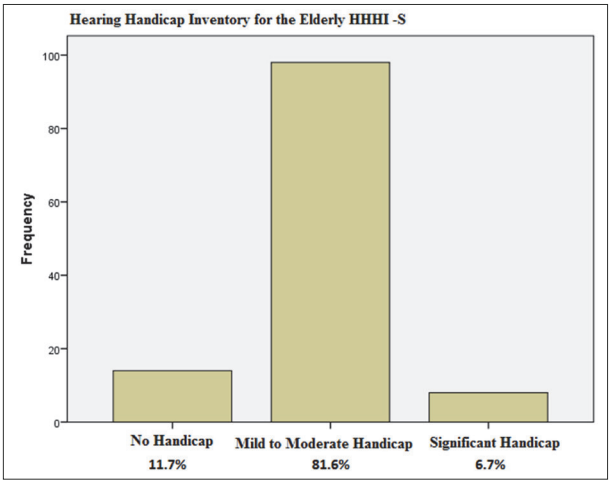

Figure 1. HHIE-S of all respondents

*HHIE-S – hearing handicap inventory for the elderly – social and situational effects;
**no handicap 0 to 8–13% probability of hearing impairment;
***mild to moderate handicap10 to 24–50% probability of hearing impairment;
****significant (severe) handicap 26 to 40–84% probability of hearing impairment

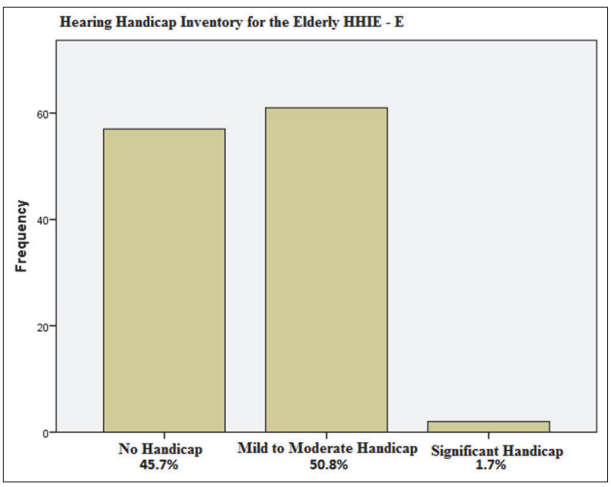

Figure 2. HHIE-E of all respondents

*HHIE-E – hearing handicap inventory for the Elderly - emotional effects;
**no handicap 0 to 8–13% probability of hearing impairment;
***mild to moderate handicap10 to 24–50% probability of hearing impairment;
****significant (severe) handicap 26 to 40–84% probability of hearing impairment

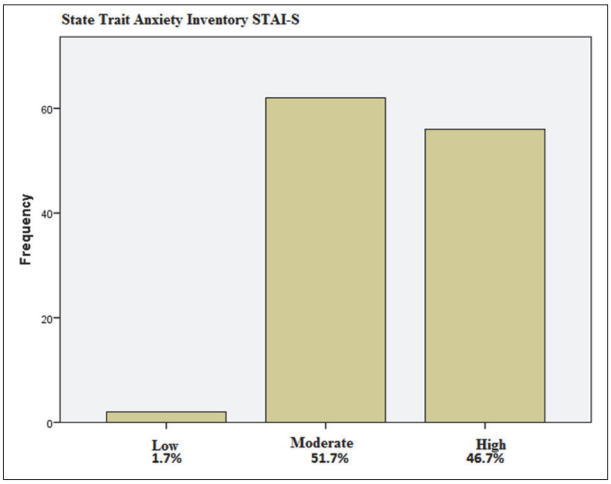

Figure 3. STAI-S of all respondents

*STAI-S – State Trait Anxiety Inventory "state anxiety";
**no or low anxiety (20–37);
***moderate anxiety (38–44);
****high anxiety (45–80)

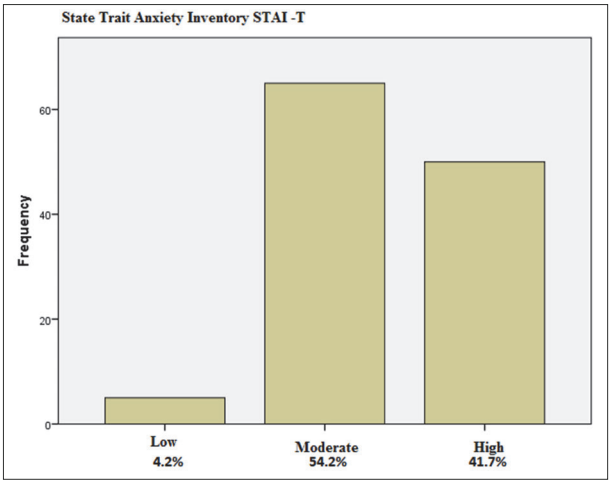

Figure 4. STAI-T of all respondents

*STAI-T – State Trait Anxiety Inventory "trait anxiety";
**no or low anxiety (20–37);
***moderate anxiety (38–44);
****high anxiety (45–80)

observed at STAI - S subscale, moderate 51.7%, while it is high in 46.7% of respondents (Figure 3). The STAI-T subscale showed a low degree of anxiety in 4.2% of subjects, moderate 54.2% and high anxiety in 41.7% of subjects (Figure 4).

For all subjects with presbycusis, using the t-test for dependent samples and using the Pirson coefficient of correlation (r) and Sig ($p < 0.05$), it was found that there was no statistically significant association between the scores of the HHIE and the STAI scale as well as their subscalesd in relation to age of respondents. One-factor analysis of variance has shown that in relation to the educational level, marital status, the time period from the diagnostics to the auditory amplification of the respondents, and in relation to the scores of the HHIE and the STAI scale, there is no statistical significance. The association of the self-assessment of the general health condition and the scores of the HHIE scale and its subscales indicates a statistically significant difference in subjects who considered their health as bad. Anova variance determined a statistically significant difference in the scales of the HHIE scale ($p = 0.004$) and its subscales HHIE-S ($p = 0.012$) and HHIE-E ($p = 0.005$) relative to the subjective assessment of the overall health status (poor, bad, good, very good) of respondents for the category of general health assessment as bad for HHIE ($p = 0.018$), HHIE-S ($p = 0.034$) and HHIE-E ($p = 0.040$).

Assessment of hearing impairment (HHIE scale) and the presence of anxiety (STAI scale) were conducted at the beginning of the study as well as after a year (test/retest). In the period of one year, 16 examinees conducted hearing amplification so that during the repeated study, three groups of respondents were identified:

Group I: hearing amplification / test - YES; retest - YES

In the group of subjects with hearing amplification ($N = 60$) performed with the measures of descriptive statistics (SD 19.33) and determined by good correlation of the test/retest scale ($p = 0.000$), the t-test did not determine the statistical significance of the difference for the total score of the HHIE test/retest ($p = 0.288$).

The statistical significance of the difference in the HHIE-S subscale ($p = 0.004$) was observed, with a lower score of hearing impairment influence on social life component on the retest. (Table 2 and 3).

Table 2. HHIE-S patients with hearing amplification*

Scales	Mean	N	Std. Deviation	Std. Error Mean
HHIE-S test	30.03	60	10.730	1.374
HHIE-S retest	26.98	60	10.749	1.376

* amplification /test - Yes; amplification /retest – Yes
**HHIE-S – hearing handicap inventory for the elderly – social and situational effects

Table 3. HHIE-S patients with hearing amplification*

	Paired Differences		t	df	Sig. (2-tailed)
	95% Confidence Interval of the Difference				
	Upper				
HHIE-S test / retest	5.078		3.006	59	0.004

* amplification /test - Yes; amplification /retest – Yes
** HHIE-S – hearing handicap inventory for the elderly – social and situational effects
*** statistical significance ($p < 0.05$)

A statistically significant difference ($p = 0.330$), as well as the STAI-S ($p = 0.132$) and STAI-T ($p = 0.783$) subscales, were not observed by the two-factor analysis of the variance of the scores on the test and the STAI scale retest.

Group II: hearing amplification / test – NO; retest – YES

In 16 subjects who did not have a hearing aid at the beginning of the study, hearing amplification was performed over the next year, as well as analysis of the HHIE and the STAI scores on the test and retest (Table 4). A statisti-

cally significant difference (p = 0.016) in the respondents after a year was established by a good correlation between the HHIE scale on the test/retest which confirms that the subjective experience of hearing impairment is lower after the period of auditory amplification (Table 5). A statistical significance of the difference (p = 0.009) was observed with the analysis of the HHIE-S subscale scores, with a lower rate of hearing disability at the retest, which indicates a significant impact of hearing amplification on the social component of subjective assessment of hearing impairment (Table 5).The statistical significance of the difference in test and retest in subjects with hearing amplification during the study was also observed on STAI-S subscale score with a lower rate of anxiety at the retest (p = 0.029) (Table 5).

Table 4. Scales of respondents with aural amplification at test and retest*

Scales	Mean	n	Standard Deviation	Standard Error Mean
HHIE test	43.12	16	22.192	5.382
HHIE retest	37.18	16	21.119	5.122
HHIE-S test	26.71	16	12.864	3.120
HHIE-S retest	21.65	16	9.956	2.415
STAI-S test	43.59	16	6.727	1.632
STAI-S retest	40.47	16	5.456	1.323

* amplification /test - No; amplification /retest – Yes
** HHIE – hearing handicap inventory for the elderly
*** HHIE-S – hearing handicap inventory for the elderly – social and situational effects
****STAI-S – State Trait Anxiety Inventory "state anxiety"
*****statistical significance (p < 0.05)

Table 5. Scales of respondents with aural amplification at test and retest*

	Paired Differences		t	df	Sig. (2-tailed)
	95% Confidence Interval of the Difference				
	Upper				
HHIE test/retest	10.599	2.704	15	0.016	
HHIE-S test/retest	8.678	2.963	15	0.009	
STAI-S test/retest	5.868	2.403	15	0.029	

*amplification /test - No; amplification /retest – Yes
** HHIE – hearing handicap inventory for the elderly
*** HHIE-S – hearing handicap inventory for the elderly – social and situational effects
**** STAI-S – State Trait Anxiety Inventory "state anxiety"
*****statistical significance (p < 0.05)

The statistical significance of the difference of the STAI-S subscale (p = 0.029) with a lower rate of anxiety at retest was noticed (Table 4.5), while STAI-T test/retest did not show a statistically significant difference (p = 0.173).

Group III: hearing amplification / test - NO; retest – NO

In a group of subjects who did not have hearing aids at the start of the study (N = 44), as well as after a year, a statistically significant difference (p = 0.002) was observed in relation to the scores of the HHIE test/retest, which showed a greater subjective hearing disability assessment after a year (Table 7).

No statistically significant difference (p = 1.00) was observed in HHIE-S subscale analysis of subjects without hearing amplification, as opposed to the HHIE-E subscale where statistically significant (p = 0.000) was observed on test and retest. Following the descriptive statistics, we can conclude that the emotional component of hearing impairment is more pronounced when measured after a period of one year (Table 6, 7).

Table 6. Scales of respondents without aural amplification at test and retest*

Scales	Mean	n	Standard Deviation	Standard Error Mean
HHIE test	44.29	44	15.733	2.428
HHIE retest	49.29	44	15.735	2.428
HHIE-E test	16.38	44	9.205	1.420
HHIE-E retest	21.38	44	9.239	1.426
STAI test	85.43	44	13.012	2.008
STAI retest	90.14	44	12.417	1.916
STAI-S test	43.57	44	6.145	0.948
STAI-S retest	45.83	44	5.938	0.916
STAI-T test	41.86	44	7.700	1.188
STAI-T retest	44.31	44	7.192	1.110

* amplification /test - No; amplification /retest – No
** HHIE – hearing handicap inventory for the elderly
*** HHIE-E – hearing handicap inventory for the elderly - emotional effects
****STAI – State Trait Anxiety Inventory
*****STAI-S – State Trait Anxiety Inventory "state anxiety"
******STAI-T – State Trait Anxiety Inventory "trait anxiety"

Table 7. Scales of respondents without aural amplification at test and retest*

	Paired Differences		t	df	Sig. (2-tailed)
	95% Confidence Interval of the Difference				
	Upper				
HHIE test/retest	-1.888	-3.244	43	0.002	
HHIE – E test/retest	-3.188	-5.573	43	0.000	
STAI test/retest	-2.237	-3.844	43	0.000	
STAI – S test/retest	-1.046	-3.757	43	0.001	
STAI – T test/retest	-1.010	-3.434	43	0.001	

* amplification /test - No; amplification /retest – No
** HHIE – hearing handicap inventory for the elderly
*** HHIE-E – hearing handicap inventory for the elderly – emotional effects
****STAI – State Trait Anxiety Inventory
*****STAI-S – State Trait Anxiety Inventory "state anxiety"
******STAI-T – State Trait Anxiety Inventory "trait anxiety"
*******statistical significance (p < 0.05)

A statistically significant difference (p = 0.000) was observed with the analysis of STAI scale scores on the test and retest in patients with no hearing amplification, and following the descriptive statistics we can conclude that the anxiety feeling is more pronounced after one year. The statistical significance of the difference (p = 0.001) on the test and retest was observed in the STAI-S subscale, with a more pronounced anxiety feeling as the current state after one year and the STAI-T subscale (p = 0.001) with a greater rate of anxiety at the retest (Table 6, 7).

DISCUSSION

Audiological treatment of patients requires the use of valid scales for assessment of hearing impairment, with the aim of planning the rehabilitation of hearing [23].

By analysis of hearing impairment in correlation with assessment of hearing disability and sense of handicap (HHIE at the beginning of the study and after a year), it is noticed that higher level of subjective hearing disability assesment was in group of patients who did not carry hearing aid from the beginning to the end of the study ($p = 0.002$). Our research is in relation to literature regarding hearing impairment and anxiety assessment [24, 25].

The analysis of the HHIE (S and E) scores is in accordance with research data [24, 25] and indicates that the majority of respondents (81.6%) with mild to moderate degree of hearing impairment have social and situational effects of hearing impairment, while the emotional component of hearing impairment in mild to moderate degree is present in 50.8% of subjects. The emotional-social experience of hearing impairment refers to the quality, type and frequency of social interactions, as well as to indicators of emotional status that are probably conditioned by inability to understand speech and establish communication. Research shows that when hearing loss is increased to a moderate level, anxiety is increased. Examination of anxiety as a possible condition in people with presbycusis was determined by STAI-S and T scale. Assessment of the presence of anxiety in the group of subjects with no hearing amplification noted more pronounced anxiety after one year ($p = 0.01$), which is in accordance with the representation of other researchers [26, 27]. Hearing disability has a significant share in assessing the overall health status as poor for HHIE ($p = 0.018$); HHIE-S ($p = 0.034$); HHIE-E ($p = 0.040$), which is significant in the planning of rehabilitation treatment.

By comparing the average of the score and determining the statistically significant difference in the score HHIE and STAI scales at test and retest is a good indicator of the effects of auditory rehabilitation. This is confirmed by the statistical significance of the test/retest scores in HHIE ($p = 0.016$), HHIE-S ($p = 0.09$) and STAI-S ($p = 0.029$) of respondents who started aural amplification over a period of one year. The data are consistent with other researches and indicate the importance of hearing amplification in reducing the sense of disability, impotence, fear, and improvement of communication, emotional and social life [27]. The statistically significant difference in the HHI test/retest scores ($p = 0.002$), HHIE-E ($p = 0.000$), STAI ($p = 0.000$), STAI-S ($p = 0.001$) and STAI-T ($p = 0.001$) in which the amplification is not conducted indicates that hearing deficit significantly affects the psychosocial life, leading to to an even greater isolation every day, a permanent state of anxiety with a decrease in mental and cognitive abilities.

The process of auditory rehabilitation gives individuals an active role in their lives, which increases self-esteem and well-being [28, 29, 30].

CONCLUSION

Hearing amplification in persons with presbycusis influences the improvement of communication, reduction of subjective assessment of hearing disability and anxiety.

Questionnaires for self-evaluation of hearing disability and anxiety are useful for assessing emotional and social/situational consequences and it is necessary to use them in clinical practice, during audiological examination, first interview, counseling, qualification and evaluation of hearing rehabilitation program effectiveness. Proper approach to audiological rehabilitation of people with presbycusis is the right path in improving life quality and process of humane aging.

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Ефекти слушне амплификације на субјективну процену слушне онеспособљености и анксиозност код особа са пресбиакузијом

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САЖЕТАК

Увод/Циљ Пресбиакузија, старачка наглувост, јесте прогресивни, билатерални сензоринеурални губитак слуха који карактерише смањена осетљивост слуха и разумевања говора у бучној средини, чиме нарушава комуникацију и значајно утиче на испољавање анксиозности.

Циљ рада је био испитати утицај слушне амплификације на испољавање слушне онеспособљености и анксиозности код особа са пресбиакузијом.

Методе Узорак су чинила 120 испитаника оба пола, старости 47–85 година са пресбиакузијом, 60 испитаника са слушном амплификацијом и 60 без спроведене амплификације. У истраживању су коришћене стандардизоване скале *Hearing Handicap Inventory for the Elderly* и *Spielberger State Trait Anxiety Inventory* за процену присуства анксиозности.

Резултати Код испитаника са слушном амплификацијом тест/ретест нема статистичке значајности у резултатима скала и подскала *STAI* и *HHIE*, сем *HHIE-S* ($p = 0,004$) са мањим резултатом на ретесту. Код испитаника код којих је током године спроведена слушна амплификација запажена је статистички значајна разлика у *HHIE* ($p = 0,016$), *HHIE-S* ($p = 0,004$) и *STAI-S* ($p = 0,029$), што говори о повољном утицају слушне амплификације. У групи без слушне амплификације запажена је статистичка значајност у односу на резултате *HHIE* ($p = 0,002$), *HHIE-E* ($p = 0,000$), *STAI* ($p = 0,000$), *STAI-S* ($p = 0,001$) и *STAI-T* ($p = 0,001$) и запажено је да су анксиозност, губитак емоционалних контаката и израженији степен слушне онеспособљености последица неспроведене слушне рехабилитације.

Закључак У аудиолошку праксу би требало увести тестове за процену слушне онеспособљености и анксиозности у циљу очувања здравља у каснијем животном добу.

Кључне речи: пресбиакузија; анксиозност; слушна онеспособљеност; социјална изолација

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Cost/effectiveness of aripiprazole vs. olanzapine in the long-term treatment of schizophrenia

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SUMMARY

Introduction/Objective Although effectiveness of atypical antipsychotics in patients with schizophrenia is mostly similar, there are significant differences in adverse effects rate and treatment costs, making comparison of their cost/effectiveness ratios essential for optimal drug choice. The aim of this study was to compare cost/effectiveness of aripiprazole and olanzapine in long-term treatment of schizophrenia.

Methods A four-state, three-month cycle Markov model was built to compare aripiprazole and olanzapine. The model assumed that patients who relapse on treatment with both aripiprazole and olanzapine are further treated with clozapine. The perspective of the National Health Insurance Fund was chosen, and the period covered by the model was 10 years. The model results were obtained after Monte Carlo microsimulation of a sample with 1,000 virtual patients. Both multiple one-way and probabilistic sensitivity analysis was made.

Results After base-case analysis aripiprazole was dominated by olanzapine, as net monetary benefit was negative (-390,341.96 ± 29,131.53 RSD) and incremental cost/effectiveness ratio (ICER) was above the willingness-to-pay line of one Serbian gross domestic product per capita per quality-adjusted life year (QALY) gained. Multiple one-way and probabilistic sensitivity analysis confirmed results of the base case simulation.

Conclusion Olanzapine has more beneficial cost/effectiveness ratio than aripiprazole for long-term treatment of schizophrenia in Serbian milieu.

Keywords: aripiprazole; olanzapine; cost/effectiveness; Markov model

INTRODUCTION

Schizophrenia is a hard, chronic, and debilitating disease, responsible for the health problems in about 1% of the world's adult pop0ulation, i.e. 24 million people around the world suffer from it [1]. The treatment of the people suffering from schizophrenia is accompanied with high percentage of relapse and rehospitalization, since patients are largely unwilling to take the prescribed medicine. Relapse, characterized by acute psychotic deterioration, has serious consequences. Apart from the risk of the person expressing behaviour dangerous for themselves or for others, endangering their personal relationships, their education or their employment status, relapse also leads to rehospitalizations, which significantly increases treatment cost. According to various studies, from 20 to more than 90% of the patients with the first episode of schizophrenia are relapsed within two years after being released from a hospital [2, 3, 4]. The therapy using antipsychotics is an important strategy in a fight against relapse. Atypical antipsychotics, compared to the old, typical ones, represent an important step forward in the treatment of schizophrenia in terms of a better profile of undesired effects, superior tolerance, and a higher level of patient compliance [5].

Olanzapine represents an atypical antipsychotic and an antagonist of dopamine D2 and serotonin 5HT2A receptors. This drug was approved for the treatment of schizophrenia, mania, depression caused by bipolar disorder, as well as for the treatment of therapy-resistant depression. Aripiprazole is an example of an atypical antipsychotic and a partial agonist of dopamine D2 receptors. FDA has approved the usage of this medicine for the treatment of schizophrenia and mania, as well as, for the treatment of some psychiatric disorders in children and adolescents. Olanzapine is an antipsychotic sedative, which often leads to increase in both body weight and cardiometabolic risk. On the other hand, aripiprazole is not a sedative, it leads to almost no increase in either body weight or cardiometabolic risk, and it does not cause the appearance of metabolic syndrome (insulin resistance, dyslipidemia, increased level of triglycerides), but in some patients it could cause a slight agitation, akathisia or problems with impulse control. As far as the efficiency of these two antipsychotics is concerned, some researches have shown that there were no differences, while others favored olanzapine [6].

If we take into consideration the limited efficiency of antipsychotics, which is often closely related to the treatment termination, relapses,

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and rehospitalization, and thus, increased treatment costs, it is necessary to evaluate the cost/effectiveness profile of antipsychotics to make an adequate choice of antipsychotics for the treatment of schizophrenia while being aware of the health system financial reality. Moreover, pharmacoeconomic analyses represent an important parameter for the evaluating introduction of new antipsychotic on the market, with the aim of choosing a therapeutic option adapted to the needs of a patient, with superior tolerance and better compliance. So far, there have not been any cost/effectiveness or cost/utility studies that would compare olanzapine and aripiprazole (two atypical antipsychotics currently highly utilized for treatment of schizophrenia) in the health and economic milieu of the countries of Southeast Europe.

The aim of our study was to compare cost/effectiveness of aripiprazole and olanzapine for long-term treatment of patients with schizophrenia.

METHODS

Our study is Markov model-based economic evaluation of aripiprazole in comparison to olanzapine for long-term treatment of patients with schizophrenia. Markov model owes its name to Andrey Andreyevich Markov (1856–1922), a Russian mathematician who first described chronic processes (like schizophrenia) through a chain of interconnected conditions. A patient transits from one state to the next according to probabilities observed from either clinical trials or observational studies. The base case population are adult patients of both sexes residing in Serbia who are in the second episode schizophrenia (of any type), and are about to receive for the second-line treatment with oral antipsychotics. Both aripiprazole and olanzapine received approved indication for the population chosen: treatment of schizophrenia in adults and in adolescents aged 15 and older. The setting for the analysis was healthcare system of the Republic of Serbia, which consists of state-owned health care facilities, and is funded by the National Health Insurance Fund (NHIF), based on the obligatory health insurance contributions from all employed adults in Serbia. Prices of drugs and health care services are controlled by NHIF and the Government of the Republic of Serbia.

The perspective for this economic analysis was that of the NHIF, and only direct medical costs were taken into account. Aripiprazole was compared with olanzapine because both drugs belong to the same pharmacotherapeutic class (atypical antipsychotics), and are alternatively prescribed for treatment of schizophrenia according to current guidelines. Aripiprazole is taken orally, 15 mg once a day, and olanzapine 5–20 mg once a day, depending on the patient's response. The period covered by the model in the study was 10 years, as it was maximal period for which earlier cohort studies reported results [7]. Costs and outcomes were discounted with annual rate of 3%, as this was the value of Referent annual interest rate of the National Bank of Serbia [8]. The main outcome of the study was the quality-adjusted life years gained, what is common for cost/utility studies. Estimates of the effectiveness of aripiprazole and olanzapine were synthesis-based, taken from meta-analyses of systematic reviews if available, or summated from available controlled clinical trials reports, which satisfied quality standards of evidence-based medicine. Estimates of costs of health states in the model (including medication costs, health services costs and other direct medical costs) were based on published data about health care resources utilization, which were multiplied by unit costs of drugs, services and materials, set by the NHIF through its legal acts or when unavailable, taken from producers [9, 10]. The dates of estimated resource quantities depended on the published studies dates, but as a rule, the most recent studies were favored; the unit costs were taken for the year 2018. All costs were reported in Serbian dinars (RSD).

This study was done in accord with standards of the institutional Committee on Ethics.

Markov chain model was used since schizophrenia with its relapses is a chronic condition, with clearly separable health states. In total, five health states were chosen:

1. remission without adverse effects;
2. remission with adverse effects;
3. relapse;
4. second episode in spite of continuous use of the first line antipsychotics, which can be present only in the first cycle of the model, later on, only relapse is possible;
5. death, according to descriptions of the natural course of the disease, since the duration of one cycle was three months (the whole model had 40 cycles), since changes of the chosen health states fitted well in this timeframe [11].

The model is presented in the Figure 1, with health states and possible transitions. Half-cycle correction was used in the model. The model was built using Microsoft Excel 2016, and simulated by Monte Carlo microsimulation run by macros written in Visual Basic by the authors. Both one-way and probabilistic sensitivity analysis (PSA) were made, and the results presented by tornado diagram and comparative table (base case *vs.* PSA), respectively.

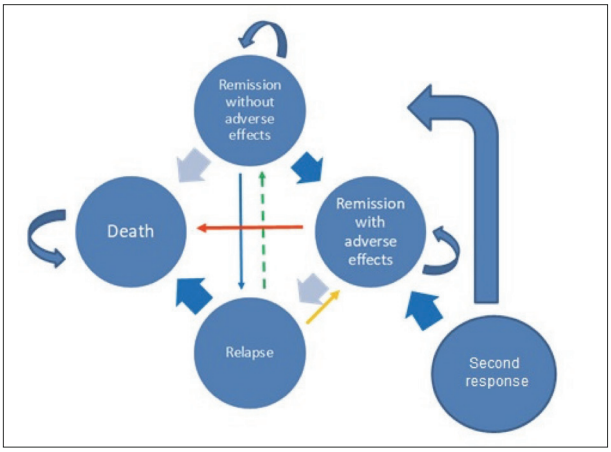

Figure 1. Graphic representation of the Markov model used in the study, with health states and possible transitions

Table 1. Values of input variables for Markov model used in the study, both for the base case and probability sensitivity analysis

Variable	Base-case value	PSA – distribution used and parameter values	Reference
Treatment response rate of second episode of schizophrenia	0.53	Beta distribution α = 53, β = 47	[19]
Three-month probability of relapse in patients taking aripiprazole	0.0473	Beta distribution α = 5, β = 95	[19]
Three-month probability of extrapyramidal syndrome in patients taking aripiprazole	0.0325	Beta distribution α = 3, β = 97	[19]
Three-month probability of metabolic syndrome in patients taking aripiprazole	0.0025	Beta distribution α = 0.25, β = 99.75	[19]
Three-month mortality rate in patients taking aripiprazole	0.0088	Beta distribution α = 0.88, β = 99.12	[20]
Three-month probability of treatment response with clozapine	0.401	Beta distribution α = 40.1, β = 59.9	[21]
Three-month probability of extrapyramidal syndrome in patients taking clozapine	0.0368	Beta distribution α = 3.7, β = 96.3	[22]
Three-month probability of metabolic syndrome in patients taking clozapine	0.0049	Beta distribution α = 0.49, β = 99.51	[23]
Three-month probability of neutropenia in patients taking clozapine	0.0021	Beta distribution α = 0.21, β = 99.79	[23]
Three-month mortality rate in patients taking olanzapine or clozapine	0.004	Beta distribution α = 0.4, β = 99.6	[20]
Utility of schizophrenia remission	0.919	Beta distribution α = 92, β = 8	[24]
Utility of schizophrenia relapse	0.604	Beta distribution α = 60.4, β = 39.6	[24]
Utility decrease due to metabolic syndrome	0.132	Beta distribution α = 13.2, β = 86.8	[24]
Utility decrease due to extrapyramidal syndrome	0.256	Beta distribution α = 25.6, β = 74.4	[24]
Costs of hospitalization	52,465.28 RSD	Gamma distribution α = 16, β = 3279.08	[25]
Costs of daily treatment with olanzapine (5–20 mg daily)	25–122 RSD	Gamma distribution α = 16, β = 5.87	[26]
Costs of three-months treatment of stable schizophrenia	5,693.14 RSD	Gamma distribution α = 16, β = 335.82	[10, 25]
Costs treating relapse of schizophrenia for three months	11,142.43 RSD	Gamma distribution α = 16, β = 696.40	[10, 25]
Costs of daily therapy with aripiprazole (15 mg)	54.68 RSD	Gamma distribution α = 16, β = 3.42	[27]
Costs of daily therapy with clozapine (200–400 mg)	35–70 RSD	Gamma distribution α = 16, β = 3.25	[28]
Costs of treating neutropenia	53,000.99 RSD	Gamma distribution α = 16, β = 3.312.56	[29]
Three-month relapse rate of schizophrenia with olanzapine	2.28%	Beta distribution α = 2, β = 98	[30]
Costs of one day of hospitalization at general ward	1,545.40 RSD	Administratively regulated	[10]
Costs of the first visit to a specialist	284.01 RSD	Administratively regulated	[10]
Costs of the first visit to a general practitioner	356.44 RSD	Administratively regulated	[10]
Cost of repeated visit to a specialist	186.98 RSD	Administratively regulated	[10]
Costs of repeated visit to a general practitioner	259.49 RSD	Administratively regulated	[10]
Costs of taking blood sample	105.33 RSD	Administratively regulated	[10]
Blood count – price	287.95 RSD	Administratively regulated	[10]
Creatinine level in serum – price	235.15 RSD	Administratively regulated	[10]
AST or ALT level in serum – price	229.15 RSD	Administratively regulated	[10]
ECG – price	600.00 RSD	Administratively regulated	[10]

PSA – probabilistic sensitivity analysis; ECG – electrocardiography; AST – aspartate transaminase; ALT – alanine transaminase

RESULTS

Base case

Values of input parameters for Markov model used in the study, both for the base case and probability sensitivity analysis, are shown in the Table 1. Base case Monte Carlo microsimulation for 1,000 virtual patients treated by aripiprazole gave the following results:

1. average cost per patient for 10 years was 428,082.91 ± 4,755.66 RSD (99% CI);
2. average number of quality-adjusted life years (QALYs) gained 6.82 ± 0.04.

Based on the same simulation, for patients treated by olanzapine:

1. average cost per patient for 10 years was 426,213.49 ± 4,186.63 RSD (99% CI);
2. average number of QALYs gained 7.43 ± 0.03.

When aripiprazole was compared with olanzapine, incremental cost/effectiveness ratio (ICER) per one more QALY gained was131,417.69 ± 127,548.34 RSD (99% CI), while monetary net benefit was negative, -390,341.96 ± 29,131.53 RSD (99% CI). Figure 2 presents ICER for each virtual patient separately, and Figure 3 presents the average ICER for the whole cohort, with 99%-confidence interval. X- and y-axes of both figures measure difference in effects and difference in costs, respectively, of the two therapeutic alternatives, aripiprazole and olanzapine. In order to be cost/effective in comparison with olanzapine, virtual patients on these graphs should be in the lower-right quadrant or below the lines shown on the graphs that pass through origin of the coordinates (axes). From Figure 3, one may learn that the majority of ICER values is above the lines that reflect RFHI's willingness to pay for one more QALY gained with new drug (aripiprazole) in comparison with the old one (olanzapine). The lines presented are lambda 1 (one GDP per capita per QALY gained), lambda 2 (three GDP per capita per QALY gained) and lambda 3 (nine GDP per capita per QALY gained).

Acceptability curve

The acceptability curve shows dependence of probability that aripiprazole is cost/effective (in comparison with olanzapine) on amount that NHIF is willing to pay for one more QALY gained with aripiprazole (again in comparison with olanzapine). If willingness of NHIF to pay for one more QALY gained ranges from 200,000 RSD to 20,000,000 RSD, changes in percentage of virtual patients from Monte Carlo simulation who fall below current willingness to pay line in ICER diagram (i.e. the probability that aripiprazole is cost/effective in comparison to olanzapine) could be read from the acceptability curve. From Figure 4 one may see that the probability of aripiprazole being cost/effective is about 13% only if the NHIF is willing to pay one to nine GDPs per capita for a QALY gained (634,156 RSD).

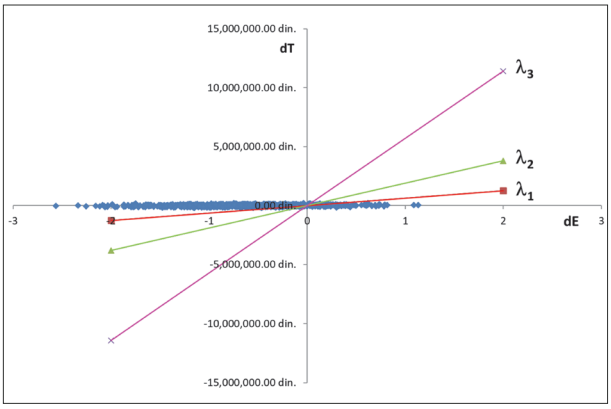

Figure 2. Base case incremental cost/effectiveness ratio for each virtual patient in the model: long-term treatment of schizophrenia with aripiprazole vs. olanzapine; the effect is on the scale marked as number of quality-adjusted life years gained

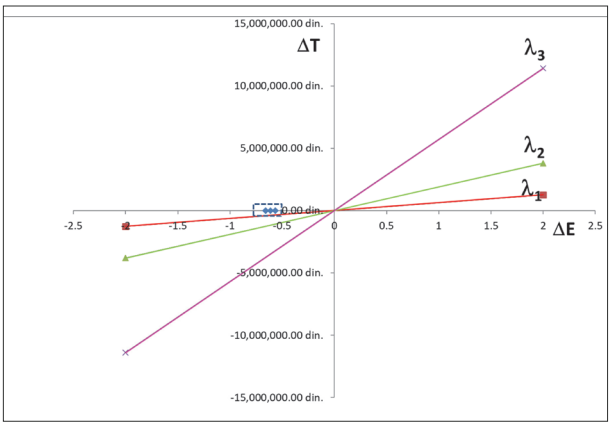

Figure 3. Base case average incremental cost/effectiveness ratio with 99% confidence intervals: long-term treatment of schizophrenia with aripiprazole vs. olanzapine; the effect is on the scale marked as number of quality-adjusted life years gained

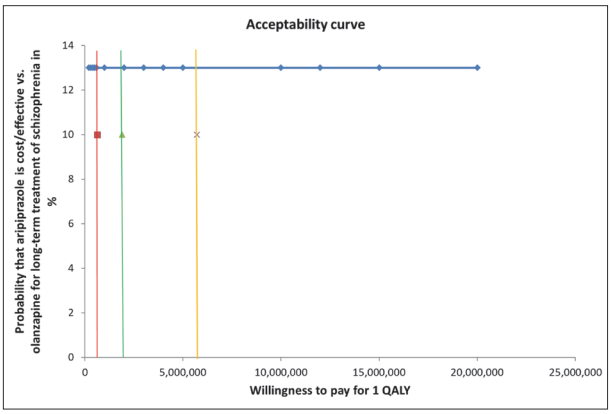

Figure 4. Acceptability curve

Red vertical line – one gross domestic product per capita for a quality-adjusted life year gained; green vertical line – three gross domestic products per capita for a quality-adjusted life year gained; yellow vertical line – nine gross domestic products per capita for a quality-adjusted life year gained
QALY – quality-adjusted life year

One-way sensitivity analysis

Within the framework of one-way sensitivity analysis values of input variables were varied ± 50% one by one, and net monetary benefit calculated for each of the varied values. Results of the analysis are shown only for four the most influential variables (for the sake of clarity) in the tornado diagram (Figure 5). One-way sensitivity analysis showed that varying values of input variables did not change results of the cost/utility analysis, since net monetary benefit remained negative even with the extreme input values.

Probabilistic sensitivity analysis

For the PSA, values of the input variables were replaced with distributions, beta distribution being used for rate and utility variables, and gamma distribution for cost variables. After Monte Carlo microsimulation, more dispersed values of output variables were recorded, and their means with 99% confidence intervals are presented in Table 2. With supra-threshold value of ICER and negative value of net monetary benefit, the PSA confirmed that aripiprazole was not cost/effective when compared with olanzapine for long-term treatment of schizophrenia.

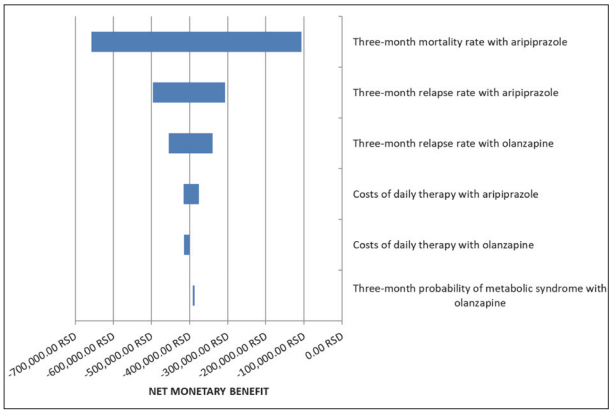

Figure 5. Tornado diagram

Table 2. Values of output variables before and after probabilistic sensitivity analysis (mean ± 99% CI)

Output variables	Base case	PSA
Costs of aripiprazole treatment per patient	428,082.91 ± 4,755.66 RSD	435,072.79 ± 11,077.85 RSD
Costs of olanzapine treatment per patient	426,213.49 ± 4,186.63 RSD	430,481.08 ± 9,273.21 RSD
QALYs gained with aripiprazole	6.82 ± 0.04	6.95 ± 0.08
QALYs gained with olanzapine	7.43 ± 0.03	7.51 ± 0.07
ICER	131,417.69 ± 127,548.34 RSD	102,750.08 ± 176,564.03 RSD
Net monetary benefit	-390,341.96 ± 29,131.53 RSD	-359,894.06 ± 58,321.83 RSD

PSA – probabilistic sensitivity analysis; QALYs – quality-adjusted life years; ICER – incremental cost/effectiveness ratio

DISCUSSION

The efficiency of olanzapine and aripiprazole in the treatment of schizophrenia has already been tested and proved in randomized controlled clinical trials. However, although both of them belong to the group of atypical antipsychotics, they have different pharmacoeconomic profiles that need to be compared in every single socioeconomic environment individually. There have been numerous cost/effectiveness analyses done worldwide with the aim of comparing olanzapine and aripiprazole, but none of them was made in the Southeast European settings. According to our model, after base-case analysis, aripiprazole was dominated by olanzapine, as net monetary benefit was negative and incremental cost/effectiveness ratio (ICER) was above the willingness-to-pay line of one Serbian GDP per capita per QALY gained. The results of our model show that olanzapine has more beneficial cost/effectiveness ratio than aripiprazole for long-term treatment of schizophrenia in Serbian milieu. Multiple one-way and probabilistic sensitivity analysis confirmed results of the base case simulation.

According to the study by Furiak et al. [12], in the United States, where olanzapine has been compared with other oral antipsychotics in the treatment of schizophrenia, it was proved to be the most cost-effective treatment strategy, not only in relation to aripiprazole, but to risperidone, quetiapine and ziprasidone as well. In another model done in the United States, olanzapine was also the dominant cost/effective choice in the treatment of schizophrenia, due to its higher efficiency and lower cost of treatment compared to aripiprazole [13]. Our results are in accordance with the conclusion of the study from Singapore, where olanzapine also proved to be more cost/effective antipsychotic than aripiprazole [14]. The same conclusion about the superiority of a pharmacoeconomic profile of olanzapine was reached in the study by Obradovic et al [15], the focus of which was compliance rate, rehospitalization rate for compliant and non-compliant patients, duration and frequency of hospitalization, and adverse event rate.

On the contrary, economic evaluation of aripiprazole and olanzapine in Italy has shown medical and economic advantage of aripiprazole over olanzapine, in terms of reduced incidence of metabolic syndrome and diabetes, and lower treatment costs [16]. Moreover, according to a cost/effectiveness analysis done in Sweden, with the patients treated with aripiprazole, there was a significantly lower risk of the development of metabolic syndrome, diabetes of cardiovascular morbidity and mortality, which confirmed that there is a superiority of the pharmacoeconomic profile of aripiprazole over olanzapine [17]. In the study with adolescents (15–17-year-olds) in England, aripiprazole was shown to be cost/effective treatment option compared to olanzapine [18].

The differences in cost/effectiveness estimate of aripiprazole *vs.* olanzapine may probably be attributed to different methods of cost estimation (some of the studies did not take into account all costs incurred by adverse effects of the drugs compared), to variations in socioeconomic milieus, and to variations in adherence rate, as well. In addition,

period covered by the models used in these studies varied, which could support the thesis that in some of these studies period covered by the model was not long enough to capture the long term outcomes in the treatment of schizophrenia. In general, the studies did not account for patient heterogeneity, which implies that different subpopulations of patients were used in various studies.

Our study also has certain limitations, which are in the first place related to source of the cost data. Since we lacked data from patient files and database of the NHIF, the costs of health states were estimated from published resource utilization studies, multiplying presented figures with unit costs set by the NHIF. Estimate of costs based on such method is certainly less reliable than from actual data, but we tried to offset this by wide distributions of cost estimates used in the PSA. Another limitation was certainly imposed by pooling all types of schizophrenia into one population, while there could have been important differences which became obtunded, i.e. some schizophrenia types could have been more responsive to one than another drug, and *vice versa*.

CONCLUSION

According to this study, olanzapine has more beneficial cost/effectiveness ratio than aripiprazole in long-term treatment of schizophrenia in the Serbian milieu. Treatment with aripiprazole is less effective and somewhat more expensive than treatment with olanzapine, therefore probability of being cost/effective in comparison to olanzapine is less than 15%. Sensitivity analysis shows that variation of input parameters over full range of possible values does not improve estimate of aripiprazole's cost/effectiveness.

ACKNOWLEDGEMENT

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The authors comply with International Committee of Medical Journal Editors recommendations.

Conflict of interest: None declared.

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Однос трошкова и ефикасности арипипразола насупрот оланзапину код дуготрајног лечења схизофреније

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САЖЕТАК

Увод/Циљ Мада је ефикасност атипичних антипсихотика код болесника који болују од схизофреније углавном слична, постоје значајне разлике код стопе нежељених реакција и трошкова лечења, што чини поређење односа њихових трошкова и ефикасности кључним за најбољи избор лека. Циљ ове студије је био да се упореде трошак и ефекти арипипразола и оланзапина код дуготрајног лечења схизофреније.

Методе Урађен је модел по Маркову са тромесечним циклусима и четири стања, да би се упоредили арипипразол и оланзапин. Модел је подразумевао да болесници код којих дође до погоршања здравственог стања после употребе или арипипразола или оланзапина буду даље лечени клозапином. Изабран је став Републичког фонда за здравствено осигурање, а временски оквир је био десет година. Резултати модела су добијени после микросимулације Монте Карло на узорку од 1000 виртуелних болесника. Урађене су мултипла једносмерна и пробабилистичка анализа сензитивности.

Резултати После анализе случајева оланзапин је био доминантан у односу на арипипразол, јер је нето монетарна корист била негативна (-390,341.96 ± 29,131.53 РСД), а прираштај односа исплативости изнад линије спремности да се плати за једну годину кориговану за квалитет у односу на српски бруто домаћи производ по глави становника. Мултипла једносмерна и пробабилистичка анализа сензитивности су потврдиле резултате симулације.

Закључак Дугорочна терапија болесника са схизофренијом у Србији помоћу оланзапина је јефтинија и нешто делотворнија од терапије арипипразолом.

Кључне речи: арипипразол; оланзапин; трошак/ефикасност анализа; Марковљев модел

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Unusual anatomy of permanent maxillary and mandibular molars – case reports

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SUMMARY
Introduction The anatomy and morphology of the roots and root canal systems of multi-rooted teeth, especially the molars, shows numerous variations. Preoperative radiography, in particular cone-beam computed tomography (CBCT), has exceptional significance in detecting anatomical variations and unusual root canal morphologies, which are extremely important to be familiar with in order to undertake successful endodontic therapy and minimize procedural errors.
Outline of cases This report presents cases of incidental diagnosis of an unusual root anatomy and root canal morphology of permanent molars in two patients. Diagnosis in the first case was made using orthopantomography and confirmed after extraction therapy. The second case reviled unusual root anatomy and root canal morphology of the permanent molar after preoperative CBCT imaging.
Conclusion Anatomical and morphological variations of roots and root canal systems can occur in any tooth. Clinicians should expect these variations, which should be thoroughly investigated when considering dental treatment.
Keywords: single-rooted molars; unusual anatomy; dental radiography

INTRODUCTION

It is known that there are numerous variations in the root and root canal anatomy and morphology of multi-rooted teeth, especially molars [1]. Knowing possible anatomical and morphological variations is extremely important for successful endodontic therapy, but also for the extraction of such teeth [2]. Permanent maxillary molars are commonly described as a group of teeth with three roots, two buccal and one palatal, while permanent mandibular molars have usually two roots, mesial and distal [3, 4]. With regard to the number of root canals, in each of the three roots of the maxillary molar there is generally one canal, but it is common to have two canals in the bucco-mesial root when there are four canals in total [5]. Mandibular molars usually have three canals, two of which are located in the mesial root, but often two canals can also be found in the distal root [6, 7].

Anatomical and morphological variations and rare abnormalities of roots and root canal systems had been shown in previous studies [1, 2, 3]. The literature shows that maxillary molars can present from the simplest to the extensively complicated root and root canal anatomy and morphology [8–14]. Not much difference was found for mandibular molars [6, 15–19]. The key for successful endodontic therapy is in proper locating, chemo-mechanical cleansing and obturation of all canals, so in addition to knowing the complicated canal morphology, it is necessary to be familiar with the simple canal morphology in order to reduce the possibility of procedural errors.

Dental radiography is of the great importance for diagnosis, administration of therapy, and post-operative monitoring. Using preoperative radiography, it is possible to estimate the number and morphology of the roots and the root canal systems [13]. Introduction of cone-beam computed tomography (CBCT) facilitated the finding of anatomical and morphological variations in everyday dental practice [19].

Despite the numerous studies of the anatomy and morphology of maxillary and mandibular molars, there is a small number of those which describe the presence of single-rooted molars.

CASE REPORTS

Cases reported in this study were acquired after signing the written consent by the patients. The study was approved by the Ethics Committee of the Faculty of Medical Sciences, University of Kragujevac, Serbia (No: 01-15837), and was conducted in compliance with the Helsinki Declaration and Guidelines for Good Clinical Practice.

Patient 1

The 51-year-old female patient reported for a dental appointment at the Department of Dentistry, Faculty of Medical Sciences, University of Kragujevac, Serbia, due to prosthetic rehabilitation. The medical history of the patient was not significant for dental diagnosis and therapy.

During the clinical examination, it was noticed that the following teeth were missing: 15,

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26, 36, 35, 46, and 47. The presence of a gangrenous root of tooth 17 was determined, as well as numerous caries lesions. Oral hygiene was inadequate. Preoperative orthopantomographic examination revealed that all the present teeth were single-rooted, including both maxillary and mandibular molars (Figure 1). The patient was referred for further dental care.

The terminal stage of periodontal disease was diagnosed for the following teeth: 16, 14, 11, 25, 27, 37, and 31. These teeth, as well as tooth 17, were indicated for extraction. After the extraction, the teeth were photographed, and it was confirmed that the extracted molars were single-rooted (Figure 2). Further conservative and prosthetic rehabilitation of the patient followed.

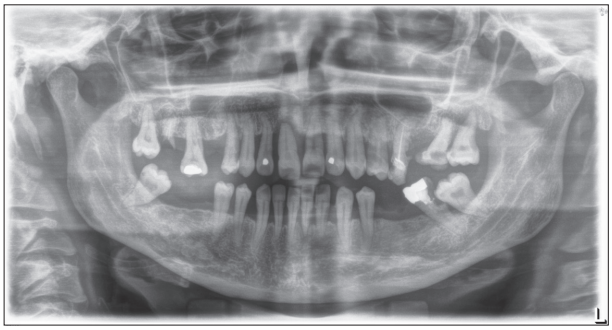

Figure 1. Orthopantomographic image of Patient 1

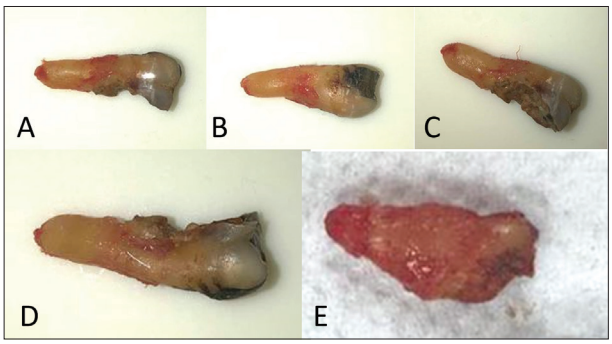

Figure 2. Extracted teeth of Patient 1; A, B, C, D: left permanent mandibular second molar; E: right permanent maxillary second molar

Patient 2

A 49-year-old female patient reported for prosthetic rehabilitation of the mandibular right segment. The patient denied any previous diseases regarding her medical history. The clinical examination revealed the absence of teeth 45, 46, and 47, numerous caries lesions, and inadequate oral hygiene. In order to consider possible implant rehabilitation, the patient was referred to the CBCT preoperative imaging.

The CBCT image revealed that the left maxillary first molar had unusual root and root canal anatomy: one root and one root canal at the transversal, sagittal, and axial cross-sections (Figure 3). The canal was ovally shaped in its entire length and had a larger bucco-lingual than a mesio-distal diameter.

Prior to implant rehabilitation, the patient was referred to further dental care, which included periodontal, restorative, endodontic, and surgical treatment.

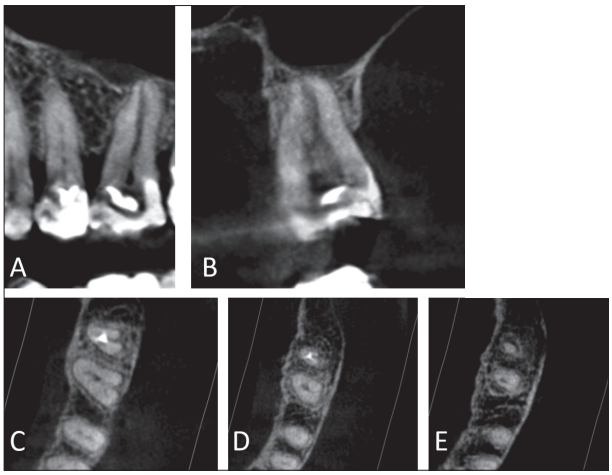

Figure 3. Cone-beam computed tomography images of left permanent maxillary first molar on transversal cross-section (A), sagittal cross-section (B), and axial cross-sections on the coronal (C), medial (D), and apical level (E)

DISCUSSION

Anatomical variations such as fusion, germination, or anomalies in the number of roots can often be diagnosed on the basis of preoperative dental radiography. Although the incidence of root variation is scarce, their presence should not be underestimated, especially if root variations are present in most of the teeth of one patient [20]. Morphological dental anomalies can be localized on a single tooth, on a group of teeth, or in the entire dentition and they are considered to be associated with the disorders of morpho-differentiation or could be attributed to the failure in invagination of Hertwig's epithelial sheath [16].

Variations in the number of roots of the permanent maxillary first molar are described in the literature, mostly regarding the complicated anatomy. The literature shows that single-rooted permanent maxillary first molars, as described in our case report, are a rare finding [20, 21, 22]. Concerning variance, single-rooted maxillary second molars were more often described, in 0.5–5% of cases, which is not negligible [8, 13, 23].

Out of all permanent molars, mandibular second molars show the most variations in the root anatomy and morphology. The presence of single-rooted mandibular second molars was found in 1.3–5.8% [8, 24].

Anatomy and morphology of third molars were also previously investigated, with many morphological variations described. In our first case, orthopantomographic image suggested that the patient had all four third molars with simple anatomy, i.e. single root. This could not be confirmed due to the lack of indications for CBCT imaging or extraction of these teeth. Nevertheless, simple anatomy should be expected, as previous studies showed that the same anatomical variations are often present in most of the teeth of the same group [24].

Previously described cases showed that single-rooted anatomy is often presented with bilateral, contralateral, or ipsilateral symmetry [8, 13, 24]. In our first case, regarding the present teeth, we showed the bilateral and contralateral symmetry in third molars, and ipsilateral symmetry in second molars (teeth 27 and 37).

Unlike the symmetrical appearance of simple anatomy, our second case presented a morphological variation in a single tooth. This result emphasizes the importance of preoperative evaluation of root canal morphology of every individual tooth, as it can facilitate canal identification, prevent the unnecessary removal of a healthy tooth structure, and reduce the incidence of procedural errors.

Anatomical and morphological variations of roots and root canal systems can occur in any tooth. Clinicians should expect these variations when considering dental treatment. Extensive preoperative radiography or utilization of CBCT should be considered during the treatment planning.

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Својеврсна анатомија сталних горњовиличних и доњовиличних кутњака – приказ болесникâ

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САЖЕТАК

Увод Анатомија и морфологија корена и система канала корена вишекорених зуба, нарочито кутњака, показују бројне варијације. Преоперативна радиографија, посебно компјутеризована томографија конусног зрака, има изузетан значај у откривању анатомских варијација и својеврсне морфологије канала корена, чије је познавање изузетно важно за успешну ендодонтску терапију и смањење процедуралних грешака на најмањи број.

Приказ случајева Ова студија показује два случајна налаза својеврсне анатомије корена и морфологије канала корена сталних кутњака два пацијента. У случају првог пацијента дијагноза је постављена коришћењем ортопантомографије и потврђена је после вађења зуба. У другом приказаном случају својеврсна анатомија корена и морфологија канала корена сталног кутњака показане су преоперативним снимком методом компјутеризоване томографије конусног зрака.

Закључак Анатомске и морфолошке варијације корена и система канала корена могу се уочити на свим зубима. Стоматолози би требало да очекују ове варијације, а треба их и детаљно истражити приликом постављања плана терапије.

Кључне речи: једнокорени кутњаци; својеврсна анатомија; дентална радиографија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Severe toxic acute liver injury

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SUMMARY

Introduction Toxic liver injury is becoming greater problem in today´s hepatology. Until today more than 900 drugs, toxins and herbs have been identified that can cause different liver injury. There was no significant research of this problem in Serbia so far.

The aim of this study is to present the patient with severe form of acute hepatitis, whose etiology is exclusively toxic.

Case outline A 23-year-old male, from Belgrade, previously healthy, got sick with signs and symptoms that correlated with acute hepatitis. Biochemical analyses pointed to severe form of acute hepatitis with impending hepatocellular failure. The diagnosis of toxic liver injury was set. It was caused by the use of number substances and supplements: ecstasy, whey protein, branched-chain amino acid (BCAA), creatine, high doses of vitamin D, glutamine, and multivitamin complex. He was treated with infusion, gastroprotective, and substitution therapy. During hospitalization, the patient's symptoms disappeared with gradual normalization of biochemical analyses of the liver. When the patient's condition was satisfying, blind percutaneous liver biopsy was performed, with the following pathohistological findings: lobular hepatitis, with no fibrosis, etiology correlates to toxic. After a month and a half since the disease had begun, the patient fully recovered.

Conclusion Increased number of persons with toxic liver injury is being registered in developed countries worldwide. Similar trend can be noted in Serbia as well. By presenting young previously healthy man with the severe form of toxic acute hepatitis and impending liver failure, we are pointing out the significance of this problem. Multidisciplinary approach is needed to reach the most effective solutions.

Keywords: acute hepatitis; toxic liver injury; toxins; supplements

INTRODUCTION

The liver represents a central metabolic organ included in degradation, metabolism, and excretion of different toxic products. So far, more than 900 drugs, toxins, and herbs were registered that can cause different kinds of liver injury. Toxic damage can affect hepatocytes or biliary tract, and may present with different clinical and biochemical manifestations. Thus, clinical presentation of toxic liver injury can only have asymptomatic elevations in aminotransferase, then as acute hepatitis of different severity, liver failure, chronic hepatitis, acute and chronic cholangitis, micro and macrovesicular steatosis or vascular damage [1, 2, 3].

Toxic liver injury is most commonly caused by drugs (drug induced liver injury – DILI), herbal products (herb induced liver injury – HILI) or other supplements which can be found in drugstores without prescriptions. This natural or synthetic substances are foreign products for the organism and in most cases have to be metabolized in the liver for degradation and excretion. During this process, different hepatotoxic metabolites can appear which can cause liver injury in sensitive people. There are two main mechanisms of toxic liver injury. The first one is direct (intrinsic), dose-depended, which leads to acute hepatocellular necrosis. The effect of these substances is predictable, and it is expected in all people who consume it, with the possibility of reproducibility. The other mechanism is idiosyncratic, due to immune mediated hypersensitivity or metabolic injury, which occurs after some time, up to a year. It is not easy to predict liver damage made in this way, as it occurs only in certain people who have predisposition, and it is not dose-dependent. During metabolization of these substances, many different intermediate products are being created which are binding to cell proteins forming neoantigens that affects the immune system (sensitization) creating toxic effects. In addition, genetically modified metabolic path can lead to creation of intermediate products, which will then have toxic effect [4]. Still, considering the fact that people usually consume different toxic substances at the same time, both mechanisms are included in the liver injury, and they cannot be discussed separately.

In the last couple of years in developed countries, studies have shown a trend of increased usage of supplements, most commonly for the purpose of bodybuilding, losing weight, staying fit or "health promotion." Thus, research conducted in the European countries (Finland, Germany, Italy, Romania, Spain, and the United

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Kingdom) showed that around 20% of people used supplement at least once [5]. Similarly, the data showed that in the USA around $28 billion is spent on supplements every year, while 52% of the general population has been using these products in 1990–2000 [6, 7].

This kind of research has not yet been conducted in Serbia, and only individual cases have emphasized the significance of consuming potentially hepatotoxic substances [8, 9]. On the market in the last couple of years, there has been a greater presence of different kind of supplements (for bodybuilding, tension relief, sleep improvement, sexual dysfunction, menopause, varicose veins, weight loss, etc.) without previously being examined for potential hepatotoxicity. After considering these facts, the aim of this paper is to present a young, healthy patient with severe form of acute hepatitis whose etiology has been proven toxic due to different supplements intake.

CASE REPORT

A 23-year old male, a student from Belgrade, single, with no children, was admitted to the Clinic for Infectious and Tropical diseases, Clinical center of Serbia, due to poor appetite, nausea, vomiting, fatigue, fever (up to 38.5°C) and yellowing of the eyes and skin. Problems started in the beginning of December 2016, four days before admission. Firstly, he was examined at the primary health care center and sent to Clinic for Infectious and Tropical diseases under suspicion of acute hepatitis. On hospital admission, he was conscious, oriented, with no signs of hepatic encephalopathy, no fever, with jaundice, clear skin with no spider nevus or palmar erythema. Liver was palpable two centimeters below the right rib cage, while the spleen was not palpable. The rest of the physical examination was normal. Biochemical analysis was typical for acute hepatitis with signs of severe acute liver injury (SALI): aspartate aminotransferase (AST) 10,606 IU/L, alanine aminotransferase (ALT) 13,862 IU/L, total-value bilirubin (TBil) 63.9 μmol/L, direct bilirubin (DBil) 33.6 μmol/L, gamma-glutamyl transferase (GGT) 120 IU/L, alkaline phosphatase (ALP) 102 IU/L, prothrombin time (PT) 32.4%, international normalized ratio (INR) 2.19. The diagnosis of acute hepatitis was set.

Epidemiological data showed that the patient lived with his parents in comfortable conditions. People he was in contact with did not have similar symptoms, and he did not travel outside of Belgrade in the previous six months. He did not smoke, and he denied the use of alcohol. Concerning psychoactive substances, he occasionally used ecstasy (3, 4 methylenedioxymethamphetamine – MDMA). He denied the use of any other psychoactive substances. He also said that in the last two years he regularly consummated whey protein from the black market, creatine in the last three months, vitamin D in the last three months 1,000 IU daily. He also suggested the use of multivitamins and amino acids in the last three years and omega-3 fatty acids.

In order to determine etiology of acute hepatitis more diagnostic procedures were conducted. Virology tests for primary hepatotropic viruses, like hepatitis A virus (anti-HAV IgM), hepatitis B virus (HBsAg, anti-HBc IgM, HBV DNA), hepatitis C virus (anti-HCV, HCV RNA), hepatitis E virus (anti-HEV IgM) were negative. Tests for infection on potentially hepatotropic viruses, such as Epstein-Barr virus, cytomegalovirus, adenovirus, and herpes simplex virus (IgM-class antibodies measured by the enzyme-linked immunosorbent assay or ELISA) were also negative. Immunological tests for autoimmune diseases were negative and metabolic liver diseases were excluded: Wilson disease (normal copper level in blood and urine, normal level of ceruloplasmin, the absence of Kaiser-Fleischer ring), hemochromatosis (normal blood level of iron, ferritin, and the percent of transferrin saturation), and alpha-1 antitrypsin deficiency. With the repetitive use of abdominal ultrasound of liver, the bile duct obstruction was excluded, while with the help of the color Doppler, vascular diseases of the liver were excluded too.

The diagnosis of severe toxic acute liver injury caused by the consumption of different kinds of substances was established. He was given therapy: glucose 10% infusion, gastroprotective drugs, and due to decreased synthetic liver function, he got infusions of fresh frozen human plasma and vitamin K injection. Since there was a chance of hepatic encephalopathy development, he was given lactulose perorally, and the restriction in daily ingestion of proteins. In the following days, his condition improved gradually. Soon he stopped vomiting, stopped feeling nauseous, and regained normal appetite. Three days after admission, he stopped having fever and abdominal discomfort. Over the course of the treatment, the patient had normal neurological and mental status and he was sleeping well. Laboratory analyses showed gradual decrease of aminotransferases and bilirubin values, with the increase of prothrombin time (Table 1).

After improvement of the patient's condition and his coagulation status, on the 26th hospital day a blind percutaneous, fine-needle-aspiration biopsy was performed. Pathohistological findings showed: portal spaces were the usual size, some of them were infiltrated with lymphocytes. In the liver parenchyma, there were signs of focal necrosis with light cellular and canalicular cholestasis. Inside the sinusoids, there were slightly multiplied Kupffer cells. Protein binding with copper staining was negative, no tumor cell infiltration. Conclusion of the pathologist: it was the case of lobular hepatitis, without fibrosis, with toxic etiology.

After a month of hospital treatment, the patient was discharged in good general health without any symptoms. Two weeks later, which is a month and a half since the beginning of the disease, all biochemical analyses returned to normal. During that visit, he brought to the hospital a list of some of the substances he had been using: whey protein, creatine monohydrate, branched-chain amino acid (BCAA), glutamine, vitamin C, vitamin D, and multivitamin. The last visit was conducted six months later, biochemical analyses were normal, and there were no signs of previous liver injury. This report was done in accord with standards of the institutional Committee on Ethics.

Table 1. Values of biochemical analyses during the course of the disease

Biochemical analyses	On admission to the hospital	After three days of treatment	After 10 days of treatment	After 17 days of treatment	After 25 days of treatment
AST (IU/L)	10,606	5,717	2,023	114	28
ALT (IU/L)	13,862	9,978	7,219	1,821	352
Total-value bilirubin (μmol/L)	63.9	52.9	45.5	23.3	14.9
Direct bilirubin (μmol/L)	33.6	26.7	23.2	9.2	6.2
Prothrombin time (%)	32.4	43.3	59.2	104	96
INR	2.19	1.72	1.34	0.98	1.02

AST – aspartate aminotransferase; ALT – alanine aminotransferase; INR – international normalized ratio

DISCUSSION

Toxic liver injury is becoming an increasingly significant problem nowadays. Researches show that herbal and dietary supplements (HDR) are frequently the cause of liver injury. Thus, the research conducted in the USA, which covered the 2004–2013 period revealed increase in liver injuries due to HDR ranging 7–20% [10]. Similar tendency was noticed in the European countries as well [5]. At the same time, in developed countries toxic etiology represents the most common cause of acute liver failure (ALF). There was a research conducted at the health center in Oregon, where toxic etiology caused ALF in up to 70% of the cases [11]. According to the American and European liver transplant registries, about 3,000 cases in Europe and 2,000 in the United States had liver transplantation due to the toxic liver injury during the 10–12 years period [12]. In the previously mentioned study from the United States, the most significant cause of severe liver injury were non-bodybuilding HDS, and they instigated the need for liver transplantation in 13% of cases, and deaths occurred in 4% of cases that used these products [10]. In the Mediterranean countries, as well as in developing countries (such as Serbia), toxic substances as a cause of ALF comes second, right after virus etiology, particularly HBV infection [13].

Our patient had toxic liver injury caused by ingestion of a great number of different potentially hepatotoxic substances. First of all, there was ecstasy, which is an amphetamine, used as a stimulant that can cause liver necrosis. It is considered that liver injury is the result of metabolized ecstasy into reactive metabolites, largely by the hepatic P450 system (CYP 2D6) which then influences the oxidation-reduction processes in the liver. Clinically it can be manifested differently from the mild damage of liver function, which recovers spontaneously, while ALF that needs liver transplantation. It can also cause liver fibrosis. Severity of liver injury is not in direct correlation with the amount of ingested substance, or with the frequency of intake, which points to idiosyncratic type of reaction. It can also cause fever, which was registered with our patient [14, 15]. He was also using whey protein and creatine, which are known for causing liver injury, especially cholestatic type with expressed jaundice. The exact mechanism of liver injury with these supplements is unknown, especially since it has been shown that whey protein reduces inflammation and portal fibrosis in rats with D-galactosamine-induced hepatitis. Still, studies that analyzed pathohistological findings, came to the conclusion that high doses of these proteins have direct toxic effect, but also prior sensitivity and the role of immune mechanism cannot be excluded [16, 17]. Our patient also used supplement BCAA, which increased their levels (L-leucine, L-valine, L-isoleucine). BCAA is associated with non-alcoholic fatty liver disease and injury, and it is proven that their combination with high fat diet (HFD) in experimental mice leads to increased hepatic apoptosis, and elevated circulation hepatic enzymes [18].

Patient also used high doses of vitamin D. The consequences of this hypervitaminosis are related to calcium metabolism and hypercalcemia, which can be manifested as dehydration, thirst, polyuria, anorexia, nausea, vomiting, constipation, fatigue, bone aches, and muscle cramps. The presence of a receptor for vitamin D in hepatocytes, cholangiocytes, stellate cells, and resident immune cells in the liver was discovered, but it is considered that vitamin D alone cannot cause significant liver injury [19]. Still, our patient used different substances, which lead to liver damage in different mechanisms, so we think that the use of high doses of vitamin D cannot be fully ignored. Our patient was also using glutamine, which was actually a good thing, since it is known that glutamine decreases oxidative stress and inflammatory response in critically ill patients with acute liver injury. In that way, glutamine can improve prognosis of these patients [20]. It is possible that this contributed a speedy recovery of our patient regardless of the clinical presentation of severe liver damage.

Liver damage was manifested as SALI in our patient, with aminotransferase levels over 10,000 IU/L and PT < 40%. There was a possibility that the patient could have developed ALF, as he had two out of three criteria (INR > 1.5, and the absence of prior liver disease), but there was no development of encephalopathy. Symptomatic and supportive therapies were administrated with suspension of all hepatotoxic substances he had previously been using, and the patient fully recovered. The absence of prior liver disease, as well the age of the patient were certainly good prognostic factors, but the influence of hepatoprotective effect of glutamine cannot be ignored [18].

Urgent hepatic transplantation remains the last therapeutic option in the treatment of patients with toxic hepatic impairment and the development of ALF. Current United Network for Organ Sharing criteria for urgent liver transplant are the following:

1. the patient being 18 or older without pre-existing liver disease;

2. life expectancy less than seven days without liver transplantation;
3. onset of hepatic encephalopathy within eight days of the first symptoms;
4. one of the following criteria: ventilator dependence, requirement for renal replacement therapy or INR > 2.0 [21].

In the end, it is necessary to emphasize that we described a young, previously completely healthy man who had severe liver injury caused exclusively by toxic effects of different substances he had been taking for a longer period. The outcome of the disease was favorable, but given the massiveness of hepatocellular necrosis, which could easily have led to ALF with uncertain outcome, we emphasize the importance of constant possible toxic liver damage warnings with different, seemingly harmless supplements and substances.

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Тешко токсично оштећење јетре

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САЖЕТАК

Увод Токсично оштећење јетре представља све већи проблем у савременој хепатологији. До сада је идентификовано више од 900 лекова, биљних производа и суплемената који могу изазвати различита оштећења јетре. У Србији нису вршена значајнија истраживања овог проблема.

Циљ рада је да се прикаже болесник са тешким обликом акутног хепатитиса чија је етиологија искључиво токсична.

Приказ болесника Мушкарац старости 23 године из Београда, претходно здрав, показао је симптоме и знаке акутног хепатитиса. Биохемијске анализе су указивале на тежак облик акутног хепатитиса са претећом хепатоцелуларном инсуфицијенцијом. Постављена је дијагноза токсичног оштећења јетре које је настало употребом више различитих супстанци и суплемената: екстазија, протеина сурутке, *BCAA*, креатина, високе дозе витамина Д, глутамина, мултивитаминског комплекса. Лечен је инфузионом, гастропротективном и супституционом терапијом. Током хоспитализације тегобе су престале, уз постепену нормализацију биохемијских параметара оштећења јетре. Са поправљањем стања урађена је слепа аспирациона биопсија јетре и патохистолошки налаз је показао да се ради о лобуларном хепатитису, без фиброзе, токсичне етиологије. Месец и по дана од почетка болести болесник се потпуно опоравио.

Закључак Повећање броја особа са токсичним оштећењем јетре региструје се у развијеним земљама широм света. Сличан тренд се последњих година може уочити и у Србији. Приказом младог, претходно здравог мушкарца, са тешким обликом акутног хепатитиса са пратећом инсуфицијенцијом јетре насталог употребом различитих токсичних супстанци, указује се на значај ове проблематике. Потребан је мултидисциплинарни приступ у циљу њеног што ефикаснијег решавања.

Кључне речи: акутни хепатитис; токсично оштећење јетре; токсини; суплементи

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Successful postoperative pancreatic fistula treatment with the use of somatostatin infusion after duodenal gastrointestinal stromal tumor resection

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SUMMARY

Introduction According to the International Study Group on Pancreatic Fistula, a postoperative pancreatic fistula is defined as every case of fluid leak on the third (or later) postoperative day, in which the level of amylase-in the collected fluid is at least three times higher than the serum amylase level. Depending on the stage and the designated management, pancreatic fistulas are divided into the following three categories: A (mild), B, and C (severe). Regardless of favorable conditions, exocrine pancreatic secretion is the key factor in fistula formation. The decrease in pancreatic secretion caused by somatostatin and its analogues combined with parenteral nutrition is a well-established treatment method in pancreatic fistula management.

Case outline The case of a 69-year-old patient who had undergone a resection of a duodenal gastrointestinal stromal tumor located directly above the major duodenal papilla is presented. Excessive drainage of amylase-rich fluid was observed in the postoperative period. Treatment comprised continuous infusion of somatostatin and parenteral nutrition. Fistula closure was accomplished on postoperative day 14, confirmed by a radical decrease in the volume of drainage and low amylase levels in the collected fluid. The patient remained in a good clinical state and was discharged from hospital on postoperative day 20.

Conclusion This is an example of the early diagnosis of a postoperative pancreatic fistula, treated conservatively with the use of somatostatin. Post-surgery clinical awareness of the importance of direct contact between the stromal tumor and pancreatic tissues, in connection with routine amylase level assessment, led to a quick diagnosis of pancreatic fistula and the therapy led to an uneventful outcome.

Keywords: pancreatic fistula; somatostatin; GIST; postoperative course

INTRODUCTION

A postoperative pancreatic fistula (POPF) is defined according to International Study Group on Pancreatic Fistula Definition as any case of fluid leak on the third (or later) postoperative day, where the level of amylase in the collected fluid is at least three times higher than the serum amylase level. Depending on the stage and therefore the designated management, pancreatic fistulas are divided into the following three categories: A (mild symptoms), B, and C (severe symptoms). Regardless of favorable conditions, the effective exocrine pancreatic secretion is the key factor in the fistula formation. A decrease in pancreatic secretion caused by somatostatin and its analogues combined with parenteral nutrition is a well-established treatment method in pancreatic fistula management, and is suitable in most cases.

POPF can either be the direct result of pancreatic surgery and its surroundings (as in our case) or of a trauma of the pancreas. POPF after a pancreatoduodenectomy remains the leading cause of morbidity and mortality after surgery. The true occurrence of POPF is difficult to assess; depending on the literature, it ranges 6.2–75.6%. The lack of a uniform definition of a pancreatic fistula – or the exact moment of pancreatic fistula diagnosis – results in such an extreme discrepancy [1].

CASE REPORT

A 69-year-old man, without a previous history of illness, was admitted to the catheterization laboratory due to the fact that he had an inferior wall myocardial infarction with ST segment elevation. Percutaneous coronary intervention was performed with the insertion of a drug-eluting stent. Three days after the procedure, melaena with corresponding anemia was observed in laboratory tests. Upper gastrointestinal endoscopy revealed a firm ulcerative duodenal inflammatory tumor located at the Vater's papilla, narrowing the lumen of the duodenum (Figure 1).

Subsequent abdominal computed tomography scans showed a 42 × 28 × 30 mm tumor with uneven margins and possible pancreas infiltration (Figure 2).

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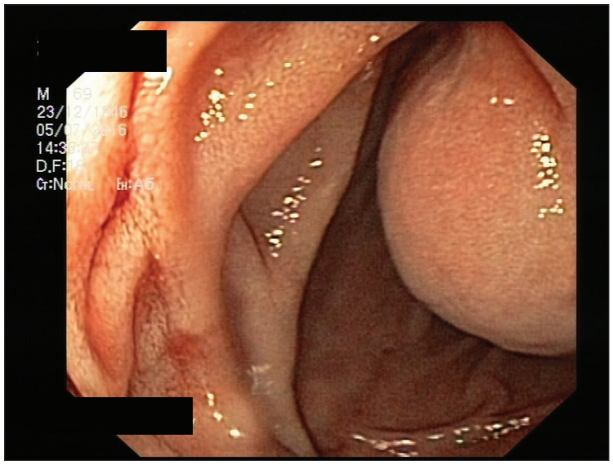

Figure 1. Upper gastrointestinal endoscopy shows the firm duodenal gastrointestinal stromal tumor-like tissue at the Vater's papilla

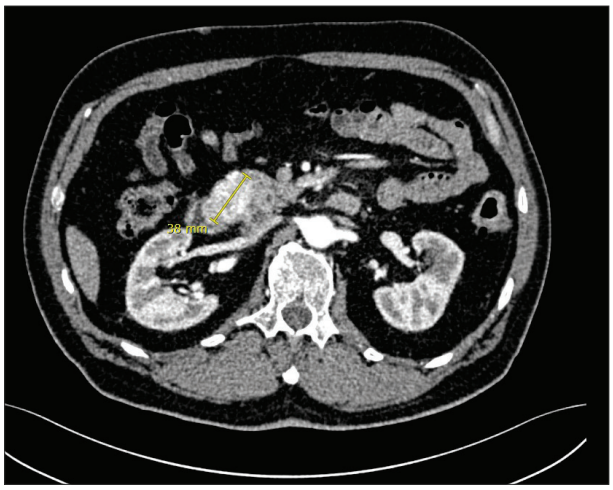

Figure 2. Abdominal computed tomography scan shows the tumor measuring 38 mm with uneven margins and possible infiltration of the pancreas

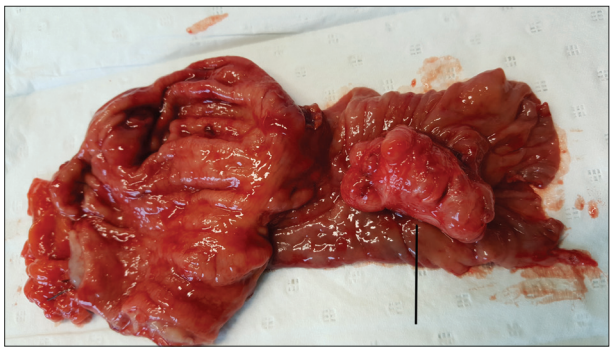

Figure 3. Postoperative view; the arrow shows the excised specimen with gastrointestinal stromal tumor

Biopsies taken during endoscopy of the tumor revealed that it was an undifferentiated inflammatory tumor. Due to the recent severe myocardial infarction, the placement of a drug-eluting stent in the coronary arteries and the necessity for anticoagulation therapy, the patient was offered the option of delaying the operation.

The patient was admitted to the surgical clinic three months later. One day before the operation, endoscopic retrograde cholangiopancreatography was performed and a 10 French stent was inserted in the common bile duct as a precaution against preoperative bile duct injuries as a landmark. During the elective laparotomy, a firm duodenal tumor with an ulceration on top was observed above the Vater's papilla. The tumor tissues were oriented towards the head of the pancreas. The tumor was carefully dissected from the pancreas, although some preparation and resection of the pancreatic tissues was unavoidable in this case. Subsequently, the proximal part of the duodenum with the tumor (just above the Vater's papilla) and the distal third of the stomach was excised. The gastrointestinal tract was then restored with a side-to-side jejunogastric antecolic anastomosis, aided with Braun's anastomosis below. Anastomoses were performed with the use of absorbable mono-filament sutures in single or double layers. The postoperative histopathology revealed a 25 × 25 mm gastrointestinal stromal tumor of the duodenum, with clean surgical margins (Figure 3).

A few hours after surgery and on the first postoperative day, serum amylase levels were 344 U/L and 248 U/L, respectively. Drainage fluid amylase levels collected on the first, third, and later postoperative days were within the range of 1,100–3,000 U/L. Due to the findings acquired by the laboratory tests, the visual assessment of the drained abdominal fluid and intraoperative preparation of the pancreatic tissue, a pancreatic fistula was diagnosed. The conservative treatment comprised total and subsequently partial parenteral nutrition (10 days in total) together with a continuous somatostatin infusion of 6 mg / 24 hours. Laboratory indicators of fistula closure were successfully obtained on the 14th day after surgery. The somatostatin dosage was then reduced to 3 mg / 24 hours for the next 48 hours and subsequently discontinued. The patient remained in a good clinical state without any elevation of inflammatory indicators during the fistula treatment period. The man was discharged from hospital 20 days after surgery. The abdominal drains were removed four days prior to discharge.

A surprisingly high amylase level from the abdominal fluid collection was observed on the seventh day of fistula treatment (9,400 U/L). The laboratory findings were contradictory to the good overall condition of the patient. Therefore, we presumed that the drainage blockage and fluid concentration caused such laboratory test results.

DISCUSSION

In the past, the available studies defined pancreatic fistula individually, which made the comparison of treatment results difficult. In 2005, Bassi et al. [2] – International Study Group of Pancreatic Fistula (ISGPF) – developed a widely-accepted definition of a POPF. According to ISGPF, the POPF is a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content three times higher than the serum amylase activity [3].

Successful treatment of POPF depends on early diagnosis. Regardless of the ISGPF definition, additional useful

predictors of fistula formation include: 1) serum amylase levels above 130 U/L four hours after surgery or on postoperative day 1; 2) amylase level in the drained abdominal fluid over 5,000 U/L on postoperative day 1 [4, 5].

Effective exocrine pancreatic secretion is the key factor in pancreatic fistula formation. The limitation of pancreatic secretion creates the desired conditions for fistula treatment and therefore is the key to pancreatic fistula therapy. Oral nutrition is restricted, followed by parenteral nutrition, aided with drugs like somatostatin and its analogues, reducing the exocrine secretion of the organ. The first successful use of somatostatin in the prevention of pancreatic fistulas dates back to the year 1979 [1, 6, 7].

Somatostatin is secreted in the central nervous system and the gastrointestinal tract (70%). This hormone inhibits the secretion of gastrin, secretin, vasoactive intestinal peptide and pancreatic enzymes, and reduces both peristaltic intestine activity and gastric emptying. All of the abovementioned results of somatostatin activity create a favourable environment for pancreatic fistula closure. Thanks to the inhibition of pepsin and hydrochloric acid production, somatostatin also plays a well-established role in the prevention and directed treatment of upper gastrointestinal bleeding caused by esophageal varices, gastric and duodenal ulcers. However, the most valuable effect of somatostatin infusion in these cases is the instant (a few minutes after administration) reduction of portal vein pressure and mesenteric circulation [8, 9, 10]. The recommended pancreatic fistula therapy includes a continuous intravenous somatostatin infusion of 6 mg / 24 hours until complete fistula closure, followed by a 50% reduction in the infusion to 3 mg / 24 hours for the next 48 hours in order to avoid a rebound effect. The only proper way to administer somatostatin is continuous infusion, because of its short, three-minute half-life. Patients with advanced kidney failure require lower doses, whereas liver failure does not affect somatostatin dosage.

The latest research on somatostatin therapy confirms its positive impact on pancreatic fistula treatment and prevention after pancreatic surgery. At the same time, a similar effect with the analogue of somatostatin – octreotide – is being questioned in terms of successful fistula treatment [1]. Parenteral nutrition is also an essential part of proper initial pancreatic fistula therapy, although more detailed information on the subject is beyond the scope of this article.

The case report presented is a good example of POPF treatment with the use of somatostatin. Clinical awareness of the importance of direct contact between the stromal tumor and pancreatic tissues, in connection with routine amylase level assessment, led to a quick diagnosis of the pancreatic fistula and the therapy led to uneventful outcome.

This case report was approved by the local ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images. Written informed consent in Polish was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of interest: None declared.

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Успешна постоперативна терапија фистуле панкреаса инфузијом соматостатина после ресекције дуоденалног гастроинтестиналног стромалног тумора

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САЖЕТАК

Увод Према Међународној студијској групи за дефиницију панкреасне фистуле, постоперативна панкреасна фистула је сваки случај цурења течности трећег (или каснијег) постоперативног дана, када је ниво амилазе у испуштеној течности најмање три пута већи од нивоа амилазе у серуму. У зависности од степена и њиме условљеног третмана, панкреасне фистуле се деле у следеће три категорије: А (благи симптоми), Б и Ц (тешки симптоми). Без обзира на повољне услове, егзокрино лучење панкреаса је кључни фактор у формирању фистуле. Смањење секреције панкреаса изазване соматостатином и његовим еквивалентима у комбинацији са парентералном исхраном добро је утемељен метод у третману панкреасне фистуле.

Приказ болесника У овом раду приказан је 69-годишњи болесник који је био подвргнут ресекцији дуоденалног гастроинтестиналног стромалног тумора, који се налазио непосредно изнад велике дуоденалне папиле. У постоперативном периоду је забележена прекомерна дренажа течности са високим нивоима амилазе. Конзервативни третман састојао се од континуиране инфузије соматостатина и парентералне исхране. Потпуно затварање фистуле је постигнуто 14. постоперативног дана, што је потврђено радикалним смањењем количине издрениране течности и ниским нивоом амилазе у сакупљеној течности. Болесник је остао у добром клиничком стању и отпуштен је из болнице 20. постоперативног дана.

Закључак Овај приказ представља пример рано дијагностиковане постоперативне панкреасне фистуле конзервативно лечене соматостатином. Постоперативно клиничко разумевање важности директног контакта стромалног тумора са ткивом панкреаса, у комбинацији са рутинским утврђивањем нивоа амилазе, довело је до брзе дијагнозе фистуле панкреаса, а терапија је довела до исхода без компликација.

Кључне речи: панкреасна фистула; соматостатин; гастроинтестинални стромални тумор; постоперативни ток

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Malaria in the 21st century – still a threatening problem

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SUMMARY
There are six parasite species (*P. falciparum*, *P. vivax*, *P. ovale curtisi*, *P. ovale wallikeri*, *P. malariae*, and *P. knowlesi*) that cause malaria in humans. *P. falciparum* is responsible for most malaria-related deaths globally. *P. vivax* is the dominant malaria parasite in most countries outside of the Sub-Saharan Africa. In 2016, 91 countries reported a total of 216 million cases of malaria. The global tally of malaria deaths reached 445,000. In 2016, 24 cases of imported malaria were registered in the Republic of Serbia, with an incidence of 0.33/100,000. According to the World Health Organization recommendations, every suspected malaria case should be confirmed by microscopy or a rapid diagnostic test before treatment. The main stone of antimalarial therapy should be artemisinin-based combinations. Since malaria occurs in Europe as an imported (though rarely also autochthonous and a hospital-borne infection), the objective of this paper is to point out current problems and attitudes in the diagnosis and treatment of malaria, without entering the data field significant for professionals (infectologists, epidemiologists, intensivists).
Keywords: malaria; antimalarials; chemoprophylaxis; laboratory diagnostics

INTRODUCTION

There are six parasite species *(P. falciparum, P. vivax, P. ovale curtisi, P. ovale wallikeri, P. malariae, P. knowlesi*) that cause malaria in humans. *P. falciparum* and *P. vivax*– pose the greatest threat. *P. falciparum* is the most prevalent malaria parasite on the African continent. In 2016, 91 countries reported a total of 216 million cases of malaria. The global burden of malaria deaths reached 445,000 victims, mostly children under five years of age [1]. The number of confirmed malaria cases reported in the European Union and the European Economic Area (EU/EEA) from 2008 to 2012 ranged 5,000–7,000 [2]. Since the late 1990s, autochthonous malaria cases occurred in some European countries (Spain, Germany, Netherlands, France, Italy, and Greece) while between January 2016 and April 2018, six sporadic hospital transmissions of malaria were identified in the EU [3].

The last autochthonous case of malaria in former Yugoslavia was registered in 1964. Since then, malaria has been recorded only as an imported, tropical disease. In the 1990–2001 period, 158 cases of imported malaria were registered in the Republic of Serbia, while in the 2001–2009 period, malaria was diagnosed in 102 patients, mainly from the Afro-Asian region [4]. In 2016, 24 cases of imported malaria were registered in the Republic of Serbia, with an incidence of 0.33/100,000 [5]. However, epidemic potential for malaria transmission is relatively small in our community [6, 7].

ACCEPTED DIAGNOSTIC PROCEDURES

According to the World Health Organization (WHO) recommendations, every suspected malaria case should be confirmed by microscopy or a rapid diagnostic test before treatment.

Parasitological diagnostics, a classic overview of thin and thick blood smear colored according to Giemsa, remain the "gold standard" of diagnostics. Thin and thick blood smear consists of a thick layer of lysed red blood cells. The blood elements, including parasites, are more concentrated, so the thick blood smear allows a more efficient detection of parasites even in small numbers (increased sensitivity). Morphology and the ratio of parasites to erythrocytes are preserved, so the typical forms of individual parasites can be identified. In the thin blood smear, the degree of parasitemia, the appearance of pigments in leukocytes, the number of thrombocytes, and other possible hematological changes can be assessed as well. A well-educated parasitologist, standardized laboratory procedures, and enough time to review are preconditions for quality performance reviews [8].

Rapid diagnostic tests detect specific antigens (proteins, enzymes) of malaria parasites. Some of the tests can detect only one species (*P. falciparum*), while others detect multiple species (*P. vivax*, *P. malariae*, and *P. ovale*). Immunochromatographic tests can target the histidine-rich protein 2 of *P. falciparum*, a pan-malarial plasmodium aldolase, and the

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parasite-specific lactate dehydrogenase. Some studies have found that the sensitivity was 86.7–93.4%, while the specificity was estimated at 98.2–99.3% [8–11].

Quantitative buffy coat method uses a fluorescence technique to detect parasites stained with acridine dye. For precise diagnosis, a check with a classic scanning technique is always recommended [12].

Molecular diagnostics most commonly use polymerase chain reaction (PCR), providing superior specificity and sensitivity compared to other mentioned methods, which is of particular importance in epidemiological and resistance studies [8, 13]. Real-time PCR may be useful as a method complementary to microscopy, particularly in cases of low parasitemia, and for species determination, especially in non-*P. falciparum* cases, in which most instances of misdiagnosis occur [13].

ACTUAL RECOMMENDATIONS FOR THERAPY AND PROTECTION

Actual therapeutic approaches have undoubtedly been marked by new therapeutic protocols. Particularly important items of data are related to the resistance of parasites [14].

Antimalarials come from different chemical structures. The 4-aminoquinolines are chloroquine, quinine, mefloquine, and amodiaquine, while the 8-aminoquinolone is primaquine. The antifolates area class of antimetabolite medications such as pyrimethamine, proguanil, and sulfadoxine. The artemisinin derivatives (artemisinin, artesunate, artemether, arteether) are sesquiterpene lactones, while atovaquone is hydroxynaphthoquinones. Various antibiotics – primarily tetracyclines and clindamycin – have antimalarial effects [15]. Current WHO recommendations for the treatment of uncomplicated *P. falciparum* malaria are presented in Table 1 [16].

Table 1. Treating uncomplicated *P. falciparum* malaria [16] – reproduced with WHO permission

Treatment of uncomplicated *P. falciparum* malaria Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended ACTs: · artemether + lumefantrine · artesunate + amodiaquine · artesunate + mefloquine ·dihydroartemisinin + piperaquine ·artesunate + sulfadoxine–pyrimethamine (SP) *Strong recommendation, high-quality evidence*
Duration of ACT treatment ACT regimens should provide a 3-day treatment with an artemisinin derivative *Strong recommendation, high-quality evidence*
Revised dose recommendation for dihydroartemisinin +piperaquine in young children Children weighing < 25 kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg of body weight per day of dihydroartemisinin and 20 mg/kg of body weight per day of piperaquine daily for 3 days *Strong recommendation based on pharmacokinetic modelling*

ACT – artemisinin-based combination therapy

According to Table 1, uncomplicated *faciparum* malaria should be treated with artemisinin-based combination therapy (ACT). Artemether–lumefantrine, dihydroartemisinin–piperaquine, artesunate–amodiaquine, artesunate–mefloquine, and artesunate–sulfadoxine–pyrimethamine are currently the most used combinations. Eighteen treatment regimens were reported (2003–2009 period) in several European countries. Atovaquone–proguanil was predominantly used, followed by older drugs, such as mefloquine, or quinine alone or in combination with clindamycin or tetracyclines [17].

Two classes of drugs are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids – quinine. Experiences with the treatment of severe malaria give priority to the treatment of artesunate in relation to other therapeutic options [18, 19]. Artesunate should be applied parenterally, best intravenously, in all cases of severe malaria in adults, children/infants, pregnant and lactating women, or inpatients with relatively high parasitemia (> 2%). It is best to treat such patients in intensive care units, since severe malaria is associated with a number of complications, including acute respiratory distress syndrome, disseminated intravascular coagulation, acute kidney injury, seizures, and severe infections, even with sepsis.

ACT is the mainstay of modern therapeutic protocols. Artemisinin and its semisynthetic derivatives, such as artesunate, artemether, and arteether dihydroartemisinin, are obtained from the plant *Artemisia annua*. They are sesquiterpene lactone containing an unusual peroxide bridge. Artemisinins are considered prodrugs activated to generate carbon-centered free radicals or reactive oxygen species, and are the most potent antimalarial agents, effective against nearly all asexual and sexual parasite stages [20].

Artemisinin component in ACT (artemether, artesunate, or dihydroartemisinin) drastically reduces the number of parasites during the first three days of treatment, but potential disadvantage may be a higher risk of recrudescence when these drugs are used in monotherapeutic regimens. Recrudescence signifies the emergence of a clinical picture of malaria from parasites that persist in erythrocytes after the initial treatment. This is why drugs from other antimalarial groups are added, which eliminate the remaining parasites and in that way prevent recrudescent malaria [20].

In Serbia, malaria is treated in infectious departments of tertiary medical institutions, adapted to the WHO's advice. Unfortunately, due to low consumption, most antimalarial drugs are not registered, so procurement takes place according to special procedures. Artemisinin-mixed treatment is the cornerstone for therapeutic approach, while artesunate is the preferred therapy for treatment of severe *falciparum* malaria.

Side effects of artemisinins occur rarely (3.4%). However, the greater concern is related to hemolysis which occurs in approximately 10–15% patients, and even more following intravenous artesunate treatment [21]. Delayed-onset anemia or postartesunate late hemolysis has been observed to occur two to three weeks following the initiation of IV artesunate, after complete parasite clearance, but this phenomenon is also described after oral administration of artemisinin drugs. Although there is no complete explanation

for this phenomenon, it unconditionally requires additional differential diagnostic and therapeutic efforts. Artemisinin resistance is a rare phenomenon, but the releases in the literature are found more often [22].

According to Centers for Control and Disease Prevention recommendations, chloroquine (or hydroxychloroquine) remains an effective choice for *P. vivax* and *P. ovale* infections. After the treatment of *P. vivax* / *P. ovale* infection, primaquine should be used, or recently introduced tafenoquine, due to the effects on hypnozoites in the liver, left after treatment, thus preventing malaria relapses [23].

It is said that 13 drugs are in advanced research development, two of which are in the advanced, final phase – artefenomel–ferroquine and lumefantrine-KAF156 [24].

Arterolane is a newer synthetic peroxide resembling the artemisinin derivative. Arterolane maleate and piperaquine effectively cures *P. falciparum* malaria by day 28 in pediatric patients, which justifies the clinical application of this combination [24, 25].

The US Food and Drug Administration approved tafenoquine for the prevention of relapse of *vivax* malaria on July 20, 2018. Tafenoquine, an 8-aminoquinoline, is used as a single-dose treatment for *Plasmodium vivax* relapse prevention. Administration of this drug, as well as primaquine, follow the same restriction and adverse events (glucose-6-phosphate dehydrogenase deficiency) [26].

CHEMOPROPHYLAXIS

Experiences of European authors show that only 10% of patients with severe malaria had taken antimalarial chemoprophylaxis and very few of them had been fully compliant [17].

The most commonly recommended regimens of chemoprophylaxis are as follows: doxycycline 100 mg once daily (started one day before traveling, and continued for four weeks after returning); mefloquine 250 mg once weekly (started 2.5 weeks before traveling, and continued for four weeks after returning); atovaquone/proguanil one tablet daily (started one day before traveling, and continued for one week after returning) [27].

Among the recommended drugs, the atovaquone–proguanil combination is the most justified one, especially in regions where there is a multi-resistant malaria. The impact of substituting atovaquone–proguanil for all mefloquine use resulted in a 2.3% decrease in estimated infections [28].

Advice on the protection from mosquito bites (repellents, insecticide impregnated bed nets, etc.) are certainly an important part of the protection.

The vaccine remains an unfulfilled dream, although work on it is still being carried out with great enthusiasm today. In July 2015, the Committee for Medicinal Products for Human Use of the European Medicines Agency gave a positive opinion for the "candidate vaccine" Mosquirix. The vaccine is awaiting the final response from the WHO and African health authorities, with whose approval Phase III of its examination has been conducted [29]. The latest information favors the vaccine which consists of the central repeat the C-terminal domain of *Plasmodium falciparum* circumsporozoite protein, fused to hepatitis B virus surface antigen (HBsAg) in a 1:4 ratio. This vaccine demonstrated protective efficacy against clinical malaria in Phase III clinical trial [30].

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Маларија у 21. веку – и даље претећи проблем

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САЖЕТАК

Постоји шест врста паразита рода *Plasmodium* (*P. falciparum, P. vivax, P. ovale curtisi, P. ovale vallikeri, P. malariae* и *P. knowlesi*) који узрокују маларију код људи. *P. falciparum* је одговоран за већину смртних случајева везаних за маларију. *P. vivax* је доминантни паразит маларије у већини земаља изван подсахарске Африке. У 2016. години 91 земља је пријавила укупно 216 милиона оболелих од маларије. Број смртних случајева у 2016. години је 445.000. У 2016. години у Србији су регистрована 24 оболела од маларије (учесталост 0,33/100.000). У складу са препорукама *WHO*, свака сумња на маларију треба да се потврди микроскопијом или брзим дијагностичким тестом пре лечења. Главни ослонац антималаричне терапије треба да буду комбинације са артемисинином. Будући да се маларија у великом броју европских земаља јавља као унесена (мада ретко и као аутохтона и болнички стечена инфекција), циљ овог рада је упознавање са актуелним проблемима и ставовима у дијагностици и лечењу маларије, без упуштања у детаље значајне за професионалце који се овим проблемима посебно баве (инфеколози, епидемиолози, интензивисти).

Кључне речи: маларија; антималарици; хемопрофилакса; лабораторијска дијагностика

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Environment and health – thirty years of successful implementation of the Montreal Protocol

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SUMMARY
The Protocol on Ozone Depleting Substances (ODS) was signed in 1987 in Montreal. The main goal of the protocol is the international consensus and action regarding the drastic decrease of production and use of these substances, which results in increased UV radiation and consequently has a negative impact on human health and ecosystem. Besides the review of the "legal and technical" implementation of the protocol until now and the withdrawal of ODS from use, this paper specially stresses the analysis of available research results regarding the positive impact on health, in correlation with the implementation of the Montreal Protocol (MP). Due to the results of the thirty-year-long use until now, the MP is referred to as one of the most successful international agreements, not only in the field of environmental protection, but also in the field of human health protection in relation to it, within a certain context. Besides the reduced negative impact of ultraviolet radiation (UV) to the ecosystem and people, we are also facing a reduced occurring trend of skin cancer, cataracts, and immune system diseases worldwide. Without the MP and its implementation, millions of people would have died because of UV radiation and the previously mentioned diseases. The treatment costs and the pressure to the health system in all the countries worldwide would have enormously increased because of that.
Keywords: Montreal Protocol; ozone layer; UV radiation; health

INTRODUCTION

Wishing to improve the quality of life by economic growth and development, the humanity constantly changes their relation towards natural, economic, and social surroundings. Lately, the conscience regarding the impact of the surroundings to the health and environment is increasing. The information on environment, and as a consequence, the impact to the living world and man (human health), as well as the society in general, represents one of the most recent heritages that resulted from democratization of the contemporary world, and that is consisted within the Aarhus Convention [1, 2].

DAMAGE TO THE OZONE LAYER AND THE CONSEQUENCES TO THE ECOSYSTEM AND HUMAN HEALTH

Human society depends on complex relations between people and the environment [3]. The ozone layer protects the entire living system of our planet from harmful ultraviolet radiation (UV-B and UV-C) sunrays. The new scientific findings from 1970s have determined that halogenated hydrocarbons (commercially known as freons), due to their chemical features, significantly damage the ozone layer.

The Earth's ozone layer is mainly significant for the protection of life on our planet. If intact, it can prevent 97–99% of the Sun's ultraviolet radiation (UV). Living tissues of organisms living on dry lands would be extremely damaged by the Sun's UV if the majority of rays were not absorbed by the Earth's atmosphere, and especially the ozone layer [4]. Given that the UV is considered the main cause of skin cancer, cataracts, and some immune system diseases, measuring the entire atmospheric ozone has become a daily practice [5, 6, 7].

Ozone depleting substances (ODS) and other greenhouse gasses, when emitted into the atmosphere, significantly impact the ozone layer depletion by reacting with ozone molecules (O_3), as presented in Figures 1 and 2.

In comparison to pre-industrialization times, the concentration of carbon dioxide, methane, and nitrogen oxide has doubled in the atmosphere [8]. In the end of the 19th century, a long time after Svante August Arrhenius has proven the greenhouse effect, its overall consequences were covered with a veil of ignorance. Until the 1980s, the issue of the ozone layer was out of the focus of scientists and the wider public [9]. In 1985, the British scientist Joe Farman discovered the ozone "hole" over the Antarctica [10]. It was proven that, at a concentration of 80 ppb, the atmospheric ozone has an especially harmful impact on human health and the entire living world in general. This was especially stressed regarding the urban living conditions, since the diseases occurrence caused by this phenomenon is constantly increasing, thus having an impact on the general public health and

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the health system [11]. The increase in number of pollution sources has driven the attention towards the mechanisms and activities against the most common air polluters [12].

THE MONTREAL PROTOCOL AS THE INTERNATIONAL COMMUNITY RESPONSE

International conventions are definitely the most significant mechanisms in the fight for the environment protection, and thus preservation of human health and biodiversity [13, 14]. The International Law on the Environment and a great number of international agreements contain regulations that, in a different way and on a different level, stress the impact of the environment to human health [15, 16]. The Protocol on ODS was signed in 1987 in Montreal (after eight years of negotiations between 197 states), with the help of the United Nations Environment Programme. Since 2004, the MP has also been in motion, with all the following by-laws [17, 18].

The MP identifies the main substances that are depleting the ozone layer and adopts specific restrictions regarding their production and consumption in future, as well as the traffic of 96 different chemicals that are known to have a depleting effect on the ozone layer and that are divided into annexes A to E. Each of these annexes is divided into several groups of similar substances. Since being set in motion in 1989, hand-in-hand with the Vienna Convention for the Protection of the Ozone Layer, the MP is considered as one of the most successful agreements in the field of environment protection [19]. The measurements of the NASA's satellite instruments of the Jet Propulsion Laboratory in Pasadena, California, have shown that, for the first time, the levels of chlorine, which depletes the ozone layer, are dropping, leading to reduction of ozone depletion [20] (Figure 3).

Chlorofluorocarbons (CFC compounds) were unknown until 1930, and until recently, they were massively used in cooling devices, air-conditioning, sprays (propellants in aerosols) and in industrial facilities [21, 22]. The MP was initially dedicated only to chemicals that were identified as ozone-depleting chemicals at that moment [23]. Shortly after the adoption of the MP emerged the need for its evolution in order to have it respond to the changes in science regarding the ozone and the climate, as well as the demands of parties and industries using the ODS and their alternatives, including hydrofluorocarbon (HFC) [24, 25].

The change in the projection of future wealth, the number of habitants of certain countries and their technological agility, has led to increased demands for HFC [26]. The danger emerging from HFC has increased with the boom of air conditioning and refrigerators market within the fast-growing economies such as China and India [27]. New scientific knowledge and findings have conditioned further development and improvement of the MP, in accordance with the current global situation and trends, through five amendments to the Protocol: London (1990), Copenhagen (1992), Montreal (1997), Beijing (1999) and Kigali (2016) [28]. Until now, the Kigali Amendment was ratified by 70

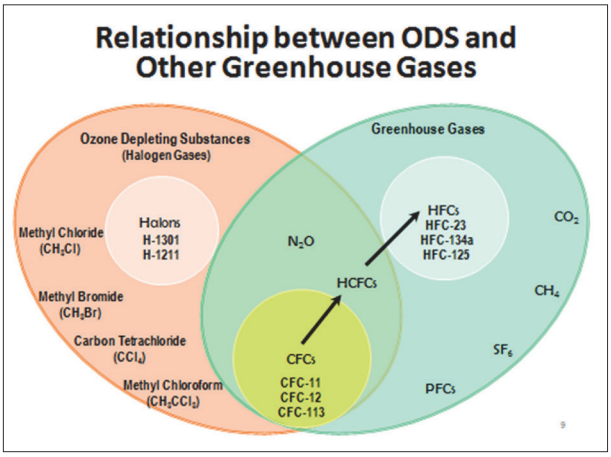

Figure 1. Relationship between the ozone depleting substances (ODS) and other greenhouse gases [6]

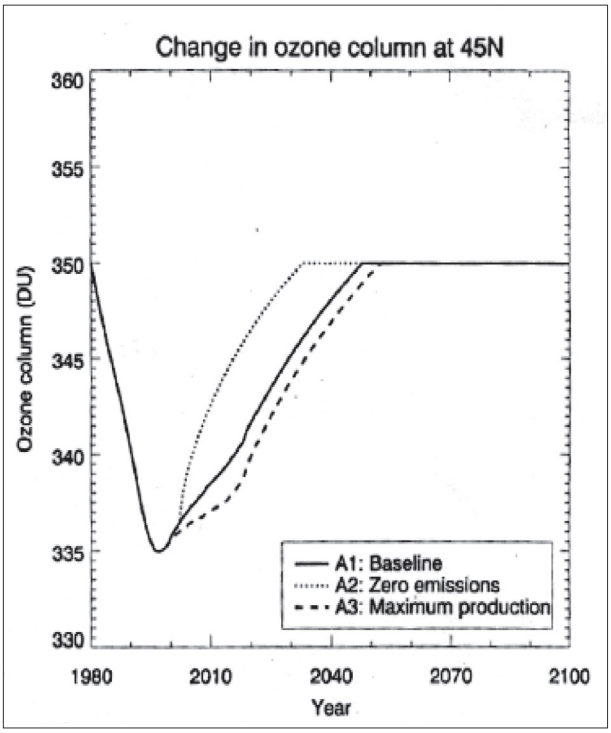

Figure 2. Change of the quantity of ozone expressed in Dobson units (DU) from 1980, with a projection for the future [7]

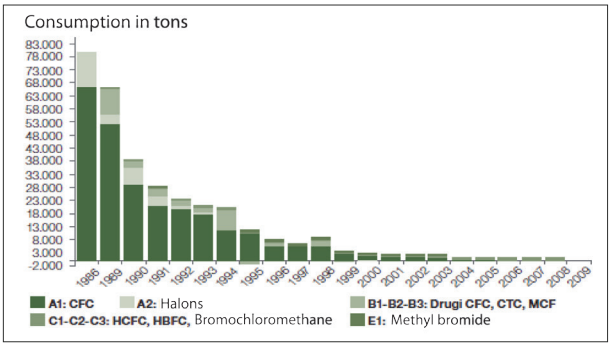

Figure 3. Reduction of ozone depleting substances in the European Union [21]

countries [29]. The countries that have ratified the Kigali Amendment have committed themselves to reduce the production and consumption of the HFC by over 80% within the following 30 years [30, 31]. With the Kigali Amendment, it was agreed that the developed countries, including European countries, should gradually reduce the use of HFC by 2035 by 15%, in comparison to the baseline values from the period of 2011–2013. The observations show that the quantity of HFC within the atmosphere is increasing [32]. Because of that, the main goal of the MP was set to be the reduction of consumption and emission of the HFC with high Global Warming Potential (GWP) by using alternatives containing low GWP.

IMPLEMENTATION OF THE MONTREAL PROTOCOL AND THE POSITIVE EFFECTS TO HEALTH OF PEOPLE AND THE ENVIRONMENT

The MP was signed more than 30 years ago. According to the UN data and MP measures. Two million people are less likely to suffer from skin cancer annually, in comparison to the previous period, and this shall save the global economy more than two billion dollars by 2050 [33]. The increased rate of occurrence of skin cancer, cataracts, and blindness is a direct consequence of depletion of the ozone layer [9]. It is estimated that by the year of 2100, the stipulated MP measures shall have aided the prevention of 283 million skin cancer cases (including 8.3 million cases of melanoma) and 46 million cases of cataracts, as well as 1.6 million of deaths from skin cancer [28]. The Sun's UV radiation is a proven human carcinogen that causes skin melanoma. Skin cancer is nowadays the most common and the fastest developing disease [5].

Numerous epidemiological researches show that outdoor workers are exposed to a significantly greater risk from developing all types of skin cancer [34]. The results of a Romanian study showed that patients suffering from basal cell carcinoma were occupationally exposed to UV radiation [35]. In the Republic of Serbia (RS), the occurrence and number of skin cancer cases has been increasing lately, along with other forms of cancers, but also the methods for their detection are becoming increasingly successful [36, 37, 38]. The Rulebook on Determination of Occupational Diseases (Official Gazette of the Republic of Serbia, no. 105/03) determines occupational diseases and workplaces, that is, jobs during which such diseases occur, as well as the conditions under which the said disease shall be regarded as an occupational disease.

Various research has shown that UV increases the likelihood of developing certain types of cataracts. Although curable with modern eye surgery, cataracts diminish the eyesight of millions of Americans, and costs billions of dollars in medical care each year. Other kinds of eye damage include pterygium (tissue growth that can block vision), skin cancer around the eyes, and degeneration of the macula [39]. For decades, the human eye has been subjected to ambient radiation, and the full spectre of sunrays contains wavelengths of a significant damaging potential. It is hard to determine

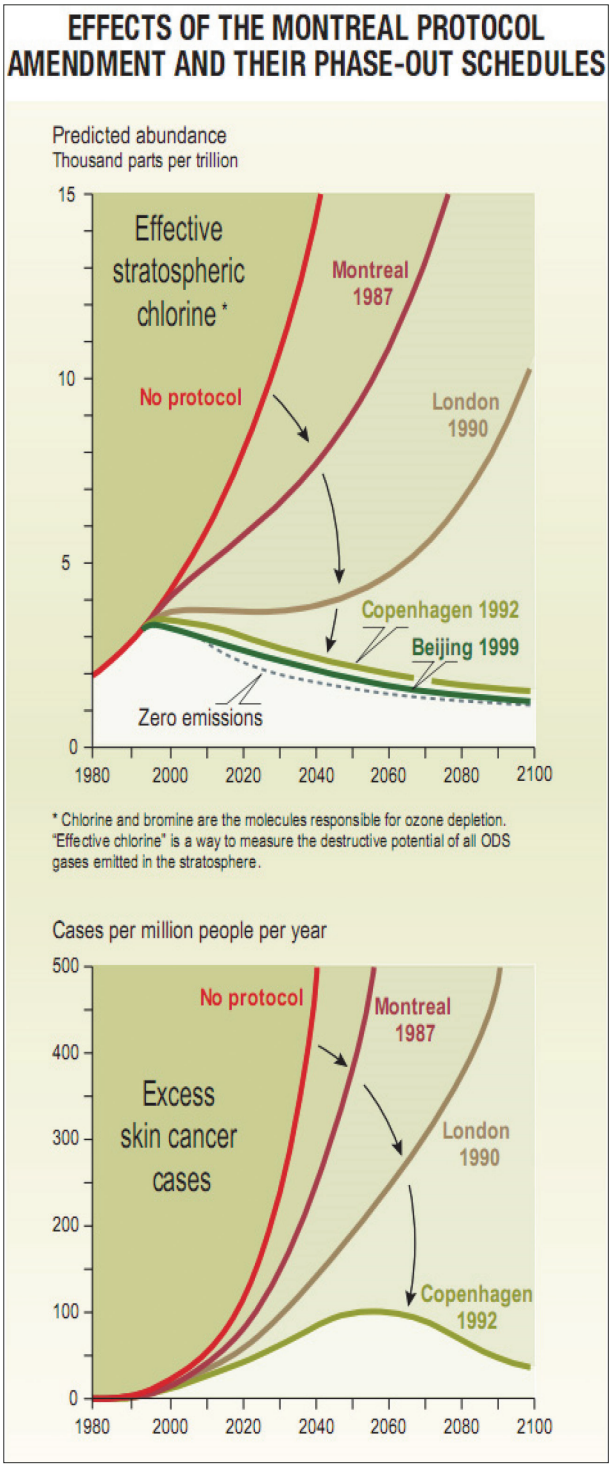

Figure 4. Effects of the Montreal Protocol Amendment [42]

the ocular dose of photodynamic damage to human lenses caused by the UV light. That is a cumulative dose of effects during a long period of exposure [40]. The most common damage to human lenses is a consequence of cumulative effect of sunlight spectrum, to which it is exposed during the lifespan [39]. About 50 million people worldwide suffer from cataracts [41]. The UV also reduces effectiveness of the immune system through the change in activities and distribution of cells responsible for initiation of immunological reactions [42]. "One American dies from skin cancer

every hour. Unprotected exposure to UV radiation is the most preventable risk factor for skin cancer" [43] (Figure 4).

In its newest report regarding the 30 years of the MP application, American EPA stated that this internationally accepted contract prevented the development of more than 45 million of cataracts cases among Americans, reduced skin cancer cases among 280 million of people and saved about 1.6 million of lives in the USA [44]. The result of that was that the healthcare fund was reduced by 4.2 trillion of dollars.

COMMENT

The implementation of the MP (during the previous 30 years) has contributed to numerous benefits, most notably in the field of ecology, but also in the field of public health. The efforts for the protection of stratospheric ozone shall result in saving 4.2 trillion dollars in the field of social security within the US during the period 1990–2165, and thus it shall prevent an estimated 6.3 million of deaths caused by skin cancer [44].

In the RS, this refers to the widest population, and especially the vulnerable target groups, which are: the youngest age group, youth, beach and pool visitors, and outdoor workers that are exposed to UV radiation on a daily basis. This especially refers to the population category within the RS that is exposed to UV radiation due to their occupation (construction workers, farmers, etc.) or their lifestyle. It is especially important that we work on raising awareness and informing individuals and institutions in the RS regarding the overall negative impact of UV rays to health of the population, and especially those youngest [45]. Finally, this shall confirm the commitment of the RS to the implementation of the Millennium Development Goals, and shall serve as a confirmation of the commitment to the EU integration process [46].

CONCLUSION

Looking over the 30 years of successful implementation of the Montreal Protocol, it could be said that, without it, by 2050 the depletion of the ozone layer in the northern hemisphere would have amounted to 50% on 45 degrees, and in the northern hemisphere, it would have amounted up to 70%. The level of UV radiation on the Earth's surface would have been doubled. That would have led to an enormous increase in the number of cases of non-melanoma cancers, melanoma cancers and eye diseases – cataracts.

Failing to do as proposed by the Montreal Protocol would only postpone or even prevent the recovery of the ozone layer. Numerous factors, including ODS and climate change, shall have a significant impact on the ozone layer and thus on human health. Therefore, it is especially significant that all countries comply with the accepted regulations, since, globally speaking, every activity counts and contributes to the overall improvement of the quality of life, population health, and ecosystem.

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Животна средина и здравље – тридесет година успешне примене Монтреалског протокола

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САЖЕТАК

Протокол о супстанцама које уништавају озонски омотач је потписан 1987. године у Монтреалу. Основни циљеви протокола су међународни консензус и акција у вези са драстичним смањењем производње и коришћења ових супстанци који за резултат имају повећано УВ (ултравиолетно) зрачење и последично негативан утицај на људско здравље и екосистем. Поред прегледа досадашње „правне и техничке" примене протокола и повлачења из употребе супстанци које уништавају озонски омотач, у раду је посебно стављен нагласак на анализу литературно доступних резултата који се односе на позитиван (тиме настао) утицај на здравље становништва у корелацији са применом Монтреалског протокола (МП). Због резултата досадашње тридесетогодишње примене, МП спада у ред најуспешнијих међународних споразума у области заштите животне средине, али у одређеном контексту и са здрављем људи које је са тим у вези. Поред смањеног негативног утицаја УВ зрачења на екосистем и људе, као позитивну последицу смањења овог зрачења имамо и смањени очекивани тренд појаве обољења коже, катаракте и имуног система са овим у вези у читавом свету. Без МП и његове примене милиони људи би умрли од последица УВ и наведених обољења. Трошкови лечења и притисак на здравствени систем у свим земљама света би се енормно повећали као резултат тога.

Кључне речи: Монтреалски протокол; озонски омотач; УВ зрачење; здравље

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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Laser surface modification of metallic implant materials

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SUMMARY
Metallic biomaterials are most commonly used as hard-tissue replacements because of their favorable mechanical features and excellent biocompatibility.
The objective of this paper is to present an overview of diverse surface modification techniques, with a special emphasis on the laser surface modification method, as well as diverse characterization techniques used for investigating the impact of the surface modification process on metallic implant materials' properties. Moreover, the effect of laser radiation on the surface its and mechanical characteristics, as well as on the structure of metallic bioimplants, is presented. The study of influence of high-intensity laser radiation on metallic materials' surface includes primarily investigations of the surface morphology modifications and specific surface structure formation since their presence enables enhanced osseointegration.
Keywords: metallic implant materials; laser radiation; surface modification; osseointegration

INTRODUCTION

Biometallics are metallic materials used in contact with cells, tissues or body fluids of the human body with the purpose of replacing or upgrading structural components of the human organism as a compensation for hard-tissue damage which may occur due to aging, illnesses, or accidents [1, 2].

Metallic implant biomaterials have been in use since the 19th century in a wide range of dental, orthopedic, cardiovascular, and other medical applications [1]. Stainless steels, cobalt-chromium alloys, and titanium-based materials are the main biocompatible metallic materials used in biomedical engineering [1–6]. Due to their excellent electrical and thermal conductivity, mechanical properties, and corrosion resistance, metallic biomaterials have been and will continue to be an essential part of medical devices in the future [2]. However, biometallics show some undesirable characteristics and because of that their further development is of prime importance [1, 6].

Biometallics must meet certain criteria in order to be used in biomedicine (see Figure 1) [1, 6].

High osseointegration ability is the essential requirement which all biometallics must fulfill [1]. Osseointegration is a process of the direct interface formation between an implant and a bone, without a negative effect on the surrounding soft tissues [5]. The inability of the implant surface to connect with the adjacent bone and surrounding tissues will cause the formation of fibrous tissue around the implant and, in turn, promote prosthesis release [7]. Therefore, it is necessary for an implant to have an appropriate surface morphology, i.e. surface chemistry, surface roughness, and sur-

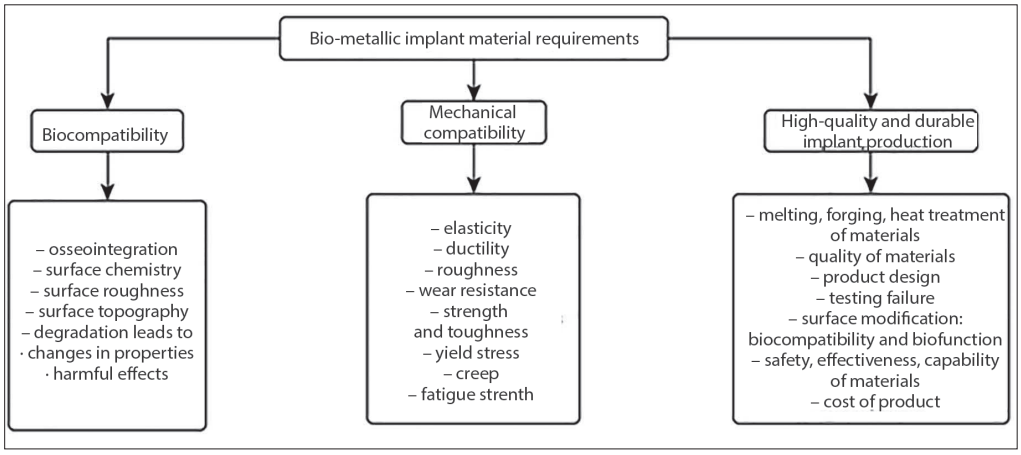

Figure 1. Implant material requirements for biomedical applications

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face topography, which will ensure its good integration. Accordingly, the implant surface modification is desirable in order to achieve improved biomechanical-biofunctional balance [8].

LASER SURFACE MODIFICATION

Surface modifications are used to improve implant biocompatibility and bioactivity, as well as to ensure proper osseointegration, with the objective of changing the surface physicochemical properties in order to improve bone healing and load transfer [7]. This can be achieved by altering the surface topography or by modifying surface chemistry.

Possibilities of changing/processing the surface of different biometallics using laser radiation are numerous and consequently various modern surface treatment techniques, such as ion implantation or coating, have lost their precedence in favor of laser processing [7, 8, 9]. Nowadays, lasers find widespread application in the medical device industry.

A laser represents a source of light radiation that emits a coherent photon beam, and as a source is stable in frequency, wavelength, and power [9]. In relation to other light sources, laser radiation is monochromatic, spatially oriented, intense, and coherent. All emitted photons of a laser beam, unlike photons in spontaneously emitted radiation, are completely identical, i.e. they have the same direction and phase.

The interaction of laser radiation and metallic targets depends on the characteristics of the laser radiation source, as well as on structural, optical and thermodynamic characteristics of the target, the focusing method, and the type and pressure of the surrounding atmosphere [10]. Laser radiation that falls on the surface is partially absorbed and partially reflected. Absorbed radiation causes heating, melting, and evaporation of the material.

A very important parameter describing the breakthrough of radiation into the material is the depth of absorption or optical breakthrough of light (Figure 2) [10]. By selecting radiation with low absorption depth, local changes in surface properties can be obtained without changing the (interior) volume of the material.

There are two mechanisms of removing surface particles using a laser: 1) laser-induced desorption (without any visible mesoscopic changes in the surface composition and structure) and 2) laser ablation (visible changes in the surface structure and composition) [11]. Laser-induced desorption and laser ablation are not completely separated, independent phenomena. Therefore, desorption and ablation should be observed as two phases in the process of laser interaction with the surface of the material [11].

Lasers provide directing a large amount of energy to a limited target area in order to achieve the desired material modification [7, 9, 10]. During the interaction of electromagnetic radiation with a solid target, the following changes can occur: radiation damage in the crystal lattice, structural changes leading to amorphization of the target and recrystallization in the collision zone, changes in the chemical composition of the target, and changes in the target surface topography caused by erosion and redeposition.

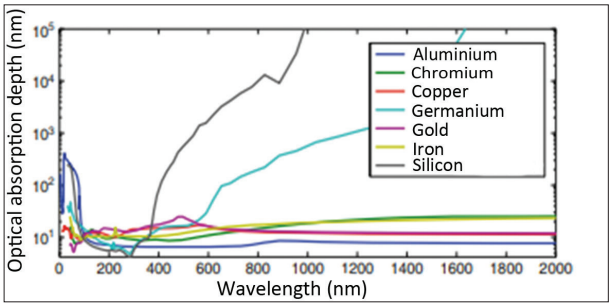

Figure 2. Optical absorption depths for diverse materials over a wide range of wavelengths [10]

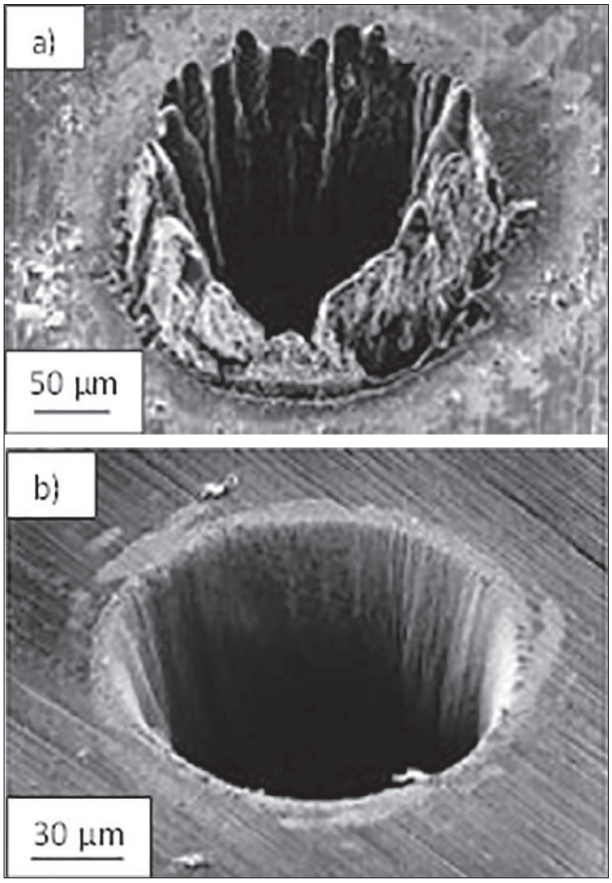

Figure 3. Craters obtained as a result of a) the femtosecond and b) the nanosecond laser radiation interaction with a steel surface [10]

The laser radiation-induced changes to the target surface depend on the characteristics of the laser beam, the number of accumulated impulses, the optical and thermophysical properties of the material, and the irradiation conditions (Figure 3) [7, 10].

If plasma is generated during the interaction of laser radiation with the material, it can significantly affect the intensity by which the radiation is acting on the surface and thus affect the formation of the crater [12]. The interaction of incident laser radiation and plasma can be expected during the use of a nanosecond and picosecond radiation, while in the case of ablation with femtosecond radiation, this interaction is absent.

LASER MODIFICATIONS OF IMPLANT MATERIALS

The surface morphological changes due to the action/interaction of the laser with the surface of the implant material can be examined using various techniques, such as light optical microscopy, scanning electron microscopy, energy dispersive spectroscopy, and profilometry [7, 13]. The first information on the surface morphological changes is obtained by light optical microscopy and scanning electron microscopy, while energy dispersive spectroscopy allows an estimate of the surface elemental composition. Topographic changes and specific surface geometry of the areas modified by the laser irradiation are analyzed by contact and non-contact profilometry.

Torres et al. [8] showed that in the case of the Ti-6Al-4V alloy, laser treatment in combination with different chemical and thermo-chemical treatments (etching and chemical oxidation) can enhance the surface bioactivity due to the formation of a stable titanium oxide layer. The laser modified surfaces manifested a rough surface covered with submicro- and nanopores.

If the energy density is close to the threshold of damage, formation of structures in the form of periodically repeated parallel waves can be expected while the surface of the target metallic material is being irradiated by the laser [14]. These structures are designated by the term laser-induced periodic surface structures (LIPSS). An important requirement for the occurrence of LIPSS is the surface roughness that allows for the intersection of the incident beam so that the polarized light, normal to the surface, can initiate electronic oscillations.

It is obvious from Figure 4 that the accumulation of a large number of impulses on the target, at a constant energy density and with different lasers, leads to an increase in the ablation depth and surface traces formation [13]. Zhang et al. [7] noticed that the laser beam radiation performance in a single-pulse and multiple-pulse mode results in different depths of damage. Ablation results in the formation of a prominent crater and the removal of the dissolved material from the surface.

Comparing the specific surface features obtained during the irradiation of a titanium implant in gaseous (air) and liquid (water) mediums, Trtica et al. [14] concluded that the liquid medium is a better choice for laser surface treatment since it results in better surface roughness (Figure 5). Also, the appearance of LIPSS is observed on the surface in both environments. In water environment, LIPSS are recorded after low-impulse interaction, while in the air atmosphere they occur after high-impulse interaction. It was found that during irradiation in the air, oxygen was absent from the central part of the laser beam, while its concentration was relatively high in the presence of water.

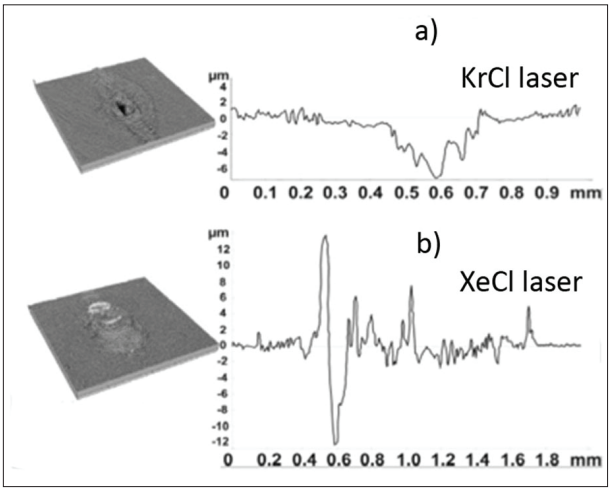

Figure 4. Profilometric analysis of the Ti-6Al-4V alloy surface after modification using a) KrCl and b) XeCl laser [13]

The water also shows a high oxidation capacity that stimulates bioactivity of the surface.

Trtica et al. [15] observed that irradiation treatment of titanium at high intensities contributes to the formation of large craters after a few pulses, and as the number of pulses increases, the creation of the surface craters with periodic structure can be expected. These properties enhance the titanium implants' biointegration potential. Also, wavelength increase results in more visible surface damage.

Laser modification improves the surface roughness [14, 15, 16]. In the air and oxygen atmosphere, the resulting surface structures correspond to the smooth, periodic dome structures. In the presence of increased oxygen concentration, an oxide surface layer is formed. In the nitrogen atmosphere, the obtained surface structure is non-compact and porous. The surface structure formed in the helium atmosphere is completely different and the presence of micropores can be noticed.

Hermann et al. [16] noticed that the presence of plasma protects the titanium surface from radiation and that further heating of the material can be achieved through the

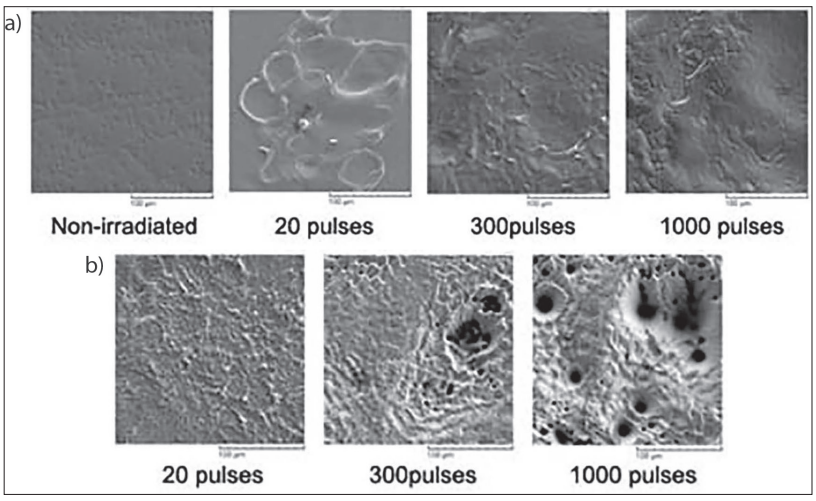

Figure 5. Scanning electron microscopy analysis of the Ti implant (target) surface after irradiation with picosecond laser pulses in a) air and b) water atmosphere [14]

plasma itself. A better transfer of energy to the material is achieved in the helium atmosphere.

LASER EFFECT ON THE IMPLANT TRIBO-MECHANICAL PROPERTIES

Wear occurs during relative movement of the joint parts that are in contact with each other, and results in the component damage [5]. The type and severity of the wear damage depend on many interaction factors and can be accompanied with processes such as corrosion, which in turn leads to the increased material loss and in extreme cases fast metallic implant failures.

Laser surface modifications can enhance wear resistance and friction properties of the implant [17]. Chen et al. [17] demonstrated that surfaces treated with high laser power showed higher hardness and wear resistance than the untreated and surfaces treated by low laser power.

One of the laser modification methods, used to improve mechanical properties, corrosion resistance, biocompatibility and wear resistance, is laser cladding [18]. Laser cladding enables the formation of the protective coating on the alloy substrate surface. Also, laser alloying, laser heat-treatment, and laser overlaying are methods which can be used in order to enhance the implant material hardness, wear, and corrosion resistance [19].

Low hardness values and poor tribological characteristics of metallic implant materials can be improved by laser powder deposition [18]. Comparing the Ti-6Al-4V substrate characteristics with the characteristics of the Ti-Al intermetallic coating formed on the Ti-6Al-4V alloy surface (Figure 6), Liu et al. [20] noticed that intermetallic coating displays lower friction coefficients due to the higher hardness values since the biometallics hardness and wear resistance are greatly influenced by each other [17–20].

The alloy microstructural characteristics, such as phase composition and grain size, greatly affect and determine alloy mechanical properties [5, 21]. There are numerous laser irradiation methods which can contribute to the achievement of excellent implant mechanical properties [21]. One of those methods is laser surface remelting. Using this method, grain refinement can be obtained in the remelting zone. Diagrams presented in Figure 7 show a great improvement in mechanical properties achieved by laser treatment [21]. Laser surface remelting increases the elastic modulus and hence metallic material stiffness and hardness, throughout the material microstructural transformations. From Figure 7 one can observe that the hardness value is the highest in the remelting zone, and the lowest in the metal substrate zone. This also applies to the elastic modulus.

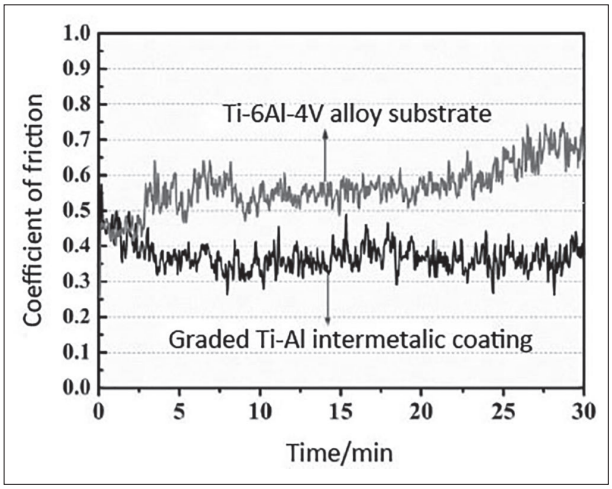

Figure 6. Friction coefficients variation for the Ti-6Al-4V substrate and Ti-Al intermetallic coating [20]

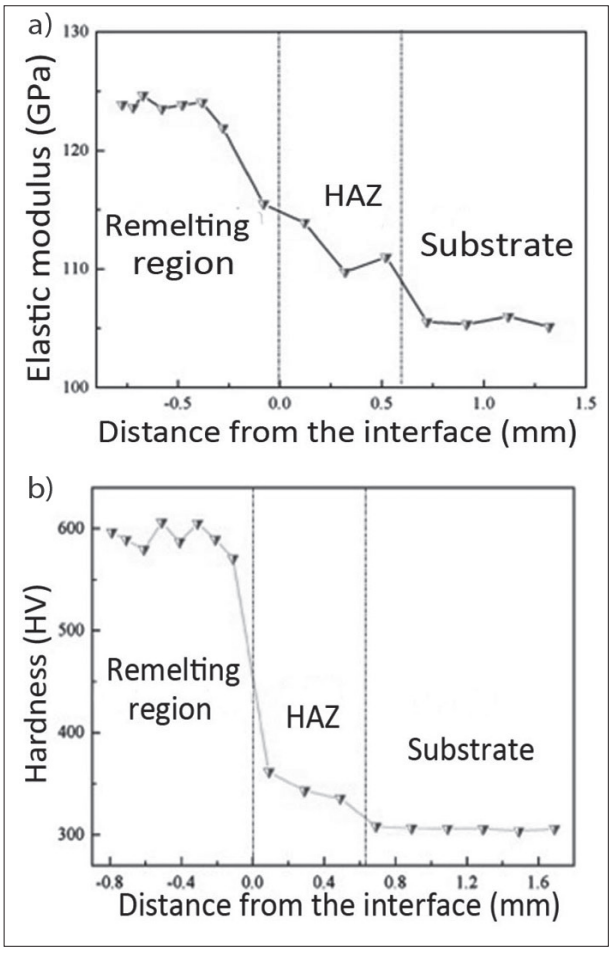

Figure 7. Elastic modulus a) and hardness b) of the Ti-Zr alloy in different laser-treated regions [21]

CONCLUSION

When developing new materials for biomedical applications, most attention is devoted to implant material biocompatibility, non-toxicity, and osseointegration. Desirable characteristics of bioimplants can be achieved by surface modifications. Laser surface modification is one of the methods by which the enhancement of mechanical, physical, and tribological characteristics can be obtained. Excellent surface roughness, high hardness value, outstanding biocompatibility, and implant surface bioactivity, non-toxicity, excellent corrosion and wear resistance, low friction coefficients and porosity can be achieved. The

interaction of laser pulses with the metallic implant material surface causes changes in the surface morphology, optical characteristics, chemical composition, etc., according to the selected parameters of the laser beam. Surface periodic structures can be formed by laser modification, and the appearance of these structures can influence the improvement of the implant surface characteristics and implant osseointegration.

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Ласерска површинска модификација металних имплантантних материјала

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САЖЕТАК

Метални биоматеријали се најчешће користе за израду имплантаната чврстих структурних делова људског тела због својих добрих механичких карактеристика и одличне биокомпатибилности.

Циљ рада је да се прегледно представе различите технике површинске модификације имплантантних материјала са посебним осврtом на методу ласерске модификације површине, као и многобројне карактеризационе методе за испитивање утицаја процеса површинске модификације на својства металних имплантантних материјала. Осим тога, представљен је и разматран утицај ласерског зрачења на површинске и механичке карактеристике, као и на структуру металних биоимплантаната. Испитивање утицаја ласерског зрачења високог интензитета на површину металних материјала првенствено обухвата испитивање морфолошких површинских промена и формирања специфичних површинских структура, које доприносе побољшању осеоинтеграције металних имплантаната.

Кључне речи: метални имплантантни материјали; ласерско зрачење; површинска модификација; осеоинтеграција

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ARTICLE FOR PRACTITIONERS / РАД ЗА ПРАКСУ

Use of intraoperative neurophysiological monitoring in surgical treatment of spinal diseases

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SUMMARY
Intraoperative neurophysiological monitoring (IONM) is a method, which uses different kinds of electrophysiological methods for monitoring and mapping of neural structures during surgical procedures with the aim to preserve them. If we know how important the function of the spine, spinal cord, nerve roots, and all other structures are, it is obvious how important it is to preserve them in surgical procedures where these structures are under risk. Although the frequency of neurological complications is not high, it is considered that these deficits are devastating complications of spinal surgery, which can have serious consequences on the quality of life and can increase health care costs. Because of that, the accent is on intraoperative neurophysiological methods development, which provide optimal monitoring of the spinal cord function during routine and complex spinal procedures and has high efficacy detecting possible neurological deficits. The concept of multimodal neuromonitoring, which is used today, relies on advantages of each modality separately and then in combination of these modalities it achieves a more reliable estimation of functional integrity. Today IONM is routinely used worldwide, but in Serbia, its use is still limited even though its advantages are well known.
Keywords: intraoperative neuromonitoring; neurological complications; spine surgery

Intraoperative neurophysiological monitoring (IONM) is a method, which uses different kinds of electrophysiological methods for monitoring and mapping of neural structures during surgical procedures with aim to preserve them. Certain kinds of IONM were used in the early 1970s and 1980s. Their use became everyday practice in different types of surgery, especially in neurosurgery and orthopedic surgery. Today IONM is routinely used worldwide, but in Serbia, its use is still limited, even though the advantages are well known.

Pathology of the spine is very diverse. There are deformities, degenerative diseases, injuries, and tumors, which could be primary and metastatic. The conservative therapy can be used in some occasions, but surgery is often the only possible option. If we know how important the function of the spine, spinal cord, nerve roots, and all other structures are, it is obvious how important it is to preserve them in surgical procedures where these structures are under risk. Recent data from literature report that new deficits in scoliosis surgery in adolescent population vary between 0.4–4.5% and in adult population 1.9–2.4% [1, 2]. Cramer et al. [3] reported the rate of neurological deficits of 0.178%, in a ten year-long retrospective study that included degenerative, neoplastic, traumatic, and infectious disease. Hamilton et al. [4] reported new neurological deficit in 1% of cases in their study from 2011, which included 108,419 spinal procedures, in adult and pediatric population. Although the rate of neurological complications is not that high, it is considered that these deficits are devastating complications of spinal surgery. Even if complications are rare, there is always a risk of neural structures injuries, which can have serious consequences on the quality of life, and an increase of health care costs [5, 6, 7]. Because of that, it is important to develop intraoperative neurophysiological methods, which could reliably monitor spinal cord during the surgical interventions.

Depending on spine pathology, symptoms could be various, but neurological deficits of varying degrees are very often present. The most often pathologies are certainly degenerative diseases of spine. The first symptom includes pain, usually lumbar pain, neck pain, or rarely arm pain, and thoracic pain is the rarest. Disc herniation in the cervical spine is usually at C5–6 level and C6–7 level, and anterior cervical discectomy and fusion is one of the most frequently performed procedures in neurosurgery. Depending on the herniated disk position and affected neural structures, clinical appearance can be either in the form of radiculopathy, myelopathy or both. Different authors reported complications in treatment of cervical myelopathy, with the most severe consequence being cervical medulla compression, from 4.4–20% [8, 9]. The rate of complications in patients without myelopathy is very low 0.09–0.6% [10, 11]. Kelleher et al. [12] found that sensitivity

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of somatosensory evoked potentials (SSEP) was 52% and specificity 100% in a study, which included 1055 cases with operation on the cervical spine. Sensitivity of motor evoked potentials (MEP) was 100% and specificity 96%, sensitivity of EMG was 46% and specificity 73%. In the lumbar spine, the most commonly affected levels are L4–5 and L5–S1. Gunnarson et al. [13] found sensitivity of SSEP 28.6% and specificity of 98.7%, EMG sensitivity was 100% and specificity 23.7% in the lumbar spine procedures. Therefore, it is considered that combined use of different modalities of IONM in these procedures provide higher sensitivity and specificity, allow timely intervention, decrease postoperative complications, and improve final outcome [14].

Primary tumors of the spine are rare, but metastatic tumors are common. Tumors can affect bone structures of the spine or they can be intraspinal. There are a few subgroups of intraspinal tumors. They can be extradural and intradural, while intradural tumors can be extramedullary and intramedullary. These tumors could be benign or malign, but due to their localization, they have a very high risk of neural complications during surgery, particularly intramedullary tumors.

During the surgical procedures, neurological deficits may arise from direct surgical injury of neural tissue, compression, traction, or compromised blood supply in the neural tissue [15]. Compressive spinal epidural or subdural hematoma can occur after surgical treatment and can be detected early using IONM [16]. In degenerative spinal disease mechanical compression from ligamentum flavum, posterior longitudinal ligament, intervertebral disc or bone structures can affect neural elements [16]. Positioning is also a crucial factor, which can cause compression or neural structures injury during spinal procedures [17]. The use of IONM in spinal surgery significantly decreases the risk of intraoperative damage of neural structures during each phase of a surgery and improves the outcome of surgical treatment.

SSEP were primarily used in scoliosis surgery and they significantly improved positive outcome of these operations. It is considered that the use of SSEP reduces paraplegia for 60%. SSEP estimate dorsal column medial lemniscus system from the periphery to the somatosensory cortex. Stimulation is performed on periphery mixed nerves, for upper extremities typically on median or ulnar nerve, while for lower extremities on posterior tibial nerve or common peroneal nerve. Needle and surface electrodes are usually used. Registration can be performed at appropriate places on the scalp, above somatosensory cortex, according to 10–20 International Electrode System, but also on subcortical and peripheral level. At the intraoperative phase of procedures, before and after positioning, we set the base line up, which serves as a control for potentials obtained during the operation. They can be recorded continuously throughout the operation, while they change the amplitude and latency, which are compared to the base line. At that moment, it is necessary to analyze all the variations in the context of technical issues, anesthesia effects, general effects, and surgical manipulation. An alarm criterion is the amplitude decrease for 50% with or without the increase of latency [18]. It is very important to keep in mind sensitivity to inhalational anesthetics, systemic factors such as hypothermia, hypotension, and hypoperfusion. In addition, not all decreases of amplitude are clinically significant. If amplitude decreases on 50% or lower of the base line, risk is higher, but an appropriate and timely reaction can lead to SSEP recovery and it can preserve the function. It is crucial whether changes occur gradually or suddenly. The most difficult is a sudden and complete loss of potentials without recovery. Stable intraoperative potentials are good predictors of a positive neurological outcome. Nuwer et al. [19] estimated the clinical efficacy of SSEP monitoring during scoliosis surgery in their extensive multicentric study, and they found that sensitivity was 92% and specificity 98.9% in detection of postoperative neurological deficits.

MEP managed to take standard place in IONM in the last three decades. In the 1980s, it was shown that transcranial use of high voltage pulses could induce contralateral motor activity. This technique is very sensitive to anesthesia, so during the time multi-pulse stimulation technique was developed with variation of anesthetics use. In the 1990s, this technique became a routine for monitoring corticospinal tract. These potentials are safe and reliable for use in spinal procedures [20]. The most common way for eliciting MEP is transcranial electrical stimulation with electrodes placed on the scalp over the motor cortex according to 10–20 International Electrode System, and with direct cortical stimulation. The most suitable for use on the scalp are corkscrew electrodes because of their stability and low impedance, and for direct cortical stimulation, strip electrodes are used. Registration can be done on peripheral muscles, as compound muscle action potential (CMAP), which are the result of α motor neuron activation and on spinal cord as the D wave. Registration from muscles is performed with needle electrodes, which are placed on the appropriate places. D wave registration is performed with special electrodes, which can be placed in epidural or subdural space. MEP is very sensitive to anesthetics and myorelaxants. Anesthesia is based on the use of propofol and opioids such as fentanyl and remifentanil, while myorelaxants can be given only at the beginning for intubation. It is very important that D wave is not under the effects of anesthesia. Amplitude and latency of D wave vary depending on the spinal cord level. If the change is more caudal, amplitude will decrease and latency will increase. Below the T9 level, it is very difficult to record a reliable D wave. It is considered that D wave is the most important during intramedullary spinal tumor operations [21]. At the beginning of the surgery, we set up the base line before and after positioning of a patient. Amplitude, latency, and intensity of stimulation are monitored. In addition, all changes of MEP are considered in the context of anesthesia, systemic effects, surgical manipulation and their development, whether they be gradual or sudden. There are different criteria, which can warn us that MEP changes could be significant. One group of authors suggest intensity of stimulation, others propose changes of amplitude, while some recommend only presence or absence of MEP [22, 23, 24]. Quinones-Hinojosa et al. [25] state

that changes in amplitude and reduction of complexity of MEP curve correlate with motor outcome. Multichannel monitoring of MEP has higher specificity, sensitivity, and prediction of postoperative motor deficits [26]. In spine surgery of intramedullary tumors, one of the most reliable criteria is combination of MEP and D wave. Complete loss of MEP without changes of D wave, or with changes above 50% of D wave amplitude correlate with temporary motor deficit. Complete loss of MEP and decrease below 50% of D wave amplitude, or loss of D wave is a predicator of permanent deficit [27].

Electromyography (EMG) records electrical activity of muscles. It can be a free-run EMG, which registers spontaneous muscle activity and it allows continuous monitoring, and it can be triggered EMG, which implies direct stimulation of peripheral motor nerves or spine roots and registration of CMAP in the appropriate muscle. Surgical manipulations in form of traction, dragging and compression lead to activation of specific muscles, and that could be registered on free run EMG. Changes can be in the form of spikes, bursts, and trains. Spikes and bursts give us information about the vicinity of a nerve root and they usually appear because of the contact with surgical instruments [28]. Trains appear when continuous force acts on nerve roots, and are clinically significant because they indicate possible injuries [28]. Use of triggered EMG is highly recommended for adequate positioning of pedicle screws, because breach of pedicle cortex can cause injuries of nerve roots and spinal cord. In anesthesia, paralytic agents are contraindicated, with the exception of myorelaxants when anesthesia is first introduced. Relaxation is checked with standard train of four methods. In addition, it is very important to determine whether there are comorbidities such as myasthenia gravis, muscle dystrophy, or similar pathology, which can have influence on EMG.

The concept of multimodal monitoring used today relies on advantages of each modality separately and then, in combination of these modalities, it achieves more reliable functional integrity estimation. In the study, which included spinal procedures of deformities, spinal stenosis and spinal tumors, Sutter et al. [29] found sensitivity of multimodal monitoring of 89% and specificity of 99%. American Academy of Neurology and American Clinical Neurophysiology Society guidelines recommend the use of intraoperative monitoring of MEP and SSEP in spinal surgery as an effective tool in prediction of increased risk of neurological complications [30].

The combination of SSEP, MEP, free-run and triggered EMG provides optimal monitoring of the spinal cord function during routine and complex spinal procedures and has high efficacy in detecting of possible neurological deficits.

This article was done in accord with standards of the institutional Committee on Ethics.

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Примена интраоперативног неурофизиолошког мониторинга у оперативном лечењу обољења кичменог стуба

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САЖЕТАК

Интраоперативни неурофизиолошки мониторинг подразумева употребу различитих електрофизиолошких метода у сврху праћења функционалног интегритета и мапирања одговарајућих нервних структура током хируршке интервенције са циљем њиховог очувања. Ако знамо колико је важна улога кичме, кичмене мождине, нервних коренова, јасно је колико је важно очувати их током операција у којима постоји могућност њиховог оштећења. Иако стопа неуролошких компликација није висока, оштећења ових структура се сматрају поражавајућом компликацијом спиналне хирургије и могу имати значајан утицај на квалитет живота и повећање трошкова лечења ових болесника. Због тога се акценат ставља на развој метода интраоперативног неурофизиолошког мониторинга које омогућавају оптимално праћење функције кичмене мождине и нервних коренова током рутинских и комплексних захвата у спиналној хирургији, и имају високу ефикасност у детекцији могућих неуролошких оштећења. Концепт мултимодалног неуромониторинга који се данас користи ослања се на предност сваког модалитета посебно, а њиховом комбинацијом постиже се много поузданија процена функционалног интегритета. Данас се интраоперативни неурофизиолошки мониторинг користи рутински широм света; међутим, код нас је његова употреба још увек ограничена, иако су њене предности веома добро познате.

Кључне речи: интраоперативни неуромониторинг; неуролошке компликације; операција кичме

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Правне реформе у области јавног здравља у оквиру приступања Републике Србије Европској Унији – преглед регулаторних стандарда

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САЖЕТАК
Приступање Европској унији (ЕУ) представља свеобухватан процес реформе и хармонизовања законодавства са прописима ЕУ који нужно мора бити праћен и имплементацијом стандарда ЕУ. Иако су надлежности Европске уније у области здравствене заштите ограничене, а здравствено право не представља значајан део европског законодавства, у бројним областима је неопходно извршити усаглашавање и спровести даље реформе. Главни фокус овог рада представља преговарачко Поглавље 28 у оквиру процеса приступања ЕУ, које у домену јавног здравља обухвата више тематских области, у којима постоје законодавни и стратешки акти ЕУ. Имајући у виду да Србија још увек није отворила преговоре о приступању у оквиру овог поглавља и у циљу ближег упознавања здравствених радника у Србији са овом тематиком, у раду се анализирају најважнији аспекти усклађивања са правом ЕУ и потребе за даљим реформама домаћих прописа.
Кључне речи: Европска унија; хармонизација законодавства; јавно здравље; процес приступања

УВОД

Процес приступања Европској унији подразумева свеобухватну реформу правног система и прилагођавање њеним стандардима у великом броју области живота. У овом раду анализирају се најважнији аспекти усклађивања српске регулативе у области здравства са правом ЕУ и потребе за даљим реформама прописа уз препоруке за даље кораке у њиховом усклађивању. Домен јавног здравља и здравствене заштите, а нарочито питање права по основу здравственог осигурања, налазе се готово у потпуности у надлежности држава чланица Уније, што чини да се ова разликује од многих других области права ЕУ. Ипак, имајући у виду сложен карактер система као што је ЕУ, у великом броју поддомена координација држава чланица довела је до усвајања прописа који чине *acquis* (скуп правних норми ЕУ), уз покретање низа иницијатива и програма усмерених на унапређење јавног здравља на подручју Уније. Додатно, од значаја за јавно здравље и здравствене раднике јесу и бројна правила ЕУ која су настала у оквиру других правних области и политика Уније, а превасходно у домену слободе кретања људи (радника) и обављања делатности у другим државама чланицама.

У последњем извештају о напретку Србије у процесу европских интеграција за 2019. годину закључено је да је Србија умерено припремљена у областима заштите потрошача и здравља, које су обухваћене преговарачким Поглављем 28 [1]. У својој анализи Европска комисија (ЕК) указује на недостатке у усклађивању законодавства и недостајућих кадровских капацитета за многа питања. Имајући у виду да Србија још увек није отворила преговоре о приступању у оквиру овог поглавља, постоји потреба за анализом законодавства и политика ЕУ у овој области, као и степена усклађености српских прописа [2]. Поред стандарда ЕУ, Србију обавезују и други стандарди, нпр. Светске здравствене организације, Уједињених нација, Савета Европе и Европског суда за људска права у Стразбуру, као и стандарди настали под окриљем других глобалних и европских организација, али они заслужују посебну анализу. Фокус овог рада представља преговарачко Поглавље 28, које у домену јавног здравља обухвата низ тематских области у којима постоје законодавни и стратешки акти ЕУ.

ЗДРАВСТВЕНО ПРАВО У ЕУ – ПОЛАЗНЕ ОСНОВЕ

Надлежности Европске уније у складу са оснивачким уговорима деле се на ексклузивне (оне које припадају искључиво ЕУ и којих је само пет), подељене (са државама чланицама, у које спада највећи број области) и координативне (у којима ЕУ у складу са чл. 6 Уговора о функционисању ЕУ подржава,

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координише и допуњује активности држава чланица) [3, 4]. У последњу надлежност спада и јавно здравље одн. заштита и унапређење људског здравља – област која је у највећој мери задржала статус националне политике, коју државе чланице воде у складу са својим уставним и културним традицијама [5, 6]. Ипак, значајан број питања у вези са здравственом заштитом, а поготово здравственим радницима и њиховим статусом, на пример у контексту слободе кретања у ЕУ и функционисања јединственог тржишта, јесте регулисан прописима ЕУ [7]. Ова питања нису обухваћена преговарачким Поглављем 28, али су од великог значаја за здравствене струке.

У складу са чланом 168 Уговора о функционисању Европске уније [8]: „… приликом утврђивања и спровођења свих политика и активности Уније обезбеђује се висок ниво заштите здравља људи. Деловање Уније, које допуњује националне политике, усмерено је на побољшање јавног здравља, спречавање физичких и менталних обољења и болести и отклањање узрока опасности по физичко и ментално здравље". Предвиђена је борба против великих опасности по здравље подстицањем истраживања њихових узрока, преноса и спречавања, као и информисање о здрављу и здравствено образовање, праћење, рано упозоравање и сузбијање озбиљних прекограничних претњи здрављу. Такође је предвиђено да Унија допуњује деловање држава чланица на смањењу оштећења здравља узрокованих дрогом, укључујући информисање и спречавање коришћења. Унија „подстиче сарадњу између држава чланица ради побољшања комплементарности њихових здравствених услуга" у прекограничним подручјима. Државе чланице, у сарадњи са Комисијом, међусобно усклађују своје политике и програме у раније наведеним областима. Члан 168 такође предвиђа да Комисија, у контакту са државама чланицама, може покренути било коју „иницијативу корисну за поспешивање наведеног усклађивања, а нарочито иницијативе које имају за циљ утврђивање смерница и показатеља, организовање размене најбоље праксе" и припрему елемената потребних за периодично праћење и оцењивање (тих напора, прим. аут.). Ова одредба је посебно значајна за Србију, имајући у виду да може представљати основу за развијање различитих облика сарадње са Унијом. Приликом деловања Уније поштују се одговорности држава чланица за утврђивање њихове здравствене политике, као и за организовање и пружање здравствених услуга и здравствене неге. Одговорности држава чланица укључују управљање здравственим услугама и здравственом негом, као и расподелу средстава која су им додељена.

ПРИСТУПАЊЕ ЕУ И ПРЕГОВОРИ – ОБЛАСТИ КОЈЕ ТРЕБА РЕФОРМИСАТИ

У Републици Србији у току је континуирани процес усклађивања законодавства са правним тековинама Европске уније. Иако у многим другим поглављима Европска комисија у тзв. скрининг извештајима одређује услове које треба испунити пре него што се отворе преговори (тзв. *benchmarks*), у случају Поглавља 28 нису постављени додатни услови ни у погледу дела I – права потрошача, нити дела II – јавно здравље. Скрининг извештај везан за Поглавље 28 је 2016. године сачинила Радна група ЕК за проширивање у процесу преговора у придруживању ЕУ [9]. Половином 2018. године је процењено да би Србија до краја исте године могла бити спремна за отварање Поглавља 28, али се то још увек није догодило. Комисија је ниво хармонизације проценила као задовољавајући, а у неким областима чак и као врло узнапредовао, као што ћемо демонстрирати у анализи која следи. У погледу здравственог кадра, Радна група ЕК је, на основу изјава српског преговарачког тима, закључила да здравственог особља, пре свега лекара, има довољно, али да је потребно унапредити његово планирање [9]. Међутим, када се ради о квалитету и безбедности у здравству, процењено је да је потребно доградити капацитете и постићи финансијску одрживост јавног здравља. Акценат се ставља на образовање здравствених радника, запошљавање младих и бољу координацију планирања радне снаге између Министарства за рад, запошљавање, борачка и социјална питања и Министарства здравља [9]. Додатно, у претходних неколико година у домену *е-здравства* су такође направљени значајни помаци.

Упркос задовољавајућим резултатима, до 2019. године још увек није дошло до одлуке Савета ЕУ да отвори ово преговарачко поглавље. Преглед свих тема дат је у Табели 1, док се у даљем тексту анализира хармонизација у овим областима. Сам процес хармонизације и његова (оквирна) динамика предвиђени су Националним програмом за усвајање правних тековина ЕУ [10]. Значајан допринос сагледавању нивоа усклађености, али и имплементације европских стандарда, пружају и редовни годишњи извештаји Европске комисије о напретку Србије као кандидата у процесу европских интеграција. У последњем доступном извештају за 2019. годину на више места се оцењује да је релативно слаба имплементација програма у доменима у којима ЕУ има координативну надлежност, попут питања скрининга рака или промоције здравих стилова живота (исхрана и физичка активност) [1]. У том смислу се и намеће потреба да се, поред даљег усаглашавања законодавства, у мери у којој то није до сада извршено, више средстава и активности усмери на реализацију програма насталих у оквиру ове политике ЕУ.

Контрола дувана представља област у којој је тек потребно извршити усклађивање. Републичка стручна комисија за контролу дувана Министарства здравља (МЗ) припремила је нацрт нове Стратегије контроле дувана у РС 2016–2025. године са Акционим планом (2016–2020), узимајући у обзир легислативу ЕУ и потребе усаглашавања националних прописа, Оквирну конвенцију о контроли дувана Светске здравствене организације (СЗО), као и успешност спровођења прописаних мера претходне стратегије [11], нове научне доказе и најбољу праксу у контроли дувана. Важећи Закон о дувану само је дели-

Табела 1. Области обухваћене преговарачким Поглављем 28
Table 1. Fields encompassed by negotiation Chapter 28

1	Контрола дувана Tobacco control
2	Озбиљне прекограничне претње по здравље (укључујући заразне болести) Serious cross-border health threats (including communicable diseases)
3	Биомедицина (трансфузија крви, трансплантација органа, ткива и ћелија, биомедицински потпомогнуто оплођење) Biomedicine (blood transfusion, organ, tissue, and cell transplantation, biomedical assisted fertilization)
4	Прекогранична здравствена заштита Cross-border healthcare
5	Фармацеутски производи, медицинска средства, активна имплантибилна медицинска средства, и *in vitro* дијагностичка медицинска средства Pharmaceutical products, medical supplies, active implantable medical devices, and *in vitro* medical diagnostic devices
6	Ретке болести Rare diseases
7	Скрининг рака Cancer screening
8	Ментално здравље Mental health
9	Превенција злоупотребе дроге Drug abuse prevention
10	Смањење штетних последица употребе алкохола Alcohol-related harm reduction
11	Неједнакости у здравству Health inequalities
12	Козметички производи Cosmetic products

мично усклађен са најновијом Директивом 2014/40/ЕУ о усклађивању закона, уредби и других прописа држава чланица у вези са производњом, презентацијом и продајом дувана и сродних производа. Ова директива се у државама чланицама примењује од маја 2016. године и њоме су уведене бројне нове мере контроле дувана. Закон о дувану није усклађен ни са делегираном Директивом комисије 2014/109/ЕУ о измени Директиве 2014/40/ЕУ успостављањем збирке сликовних упозорења за употребу на дуванским производима. С друге стране, Закон је усклађен са Препоруком 2003/54/ЕУ од 2. децембра 2002. о превенцији пушења, тиме што се уводи забрана пушења у затвореним просторијама. Закон је само делимично усклађен са Препоруком Савета 2009/Ц 296/02 о средини без дуванског дима јер не прописује потпуну забрану пушења у угоститељским објектима. Неусклађеност у овој препоруци примећује и Европска комисија у свом извештају [1]. Припрема предлога закона у области контроле дувана, као и подзаконских аката, у надлежности је Министарства здравља, Министарства финансија и Министарства трговине, телекомуникација и туризма. За инспекцијски надзор над спровођењем Закона надлежни су санитарни, здравствени, инспектори за лекове и медицинска средства, тржишни инспектори, инспектори рада и туристички инспектори, просветни инспектори, сваки у оквиру свог делокруга рада који је прописан посебним законом. Подељена надлежност значајно отежава контролу примене ових прописа. Законом о заштити становништва од изложености дуванском диму је, у оквиру Института за јавно здравље Србије, основана Канцеларија за превенцију пушења. Додатно, за област контроле дувана Министарство здравља је основало Републичку стручну комисију за контролу дувана као своје експертско и саветодавно тело. Сачињен је нацрт измена Закона о заштити становништва од изложености дуванском диму, којим се прописује потпуна забрана пушења у затвореним просторима и за све угоститељске објекте. Оног тренутка када измене буду усвојене, биће постигнуто потпуно усклађивање са делом Препоруке Савета 2009/Ц 296/02 у вези са простором без дуванског дима.

Са друге стране, као пример усклађености са прописима ЕУ издваја се област **озбиљних прекограничних претњи по здравље** (укључујући заразне болести). Нови Закон о заштити становништва од заразних болести донет 2016. године у великој мери је усклађен са регулативом ЕУ [12], као и Међународним здравственим правилником (МЗП) СЗО. Кроз МЗП, СЗО подржава државе чланице у заједничком послу спасавања здравља од прекограничног ширења инфективних болести и других ризика по здравље. Мере превенције заштите од заразних болести су, ипак, остављене појединачним националним законодавствима на регулисање [13]. Према Извештају о напретку Србије у процесу европских интеграција: „капацитети за надзор и реаговање и даље су ограничени и потребно их је модернизовати. Још увек није уведен централизован здравствени информациони и комуникациони систем“ [1], те је потребно радити у том правцу.

Област **биомедицине (трансфузија крви, трансплантација органа, ткива и ћелија, и биомедицински потпомогнуто оплођење)** представља даљи домен у коме је у извесној мери извршено усклађивање са актима ЕУ, кроз усвајање Закона о трансфузијској медицини (2017), Закона о биомедицински потпомогнутој оплодњи (2017), Закона о људским ћелијама и ткивима (2018) и Закона о пресађивању људских органа (2018). Претходни сет закона – Закон о лечењу неплодности поступцима биомедицински потпомогнутог оплођења (2009), као и други закони у области биомедицине, на недоследан начин су дефинисали услове, организацију и делатност у биомедицини, као и инспекцијски надзор над обављањем те делатности, те на тај начин ова област није била правно регулисана у складу са савременим стандардима медицинске науке и струке, као ни с прописима Европске уније [14]. Према процени Европске комисије, доношењем новог сета закона постигнут је ограничен напредак у усклађивању са правним тековинама које се односе на крв, ткива, ћелије и органе, након доношења Закона о трансфузијској медицини и Закона о биомедицински потпомогнутом оплођењу. Општи административни и технички капацитети Управе за биомедицину као надлежног органа за вршење надзора над сектором и даље су слаби [1].

Прекогранична здравствена заштита представља тему која ће у контексту европског права и слободе кретања грађана ЕУ на значају добити тек после

могућег приступања ЕУ. При изради нацрта Закона о правима пацијената РС (Закон о правима пацијената, Службени гласник РС, бр. 45/2013) увидела се потреба да се и ово питање уреди, међутим, то је остављено за каснији период [15]. Након приступања ЕУ, очекује се повећање броја захтева пацијената за прекограничну здравствену заштиту, те повећање обима посла и трошкова, како на националном тако и на локалном нивоу. Иако Закон о здравственој заштити садржи одредбе о прекограничној здравственој заштити, национални правни оквир није усаглашен са Директивом 2011/24/ЕУ о правима пацијената у прекограничној здравственој заштити, те са Регулативом (ЕК) 883/2004 о координацији система социјалне сигурности и Уредбом (ЕК) 987/2009 којом се установљава процедура примене Уредбе 883/2004. Усаглашавање ће бити потребно по следећим питањима: именовање националне контакт тачке за комуникацију у прекограничној здравственој заштити; увођење упоредивог система осигурања за грешку у лечењу; могућности здравствене заштите у иностранству о трошку осигурања; права и могућности пацијента на даљински приступ сопственом сету здравствених података; успостављање транспарентног административног поступка за могућност лечења странаца у Србији; признавање рецепата издатих у другој држави чланици; информатичка подршка свим овим процесима, као и развој међусобних механизама подршке са другим земљама чланицама и др. С обзиром на очекивани повећани обим посла због примене прописа ЕУ, биће потребно унапредити кадровске капацитете и структуру у свим наведеним институцијама.

Следећи скуп правила ЕУ односи се на релативно хетерогену групу коју чине **фармацеутски производи, медицинска средства, активна имплантибилна медицинска средства, и *in vitro* дијагностичка медицинска средства**. Закон о лековима и медицинским средствима из 2010. године је углавном, са накнадним изменама, обухватао стандарде који се користе у ЕУ и представља унапређену регулативу и политику везану за лекове у овој области. Неки делови регулативе ЕУ нису били усвојени, као на пример признавање одлука издатих од стране Европске агенција за лекове (*EMA*) или других надлежних тела у ЕУ. У циљу хармонизације, донет је Закон о медицинским средствима (Службени гласник РС, бр. 105/2017), који је усаглашен са прописима ЕУ. У делу који се тиче лекова, Закон о лековима и медицинским средствима из 2010. године још увек није мењан. Његове измене се, према Плану рада Владе, очекују у децембру 2019. године.

Највећи део регулативе ЕУ у **области ретких болести** није обавезујући. Ипак, национални оквир је у последњих неколико година унапређен, у смислу доношења Закона о превенцији и дијагностици генетичких болести, генетички условљених аномалија и ретких болести, као и Одлуке о оснивању буџетског фонда за лечење обољења, стања или повреда који се не могу успешно лечити у Републици Србији. Очекује се усвајање националне Стратегије за ретке болести у Републици Србији, са одговарајућим Акционим планом, чиме ће се делимично одговорити на многобројне проблеме са којима се суочавају оболели од ретких болести и чланови њихових породица [16, 17].

У **области скрининга рака** не постоји обавеза правног усклађивања. Уместо тога, планови усаглашавања подразумевају минимално усклађивање домаћих прописа са одлукама ЕУ. Национални програм за усвајање правних тековина ЕУ наводи конкретне планове и мере до 2021. године [10]. Када се ради о пракси, према последњој оцени Европске комисије, промоција здравља по питању незаразних болести још није напредовала. Национални скрининг рака за колоректални карцином, карцином дојке и карцином грлића материце споро напредује – у многим деловима земље се обавља само спорадично и несистематично [1].

Највећи део регулативе ЕУ у **области менталног здравља** није обавезујући. Област менталног здравља у Републици Србији је, међутим, мултисекторског карактера, тако да прописи релевантни за ову област сежу бар у три сектора: сектор здравља, сектор социјалне заштите и сектор правде, а релевантан је и сектор образовања, те реформе у овој области представљају посебан изазов [18, 19]. Осим тога, правни акти који не представљају регулативу ЕУ, као на пример Конвенција УН о правима особа са инвалидитетом (коју је Србија ратификовала 2009. године), обавезују и земље чланице ЕУ.

У поступку усклађивања **области психоактивних контролисаних супстанци** односно **превенције злоупотребе дрога** са прописима Европске уније, 2018. године су усвојене измене и допуне Закона о психоактивним контролисаним супстанцама. Измене су у складу са регулативом ЕУ: Регулатива (ЕК) бр. 1920/2006, релевантним одлукама Савета ЕУ (2005/387/ЈХА и 2001/419/ЈХА), Стратегијом о дрогама ЕУ (2013–2020).

У погледу **смањења штетних последица употребе алкохола**, Влада Републике Србије је усвојила Уредбу о националном програму превенције штетне употребе алкохола и алкохолом узрокованих поремећаја у Републици Србији (Службени гласник РС, бр. 115/2017), која је ступила на снагу 30. децембра 2017. године. Акт је усаглашен са препорукама и закључцима ЕУ.

Правни прописи Републике Србије су у великој мери усклађени са тзв. Комуникационом студијом и препорукама ЕУ у **области неједнакости у здрављу**. Неки од националних правних аката су у процесу дораде, чиме се иде у корак са ЕУ и међународним законодавством (јавно здравље, борба против ХИВ/АИДС). У извештају о напретку Србије у интеграцијама ЕУ истакнуто је да је неопходно побољшати приступ услугама здравствене заштите особама са инвалидитетом, особама које живе са ХИВ-ом, деци и одраслима који користе дроге, затвореницима, женама које се баве проституцијом, ЛГБТ особама, интерно расељеним лицима и Ромима [1]. У односу на осетљиве друштвене групе то препознаје и истиче и домаћа литература, али уз шири, међусекторски приступ [20, 21].

У погледу **козметичких производа**, претходни Закон о здравственој исправности предмета опште употребе из 2011. није био усаглашен са Уредбом

бр. 1223/2009. Нови Закон о здравственој исправности предмета опште употребе донет је у априлу 2019. године (Службени гласник РС, бр. 25/2019). Њиме је транспонована Уредба и обезбеђен висок ниво заштите здравља људи, као и функционисање унутрашњег тржишта и слободног кретања козметичких производа на тржишту, те дефинисани захтеви у погледу безбедности козметичких производа. Имајући у виду сложену тематику, Закон о предметима опште употребе потпада и под преговарачко Поглавље 1 са Европском унијом – слободно кретање робе.

Регулатива која се тиче **превенције повреда и промовисања безбедности** и у националним и у међународним оквирима потпада под различите секторе. Када се ради о здравству, национална правна регулатива је у великој мери усклађена са регулативом ЕУ. Неки од националних правних аката су у процесу дораде, чиме се иде у корак са ЕУ и међународним законодавством (Стратегија јавног здравља, протоколи за заштиту од злостављања и занемаривања деце, жена, старијих особа...).

ПИТАЊА КОЈА НИСУ ОБУХВАЋЕНА ПОГЛАВЉЕМ 28

Постоји низ питања која нису обухваћена Поглављем 28, јер примарно имају други циљ, мада битно утичу на здравље, те су обухваћена другим поглављима у оквиру преговора са ЕУ. Ова питања, између осталог, обухватају и тематику слободе кретања и обављања делатности здравствених радника из других држава чланица ЕУ. Додатно, право грађана (додуше ограничено) да траже здравствене услуге код страних пружалаца у извесном смислу ствара и „европско тржиште здравствених услуга за које је потребна регулација“ [22]. У процесу хармонизације потребно је донети и ускладити прописе у областима признавања академских и професионалних квалификација, између осталог, и за професије у здравству. Хармонизација регулативе у овој области је предуслов за остваривање слободе кретања, слободе пружања услуга и слободе настањивања држављана Републике Србије у ЕУ, али и држављана чланица Европске уније и држава потписница Споразума о европском економском простору, када желе да раде у Србији. Европска унија ова питања уређује Директивом 2005/36/ЕЗ о признавању професионалних квалификација и Директивом 2013/55/ЕУ о измени Директиве 2005/36/ЕЗ и Уредбе ЕУ 1024/2012 о административној сарадњи путем Информационог система унутрашњег тржишта. Пред оне који желе да реализују ову слободу постављају се разни захтеви везани за време студирања и диплома, односно квалификација и способности стечених у другој држави чланици. Да би се ти захтеви испунили, било је потребно дефинисати методе поређења диплома или професионалних искустава стечених у разним државама чланицама ЕУ и установити узајамно поверење између њих. Министарство просвете, науке и технолошког развоја Републике Србије сачинило је Нацрт Закона о регулисаним професијама и признавању професионалних квалификација, којим се, између осталог, прописује режим аутоматског признавања професионалних квалификација на основу минималних услова оспособљавања и то за професију доктора медицине (укључујући и доктора медицине специјалисту и доктора опште медицине специјалисту), доктора денталне медицине (укључујући и доктора денталне медицине специјалисту), фармацеута, медицинску сестру опште неге и бабицу. Иако се ради о здравственим професијама, напори у хармонизацији ове регулативе потпадају под преговарачко Поглавље 3, а не Поглавље 28, с обзиром на то да ово нису једине професије за које је потребно ускладити услове за признавање квалификација и с обзиром на то да ова материја примарно представља право пословног настањивања и слобода пружања услуга.

На овом месту неопходно је нагласити и постојање европског система за издавање дозвола за стављање лекова у промет. Овај режим посебно је важан због приступања заједничком тржишту 28 држава чланица, као и могућности добијања једне дозволе за дистрибуцију лека кроз централизовану, децентрализовану и процедуру међусобног признања дозволе за промет лекова – Директива 2001/83/ЕЗ и касније измене и допуне. Ради примене овог режима, у свим чланицама ЕУ формирана су специјализована тела, а сарадња се обавља и кроз Европску агенцију за лекове и њена стручна тела [23].

Као што је већ истакнуто, тематика јавноздравствене политике обухвата много више од саме здравствене заштите. Отуда је 2006. године, док је Финска председавала Европској унији, концепт „Здравље у свим политикама“ (*Health in All Policies – HIAP*) први пут употребљен за међусекторску сарадњу у правцу реализације заједничких циљева [24].

Приступ „Здравље у свим политикама“ значи да се здравствена питања узимају у обзир приликом доношења одлука у различитим секторима који укључују и здравље, као што су транспорт, пољопривреда, коришћење земљишта, становање, јавна безбедност и образовање. Тако се афирмише улога јавног здравља у свим политикама које погађају здравствено стање, као што је то дефинисано у оквиру „Десет битних јавно-здравствених услуга“ [25]. Овом стратегијом се промовише могућност сектора јавног здравља да се повеже са широким дијапазоном партнера. Треба имати у виду да правне норме нису замена за односе између сектора, засноване на поверењу и веровању у потребу за применом политике *HIAP*. Пренормирање може чак ићи на штету флексибилности тиме што ће се технички обављати извештавање, без неке стварне дубље сарадње [26, 27]. У зависности од процене и врсте система, земље имају различите ставове о начину увођења политике *HIAP* [28–32].

ЗАКЉУЧАК

Иако је тренутак приступања ЕУ неизвестан, степен постојеће интеграције са Унијом и њеним чланицама,

као и транснационални карактер већине јавноздравствених претњи захтева усклађивање са стандардима ЕУ који проистичу из најбољих пракси држава чланица, а уједно спадају и у највише стандарде заштите здравља и права на здравствену заштиту на свету. Иако са ограниченим надлежностима, ЕУ представља драгоцену платформу за сарадњу и унапређење националних здравствених система уз значајне могућности хармонизације и усклађивање регулаторних оквира. Премда су надлежности Европске уније махом координативне, она је у области јавног здравља развила многе програме који улазе у бројне домене људског здравља и здравствених активности које се одигравају на различитим нивоима управљања и у интеракцији бројних подсектора друштва – здравства, социјалне заштите, образовања, одбране, цивилне заштите, унутрашњих послова итд.

Може се закључити да је у претходном периоду постигнут завидан ниво хармонизације у погледу области обухваћених преговарачким Поглављем 28, али како сведочи и извештај о напретку у процесу придруживања, остаје потреба за значајним усклађивањима законодавства. Такође, постоји потреба за интензивним и континуираним ангажовањем институција Србије како би се створили услови за даљу хармонизацију, а пре свега кроз ажурно спровођење већ усвојених програма усклађивања на националном нивоу, као и кроз усаглашавање политика различитих сектора (на пример у области дувана – сектора финансија и здравља). Додатно, као већи проблем намеће се имплементација наведених стандарда, нарочито имајући у виду лимитиране буџетске могућности за спровођење едукативних или превентивних програма, као и ограничене капацитете у здравству, социјалној заштити, образовању и јавној управи, забрану запошљавања у јавном сектору, као и недовољно усклађену динамику планирања различитих сектора, која је за јавно здравље од посебно великог значаја. Србији предстоји напор у даљем усаглашавању законодавства са *acquis* у области здравља, али оно што ће, пре свега, представљати изазов јесте примена нове регулативе у пракси, с обзиром на то да она захтева, пре свега, повећање кадровских капацитета у великом броју сектора.

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Не постоји конфликт интереса.

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Legal reforms in the field of public health and the accession of the Republic of Serbia to the European Union – a review of regulatory standards

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SUMMARY

Accession to the European Union (EU) is a comprehensive process of reforms and harmonization of legislation with EU regulations, which must be accompanied by the implementation of EU standards. Although the EU competencies in the field of health care are limited, and health law does not represent a large part of the EU legislation, harmonization and further reforms are needed in a number of areas. The main focus of this paper is the negotiation Chapter 28 within the EU accession process, which covers a number of thematic areas in the field of public health encompassing various legislative and strategic acts of the EU. At the moment, the EU has still not opened the negotiations in this field with Serbia. In order to introduce health professionals in Serbia to current developments, the paper analyzes the most important aspects of alignment with EU legislation and the need for further regulatory reforms.

Keywords: European Union; harmonization of legislation; public health; accession process

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови**,** наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh)*.

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад, метаанализа, претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор метаанализе и прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°*C*), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине - насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5.000 речи, а за претходно и кратко саопштење, приказ болесника, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3.000 речи; радови за остале рубрике могу имати највише 1.500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и претплатници на часопис за годину у којој се рад предаје Уредништву, или измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3.000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

АДРЕСА:
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The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

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