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SADRŽAJ

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POSSIBLE FACTORS OF SUCCESS IN TEACHING ESOPHAGEAL SPEECH

MOGUĆI FAKTORI USPEHA U EDUKACIJI EZOFAGUSNOG GOVORA

Sanja KRESIĆ[1], Mila VESELINOVIĆ[1, 2], Gordana MUMOVIĆ[1, 2] and Slobodan M. MITROVIĆ[1, 2]

Summary

Introduction. Well-established esophageal voice and speech is the most human-like form of communication of laryngectomized patients. **Material and Methods.** The study sample consisted of 28 patients of the Department of Ear, Nose and Throat, Clinical Center of Vojvodina in Novi Sad. All patients underwent total laryngectomy because of laryngeal cancer previously confirmed. The patients were divided into two groups based on the success of mastering esophageal voice and speech, group 1 being successful and group 2 being unsuccessful. **Results.** All patients were subjected to total laryngectomy and had their hyoid bone removed (100%). Esophageal speech was rated excellent and good in 71% and 29% of patients from group 1, respectively. There was no significant difference between the successful (group 1) and unsuccessful group (group 2) in time when teaching began (χ^2 =5.14, p=0.023). Neither was there a statistically significant difference between these two groups regarding the methods applied in teaching esophageal speech (χ^2 = 2.02, p=0.155, which is greater than 0.05). **Conclusion.** The effectiveness of teaching esophageal speech depends significantly on the motivation of the patients. It was found that the patients who mastered esophageal speech successfully had been learning it longer than those who did not master it. The success in mastering esophageal speech did not depend on whether the patients were trained individually or collectively, whereas neither method of training was successful in group 2.

Key words: Speech, Esophageal; Laryngectomy; Laryngeal Neoplasms; Treatment Outcome; Education; Motivation; Rehabilitation

Sažetak

Uvod. Kvalitetno uspostavljen ezofagusni glas i govor je najhumaniji vid komunikacije bolesnika kojima je urađena laringektomija. **Materijal i metode.** Uzorak je činilo 28 pacijenata Klinike za bolesti uva, grla i nosa Kliničkog centra Vojvodine u Novom Sadu. Kod svih je bila urađena totalna laringektomija zbog prethodno potvrđenog karcinoma larinksa. Podela na dve grupe izvršena je prema uspešnosti u svalađivanju ezofagusnog glasa i govora, pacijenti grupe I bili su uspešni, a iz grupe II, neuspešni. **Rezultati.** Kod svih pacijenata u obe grupe urađena je totalna laringektomija i odstranjena je hioidna kost (100%). Ezofagusni govor pacijenata iz I grupe (uspešnih) je u 71% slučajeva ocenjen kao odličan, a kod preostalih 29% iz te grupe kao dobar. Ne postoji statistički značajna razlika u vremenu započinjanja edukacije između pacijenata grupe I i grupe II (χ^2 = 5,14; p = 0,023). Ne postoji statistički značajna razlika između grupe uspešnih i neuspešnih pacijenata u primenjivanoj metodi učenja ezofagusnog govora (χ^2 = 2,02, p = 0,155, što je veće od 0,05. **Zaključak.** Na uspešnost edukacije ezofagusnog govora značajno utiče motivacija pacijenta a oni koji su uspešno naučili ezofagusni govor duže su edukovani od onih koji ga nisu naučili. Pacijenti uspešni u edukaciji ezofagusnog govora su uspešni bez obzira da li su edukovani individualno ili u grupi, dok kod neuspešnih nijedan način edukacije nije dao rezultat.

Ključne reči: Ezofagealni govor; Laringektomija; Laringealne neoplazme; Ishod lečenja; Edukacija; Motivacija; Rehabilitacija

Introduction

As stated by Mitrović, total laryngectomy is a radical surgery on the larynx, which favors radicality in the treatment of malignant tumors of the larynx in relation to other functions of the larynx, primarily respiratory and phonation. It is also a proof that man can live without the larynx [1]. Well-established esophageal voice and speech is the most human-like form of communication in laryngectomized patients. The success rate in teaching esophageal voice and speech ranges from 30% to 91% [2]. Đukić et al. [3] have reported that teaching is successful in 84% of cases. According to Dragičević [4], the overall effectiveness of teaching esophageal voice and speech is 66.7%. Multidisciplinary approach to the rehabilitation of the laryngectomized patient is the basic prerequisite for successful mastering of esophageal voice and speech. Well-trained and dedicated team of experts is the motivational support to discouraged patients. Not infrequently, the patient seeks help for the first time only after the first oncological check-up, or upon the completion of postoperative

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radiotherapy, and sometimes several years after the completion of oncological treatment. It is undoubtedly ideal if the active part of rehabilitation begins as soon as possible, preferably 1.5 to 2 months after treatment (operative or combined with radiotherapy), but it should be said that it is never too late to start exercise [3]. Petrović Lazić [5] suggests to start rehabilitation as soon as the local and general condition of the patient allows it, 2 to 4 months after surgery on average. Mumović [6] suggests to begin with training 6 weeks after surgery and 2 months after completion of radiation therapy. However, teaching may be discontinued temporarily in case of more severe radiation therapy side effects. The same author also believes that teaching esophageal speech should begin within 6 months after surgery.

According to Vekić [7], patients who train from 1 to 3 months have better quality of articulation of esophageal voice and speech. Calcaterra and Zwitman [8] point out that despite adequate training in esophageal voice and speech, only 50% of people can master this type of speech. Training usually lasts 3 to 6 months.

Training can be conducted individually and in groups, that is collectively. In his study, Veselinović [9] states that the individual approach to rehabilitation is convenient at first while getting to know the patients and providing them necessary information on training at the very beginning when the patient needs to master the act of burping. Later, the patient should join the group where treatment will be encouraged by the progress made by people with the same problems.

The aim of this study is to identify possible reasons which are important for success in teaching esophageal voice and speech.

Material and Methods

The sample consisted of 28 patients treated at the Department of Ear, Nose and Throat, Clinical Center of Vojvodina in Novi Sad. All patients underwent total laryngectomy for laryngeal cancer previously confirmed and they were divided into two groups based on the success of mastering esophageal voice and speech, group 1 being successful and group 2 being unsuccessful.

Data on the patients' gender, age, education, occupation, extent of surgical resection, time when rehabilitation started and duration of rehabilitation were collected through the questionnaire and interviews with patients.

Data about motivation are subjective experience of each patient and they were obtained through interviews. All data collected were processed by software package *Microsoft Excel 2007* and statistical package *Statistica 5,5*. All the results are presented in tables and graphs. The whole text has been processed in *Word 2007.*

Results

Group 1 consisted of 14 patients (13 men and 1 woman, that being 93% and 7%, respectively), who had successfully mastered esophageal voice and speech and group 2 included 14 patients (11 men and 3 women, i.e. 79% and 21%, respectively) who had failed at it. There was no correlation between the genders regarding the success rate (χ^2 test=1.93; p = 0.164).

The age ranged from 61 to 70 and 41 to 50 in 50% and 36% of patients from group 1, respectively and 7% of patients were over 70 years old. The age distribution in group 2 was as follows: 43% of patients were between 61 and 70 years of age, 29% of them were over 70 years of age and 14% were in the age group from 41 to 50 and 51 to 60 years, each. No statistically significant difference was found among the age groups regarding the success rate (χ^2 = 2.19; p = 0.139).

As for the educational structure, the highest percentage of subjects in both group 1 and group 2 had secondary vocational education (64% and 57%, respectively), whereas 28% and 29% of the patients from group 1 and group 2, respectively, finished primary education and 14% of subjects from group 1 had only incomplete primary education and only 8% of patients from group 2 had university degree. There were no statistically significant differences in the educational structure between group 1 and 2 (χ^2=1.03; p=0.308).

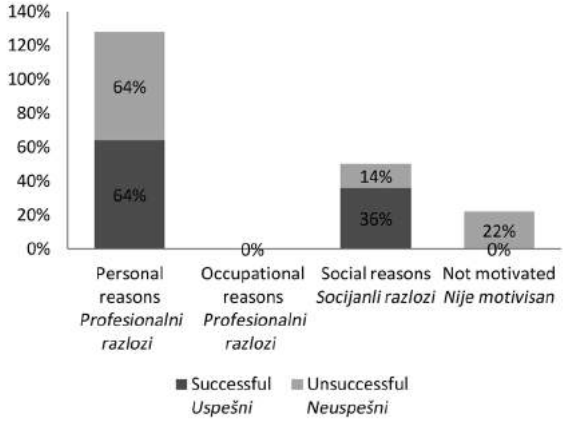
As for the employment status, the percentage of retired, employed and unemployed patients was 57%, 29% and 14% for group 1, respectively; whereas 86% and 14% of the patients from group 2, were retired and employed, respectively.

Employees from both groups belong to the group of non-vocal non-professionals. There was no statistically significant difference between group 1 and 2 regarding occupation (χ^2 =2.15; p = 0.142).

All patients from both groups were subjected to total laryngectomy (100%). None of the patients underwent total laryngectomy with partial pharyngectomy or total laryngectomy with partial pharyngectomy along with resection of the base of the tongue. All patients from both groups had their hyoid bone removed.

Rehabilitation began 2 to 4 months after surgery in 57% of the patients from group 1, 1 month after surgery in 14% and more than 6 months after surgery in 29% of these patients.

In group 2, rehabilitation started in the largest number of patients more than 6 months after surgery (57%), 2 to 4 months after surgery in 29% and 4-6 months after surgery in 14% of these patients. There was no statistically significant difference in the time of commencement of training between the successful and unsuccessful group (χ^2 = 5.14; p=0.023).

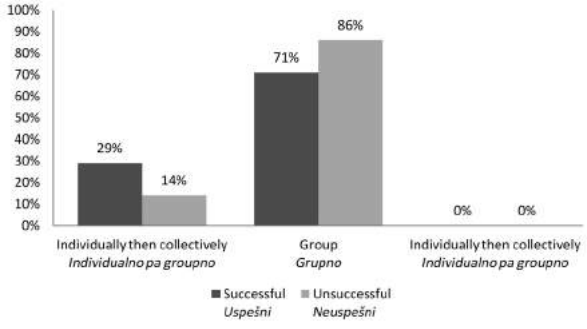


Graph 1. Motivation
Grafikon 1. *Motivacija*

The reasons for the motivation of patients in both groups are shown in **Graph 1.** All patients from group 1 were motivated.

In both groups, the majority of patients (64%) were motivated by the personal reasons. It is interesting to note that none of the patients from both groups was motivated by occupational reasons, although there were employed subjects in both groups. In group 1 and group 2, there were 34% and 14% of the patients who were motivated by social reasons. In group 2, 22% of patients were not motivated. Patients who have been successful in training in a number of cases were motivated by patients who have been unsuccessful (χ^2=24.72 p=0,000).

Considerably more patients from both groups, group 1 and 2, were trained to esophageal voice and speech collectively than individually, the percentage being 71% and 86%, respectively. However, 29% of the patients from group 1 and 14% of those from group 2 were trained individually **(Graph 2)**. The difference between the successful and unsuccessful group was statistically significant (χ^2 =25,44 p=0,000) and it can be explained by the fact that those who have mastered esophageal voice and speech would have been successful regardless of the method of training, whereas none of the training methods yielded the desired results in group 2.



Graph 2. Methods in teaching esophageal voice and speech
Grafikon 2. *Metoda edukacija ezofagusnog glasa i govora*

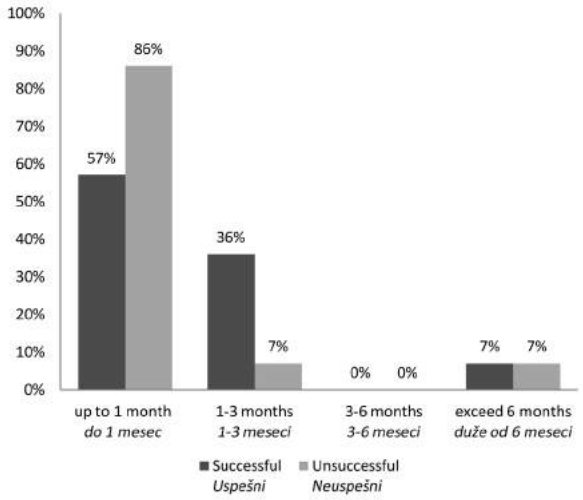
Graph 3 shows the duration of training in both groups. Training lasted up to a month in 57% and 86% of patients from group 1 and 2, respectively. There are differences in the number of respondents who have had training from 1 to 3 months. Training lasted over 6 months only in 7% of patients in both groups. There was a statistically significant difference in the length of training of patients from successful and unsuccessful group. Training was much longer in those who mastered esophageal voice and speech successfully. This is supported by the value of chi - square test χ^2 =25.44, p=0.000.

Aspiration method was applied in 50% of the patients from the successful group and 60% of those from the unsuccessful group, whereas deglutition method was applied in 50% and 40% of the patients from the successful and unsuccessful group, respectively.

Injection method was not applied et al. There was no statistically significant difference between these two groups regarding the method of learning esophageal speech (χ^2=2.02, p=0.155, which is greater than 0.05). Esophageal speech of patients was rated excellent and good in 71% and 29% of the patients from group 1, respectively.

Discussion

Men suffer from cancer of the larynx 4-5 times more often than women [5]. Rosso et al. [10] state that laryngeal carcinoma occurs more frequently in men than in women, the ratio being 91.5% : 8.5%. Studies done by Stanković et al. [11] as well as Tićac et al. [12] also confirm that men are more often affected than women are. Mumović [13] found



Graph 3. Duration of training
Grafikon 3. *Dužina trajanja edukacije*

the ratio to be 90.9% of men and 9.1% of women. In Dragičević's research [4], the percentage of male patients was also higher. As for the present study, there was only one woman in the successful group and three women in the unsuccessful group. These results suggest that men are more likely to suffer from malignant tumors of the larynx than women do, which is similar to the results of previous research.

The results of this research show that the majority of patients are aged between 61–70 years. Dragičević [4] and Stanković [11] have also concluded that the majority of patients with malignant tumors of the larynx are aged 61 to 70 years. Woodard et al. [14] reported an average age of 63 years. According to Tićac et al. [12], cancer of the larynx occurs mainly in people aged 50 to 60 years, whereas Igissinov et al. [15] have reported that the disease is most common in the seventh decade of life. According to Mumović [13], 80% of patients are aged between 50 and 70 years.

Patients who underwent total laryngectomy should start learning esophageal voice and speech as soon as possible, within six months after surgery, but not before the wound has healed and the swallowing function has been resumed [6, 16]. Petrović Lazić [5] states that rehabilitation should begin as soon as the local and general condition of the patient allows it, that is 2 to 4 months after surgery, on average. According to Dragičević [4], this period is 4.72 months on average, ranging from one to 13 months. Stanković [16] recommends beginning the rehabilitation of esophageal voice and speech as early as 3-4 weeks after surgery, while Mumović [6] suggests it 6 weeks after surgery. In this study, the majority of patients from the successful and unsuccessful group started rehabilitation from 2 to 4 months and 6 months after surgery, respectively. Veselinović [9] believes that individual approach to rehabilitation is appropriate at the beginning and the patients should join a group later where they will be encouraged by the progress made by people with the same problems. The results presented here show that the training in both groups was conducted mostly collectively. Calcaterra and Zwitman [8] state that training usually lasts 3 to 6 months. Sokal et al. [17] reported that the continuous speech rehabilitation had lasted 3 to 8 months.

Good [18] believes that training should last 6 to 12 months. Taptapova [19] reported that most patients master esophageal speech in 4 to 6 weeks.

The length of training depends on the pace of progress of each individual patient [9]. In this study, the majority of patients in both groups were trained for a period of one month. Training lasted up to a month in 57% of the patients from the successful group and 86% of those who failed in mastering esophageal voice and speech.

Those who were successful in mastering esophageal voice and speech had had intensive rehabilitation in hospital conditions for three weeks, twice a day, 30 exercises in total. Vocal prostheses was indicated to be implanted in those patients who had not mastered esophageal speech successfully during that period. Hospital phoniatric rehabilitation ensures complete implementation of the rehabilitation program, and the motivation for the rehabilitation and social reintegration is significantly higher in those rehabilitated in hospital compared to outpatients [2]. Veselinović [9] claims that continuous training should not last longer than 6 months because he believes that the patient and the therapist become surfeited after that time. In this study, training lasted over 6 months only in 7% of patients from both groups.

Esophageal voice and speech after speech rehabilitation were scored according to Stanković [16]. The present results indicate that 71% of the group who had mastered the esophageal voice and speech successfully were rated excellent, which means that they also had achieved full automaticity in the production of esophageal voice and speech. Esophageal speech in the remaining 29% of the patients was rated good since continuous esophageal voice and speech were established, but some syllables were periodically voiceless. In his research, Dragičević [4] reported 66.7% of patients to have mastered esophageal speech successfully, and were rated 5, 4, 3. Sokal et al. [17] found that 20% of patients mastered esophageal speech successfully, 46.67% of patients were rated good, 13.33% of patients were rated adequate, and 20% of patients used whisper. The results of these studies are considerably inferior to those presented here.

Sokal et al. [17] evaluated the time elapsed since surgery, duration of rehabilitation, extensiveness of surgery, and concluded that the success rate of training was not affected by any of them. In this study, there was a statistically significant difference in the duration of rehabilitation. Training was considerably longer in the patients from the successful group than in those from the unsuccessful one. The present results show that a large percentage of patients from the unsuccessful (86%) group completed training in less than a month, which may imply that intensive hospital treatment was not enough to master the technique of esophageal voice and speech. In addition, they were not sufficiently motivated to continue their training in an outpatient setting. It also shows that there are reasons for the failure in training.

Bohme [20] states that the success of training depends on general factors, such as psychological ones, motivation being one of the most important [21]. Đukić et al. [3] emphasize the importance of assessing the level of motivation during the first contact with the patient in order to give support adequate to that level. Patients are motivated by personal and social reasons, and a desire to return to their former environment as soon as possible. The results of this research show that there is a statistically significant difference in the motivation of the patients from the successful and unsuccessful group. The successful patients were much more motivated compared with the unsuccessful ones, as confirmed by other studies.

The subjects of this study particularly emphasized personal and social reasons for motivation. This study could not prove the importance of a method of training in terms of success, showing that the successful patients achieved good results regardless of the method applied whereas none of the methods gave desired results in unsuccessful patients. The values of χ^2 tests confirm the statement that considerably more patients from this study sample were included in collective than individual training of esophageal voice and speech. Neither did teaching methods affect the success of esophageal speech.

Conclusion

The effectiveness of teaching esophageal speech depends significantly on the motivation of the patients, and those who mastered esophageal speech had been trained longer than those who failed. In addition, the patients who mastered esophageal speech were successful whether they were trained collectively or individually, whereas neither of the method gave results in the unsuccessful group. Consequently, the success of training depends more on other factors than on the choice of method between collective or individual training.

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MICROMORPHOLOGICAL CHARACTERIZATION OF ADHESIVE INTERFACE OF SOUND DENTIN AND TOTAL-ETCH AND SELF-ETCH ADHESIVES

MIKROMORFOLOŠKA ANALIZA ODNOSA ADHEZIVNIH SREDSTAVA SA POTPUNIM NAGRIZANJEM GLEĐI I DENTINA I SAMONAGRIZAJUĆIH ADHEZIVA SA ZDRAVIM DENTINOM

Milan DROBAC, Igor STOJANAC, Bojana RAMIĆ, Milica PREMOVIĆ and Ljubomir PETROVIĆ

Summary

Introduction. The ultimate goal in restorative dentistry has always been to achieve strong and permanent bond between the dental tissues and filling materials. It is not easy to achieve this task because the bonding process is different for enamel and dentin – dentin is more humid and more organic than enamel. It is moisture and organic nature of dentin that make this hard tissue very complex to achieve adhesive bond. One of the first and most widely used tools for examining the adhesive bond between hard dental tissues and composite restorative materials is scanning electron microscopy. The aim of this study was scanning electron microscopy analyzes the interfacial micro morphology of total-etch and self-etch adhesives. **Material and Methods.** Micro morphological characteristics of interface between total-etch adhesive (*Prime & Bond NT*) in combination with the corresponding composite (*Ceram X Mono*) were compared with those of self-etching adhesive (*AdheSE One*) in combination with the corresponding composite (*Tetric EvoCeram*). The specimens were observed under 1000 x magnification of scanning electron microscopy (*JEOL, JSM-6460 Low Vacuum*). Measurement of the thickness of the hybrid layer of the examined composite systems was performed with the software of the device used (*NIH Image Analyser*). **Results.** Micromorphological analysis of interface showed that the hybrid layer in sound dentin was well formed, its average thickness being 2.68 μm, with a large number of resin tags and a large amount of lateral branches for specimens with a composite system *Prime & Bond NT - Ceram X Mono.* However, the specimens with composite systems *Adhese One - Tetric EvoCeram* did not show the presence of hybrid layer and the resin tags were poorly represented. **Conclusion.** The results of this study suggest that total-etch adhesives bond better with sound dentin than self-etch adhesives.

Key words: Dental Bonding; Dentin-Bonding Agents; Composite Resins; Adhesives; Dental Etching; Acid Etching, Dental; Microscopy, Electron, Scanning; Dentin + ultrastructure

Sažetak

Uvod. Ostvarenje snažne i trajne veze između tvrdih zubnih tkiva i ispuna oduvek je bio cilj kome se težilo u restaurativnoj stomatologiji. Ovaj zadatak nije lako ostvariti imajući u vidu da je proces adhezivnog vezivanja različit za gleđ i dentin − dentin je vlažniji i sadrži više organske komponente u odnosu na gleđ. Upravo ta vlažnost i organska priroda čine ovo tvrdo tkivo veoma složenim za ostvarenje adhezivne veze. Jedan od prvih i najšire korišćenih alata za ispitivanje adhezivne veze između čvrstih zubnih tkiva i kompozitnih restaurativnih materijala je skening elektronska mikroskopija. Cilj istraživanja bila je skening elektronska mikroskopska analiza odnosa adhezivnih sredstava sa potpunim nagrizanjem gleđi i dentina i samonagrizajućih adheziva sa zdravim dentinom. **Materijal i metode.** Poređene su mikromorfološke karakterisktike adhezivne veze adheziva sa potpunim nagrizanjem (*Prime&Bond NT*) u kombinaciji sa pripadajućim kompozitima (*Ceram X Mono*) i samonagrizajućeg adheziva (*AdheSE One*) u kombinaciji sa pripadajućim kompozitima (*Tetric EvoCeram*). Uzorci su posmatrani pod uvećanjem 1 000 x skening elektronskom mikroskopijom (*JEOL, JSM-6460 Low Vacuum*). Merenje debljine hibridnog sloja ispitivanih kompozitnih sistema izvršeno je pomoću softvera samog uređaja (*NIH Image Analyser*). **Rezultati.** Mikromorfološka analiza međuspoja pokazuje da je hibridni sloj u zdravom dentinu dobro formiran, prosečne debljine 2,68 μm, sa brojnim produžecima smole i izraženim prisustvom lateralnih grana za uzorke sa kompozitnim sistemom *Prime&Bond NT – Ceram X Mono*, dok se kod uzoraka sa kompozitnim sistemom *AdheSE One – Tetric EvoCeram* ne uočava prisustvo hibridnog sloja, a produžeci smole oskudno su zastupljeni. **Zaključak.** Rezultati ove studije ukazuju da se adhezivi sa potpunim nagrizanjem gleđi i dentina bolje vezuju sa zdravim dentinom od samonagrizajućih adheziva.

Ključne reči: Adhezivno vezivanje; Sredstva za vezivanje dentina; Kompozitnimaterijai; Adhezivi; Nagrizanje zuba; Nagrizanje zuba kiselinom; Skening elektronska mikroskopija; Dentin + ultrastruktura

Introduction

Adhesion is the interaction of the molecules at the interface of two different materials [1]. The sur-

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Abbreviations
SEM – scanning electron microscopy/*skening elektronska mikroskopija*

faces of these materials are called adherents or substrates, and the substance that binds these two materials is called an adhesive. This interaction is defined as an adhesive bond. The most important step in the realization of adhesion is to make a close contact between the adhesive and the substrate. The ultimate goal in restorative dentistry has always been to achieve a strong and permanent bond between the dental hard tissues and restorations [2]. Dentin contains a large amount of water and organic structures, especially collagen type I, which makes it very difficult to bond to [3]. The structure and properties of dentin are different and depend on the location. The properties of dentin which are important for the realization of adhesive bond are: a) dentin permeability, b) number and orientation of dentin tubules, c) changes in dentin structure and d) mechanical properties [4].

One of the earliest and most widely used tools for analyzing the adhesive bond has been scanning electrone microscopy (SEM) [5]. The principle of SEM is based on pseudo three-dimensional picture that is formed point by point and line by line from secondary electrons [6]. Electrons are emitted in response to the collision of the electron beam and the test sample. The number of secondary electrons emitted from any one point on the surface depends on the difference in the structure, composition and texture of the surface.

Thanks to the short wavelength of the electron beams, SEM provides sufficient resolution to identify a few micrometers wide formations, such as a hybrid layer. Although the concept of hybridization was first introduced by Nakabayashi et al. in 1982 (using SEM) as the formation of a resin-reinforced dentin zone, it took other researchers almost ten years to accept this theory and examine other details of micromechanical bonding mechanism [7]. Thanks to the fact that SEM images of hybrid layer are of high magnification and of high quality, this test method has become the most popular in studying the mechanism of formation of adhesive bond. The most commonly used variant of SEM is low vacuum SEM [8, 9]. The low vacuum SEM is used for testing unfixed biological samples under low vacuum and wet conditions [10]. The most successful method for observing soluble samples using SEM technique is replication technique, which involves taking an impression of the test surface using silicon impressions, outpouring thus obtained impressions in epoxy resin, after which this replica is set in vacuum conditions in the SEM [11, 12]. Thus, the replica technique is used for semiquantitative analysis of marginal adaptation of adhesive restorations placed and followed up for several years *in vivo* [11]. The resolution obtained under the SEM is highly dependent on the accuracy of impression and preparation techniques of replicas. It is recommended to use a very low viscosity impression materials (light-body, polyvinyl siloxane based), and non-shrinking epoxy resin. The details obtainable with a replication technique do not allow examination of biomaterial-tooth interface, i.e. hybrid layer, because the clear detail can be seen up to 1000 x magnification.

Dentin is a vital, hydrated tissue, whose structure and properties vary depending on the location [3]. Instrumentation of dentin using burs results in smear layer production [13], which consists of hydroxyapatite, denatured collagen and dentin debris particles. It has a weak bond with underlying dentin, the bond being only 5 MPa [14]. The smear layer penetrates into the dentin tubules to form smear plugs, and thus reduces dentin permeability to 86% [15]. Contemporary adhesives can be classified according to their interaction with the smear layer. Consequently, there are two strategies for achieving bond and four types of adhesives:

1. Total-etch adhesives, 30-40% phosphoric acid is used to treat enamel and dentin simultaneously and to remove smear layer

a) three-step adhesives (conditioner + primer + resin)

b) two-step adhesives (conditioner + primer/resin)

2. Self-etch adhesives, without the conditioning step. They consist of non-rinsing acid monomer, which makes the smear layer permeable without its complete removal.

a) two-step self-etch adhesives (acid primer + resin)

b) one-step self-etch adhesives (all-in-one).

Bonding agents have constantly been improved in order to reduce the number of clinical steps and simplify their application [16]. The application of bonding agents results in the formation of resin reinforced layer of dentin (hybrid layer) and penetration of resin into dentin tubules (resin tags). Conditioning step (total-etch adhesives) results in complete removal of smear layer and wide opening dentin tubules, and improves adhesive penetration. In contrast, self-etch adhesives are not efficient enough to dissolve the smear plugs, and therefore remain in dentinal tubules as a part of a hybrid complex. Such hybrid complex is characterized by poorly formed resin tags, which result in inferior clinical performance of these adhesives [17].

The aim of this study was to apply SEM to analyze the interfacial micromorphology of total-etch and self-etch adhesives and sound dentin, the null hypothesis being that there are no important differences in the microstructure of the interfaces between the tested adhesive systems.

Material and Methods

The teeth used for SEM analysis were non erupted third molars of the maxilla and mandibula, extracted by surgical procedure, at the Ward of Oral surgery of the Department of Dentistry of Vojvodina. The teeth damaged during surgery were not included in the study sample, which consisted of 20

teeth – 10 teeth for each adhesive system. The residual parts of the soft tissues of the tooth were removed with a surgical curette after tooth extraction. The teeth were immersed in 0.5% solution of chloramine (bacteriostatic/bactericidal) at 4° C , and after seven days, they were rinsed with distilled water and stored in deionised water (ISO 3696) at 4° C. Deionised water was completely replaced every 48 hours. The time interval between tooth extraction and its being tested in the experiment was limited to one month. The use of human teeth for experimental purposes was approved by the Ethics Committee of the Department of Dentistry of Vojvodina and the Ethics Committee of the Faculty of Medicine in Novi Sad.

After removing enamel on occlusal surface with high-speed handpiece with copious air-water spray using diamond bur (*Diamantsheibe, Edenta, Switzerland*), a flat surface of dentin was achieved, which was then treated with silicon carbide abrasive papers (*SiC 600-grit paper, 3M*) under running water using custom made grinding cylinder [4]. The result was a flat surface of dentin. The depth was approximately halfway between the pulp chamber and enamel-dentine junction. Adhesives were applied on thus prepared dentin surface (**Table 1**) according to the manufacturer's instructions. Adhesive *AdheSE One* was applied and agitated for 30 s, then air was dispersed until there was no water movement, and treated for 10 s.

Adhesive *Prime&Bond NT* was applied on dentin surface after conditioning with *Conditioner 36* (Dentsply DeTrey) for 15 s, which was followed by rinsing with water spray for 10 s.

The excess water was blotted with cotton pellet. Immediately after blotting, 2–3 consecutive coats of adhesive *Prime&Bond NT* for 20 s with gentle agitation were applied using fully saturated applicator. The moist surface was treated with a soft blow of air before light-polymerization for 10 s. *AdheSE One* F was directly applied to the dentin surface. When the dentin surface was completely coated, the adhesive was brushed into the entire surface for 30 seconds. Excess amounts of *AdheSE One* were dispersed with a strong stream of air until a glossy, immobile liquid film resulted. Light-cure *AdheSE One* was applied for 10 seconds.

The proprietary restorative resin composite of each adhesive was set on each sample tooth in one layer (2 mm thick). Adhesives and resin composites were light-cured with polymerization device (*Smarlite IQ2, Dentsply, Caulk, DE Milford, Serial No.B 21581*) in compliance with the manufacturer's instructions.

Thus formed samples were cut longitudinally through the tooth and composite to expose the adhesive interface. The adhesive interface was then treated with conditioner (*Uni-Etch, Silica gel free, Bisco, Schaumburg, IL, LOT 0800012148*) for 60 s, rinsed with copious air-water spray, and treated with 2% sodium-hypochlorite solution for 60 s to eliminate organic component of dentin [18]. Preparation of samples of biological tissues (teeth) for SEM was done in accordance with the conditions of low vacuum. The samples were then coated with gold 15-20 nm thick (*SCD050 Sputter Coater; BAL-TEC,PA,USA*), placed on aluminum carriers and examined using a scanning electron microscope (*JEOL, JSM-6460 Low Vacuum, Tokyo, Japan*) at 1000 x magnification [19].

After the identification and micromorphological analysis of hybrid layer, the hybrid layer thickness was measured as the distance between the

Table 1. Chemical composition and instructions for use of the tested adhesives
Tabela 1*. Hemijski sastav i način aplikacije adhezivnih sredstava uključenih u ispitivanje*

Adhesive/Manufacturer *Adheziv/Proizvođač*	Chemical composition *Hemijski sastav*	Application *Uputstvo za upotrebu*
AdheSE One (Ivoclar Vivadent, Schaan, Liechtenstein) LOT M50900	Derivatives of bis-acrylamide, water, bis-methacrylamide dihydrogen phosphate, amino acid acrylamide, hydroxy alkyl methacrylamide, silicon dioxide, catalysts, stabilizers/*Bis-akrilamid, voda, bis-metakrilamid dihidrogen fosfat, amino- acid akrilamid, hidroksil alkil metakrilamid, visokodispergovan silikon dioksid, katalizatori, stabilizatori.*	Apply and agitate for 30 s; air disperse until there is no water movement; light-curing for 10 s./*Aplikovati adheziv na površinu dentina 30 s koristeći pokrete utrljavanja, višak adheziva odstraniti jakom strujom vazduha do dobijanja sjajnog tečnog filma koji se ne pokreće, polimerizovati svetlošću 10s.*
Prime&Bond NT (Dentsply Caulk, Milford, DE,USA) LOT 0905000886	PENTA, UDMA1, T-resin (cross-linking agent), 1 D-resin (small hydrophilic molecules), butylated hydroxy toluene, 4-ethyl dimethyl aminobenzoate, cetylamine hydrofluoride, acetone, silica nanofiller/*PENTA, UDMA1, T-smola (sredstvo za unakrsno povezivanje), 1 D-smola (mali hidrofilni molekuli), butilatizirani hidroksitoluen, 4-etil dimetil aminobenzoat, ketilamin hidrofluorid, aceton, silika nanopunilo*	Condition dentin surface with Conditioner 36 (Dentsply DeTrey) for 15 s, rinse for 10, remove water excess with cotton pellet, apply adhesive for 20 s using rubbing movements, air blow gently 5 s, light cure 10s. *Četkati površinu dentina sa Conditioner 36 (Dentsply DeTrey) u trajanju 15 s, ispirati 10 s, odstraniti višak vode kuglicom vate, adheziv aplikovati pokretima utrljavanja tokom 20 s, blagom strujom vazduha u trajanju 5 s istanjiti sloj adheziva, polimerizovati svetlošću 10 s.*

top of the layer and height of the scalloped convexities at the base of the hybrid layer between adjacent resin tags, using microscope software (*NIH Image Analyser*) [18].

Results

The SEM analysis of the relations of composite systems and sound dentin was performed on a sample of human teeth in laboratory conditions. The samples were examined under magnification of 1000 x with scanning electron microscopy (*JEOL, JSM-6460 Low Vacuum*). The thickness of the hybrid layer of the tested composite systems was measured with the software of the device itself (*NIH Image Analyser*) at five points on each sample (**Figure 1**). The thickness of the hybrid layer is shown in the microphotography as the distance between the arrowheads. Three measurements were made at the locations of approximately the same thickness, and the other two at the point of minimum and maximum thickness of the hybrid layer. The mean value of the measured thickness of the hybrid layer was then calculated and it

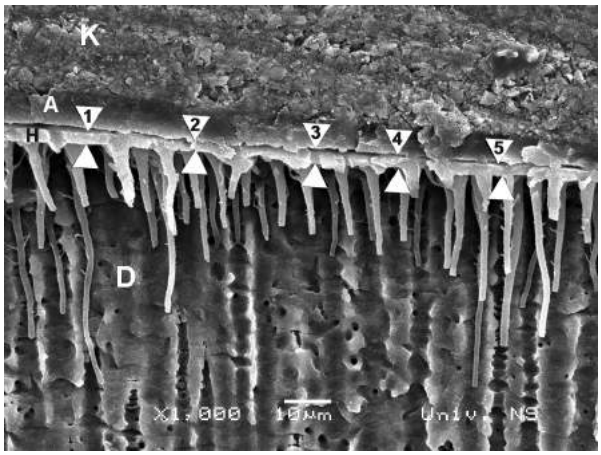

Figure 1. Measurement points across the image, SEM microphotography of acid - NaClO treated specimens for composite system *Prime&Bond NT – Ceram X Mono* and sound dentin (K - composite, A - adhesive layer, H - hybrid layer, D - dentin)
*1-5 hybrid layer measurement points across image
Slika 1. *Raspored tačaka na kojima je vršeno merenje, SEM mikrofotografija uzoraka tretiranih kiselinom i NaClO kompozitnog sistema Prime&Bond NT – Ceram X Mono povezanog sa zdravim dentinom (K – kompozit, A – adhezivni sloj, H – hibridni sloj, D – dentin)*
** mesta označena strelicama 1−5 su tačke na kojima je merena debljina hibridnog sloja*

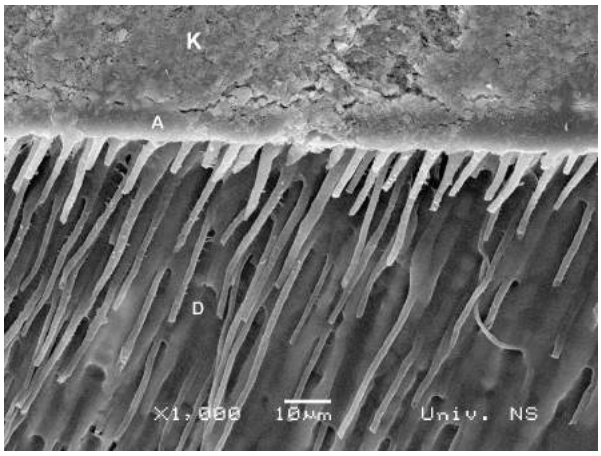

Figure 2. SEM microphotography of acid - NaClO treated specimens for composite system *Prime&Bond NT – Ceram X Mono* and sound dentin representing resin-dentin interface (K - composite, A - adhesive layer, D - dentin)
Slika 2. *SEM mikrofotografija uzoraka tretiranih kiselinom i NaClO koji prikazuju adhezivnu vezu koju formira Prime&Bond NT – Ceram X Mono sa zdravim dentinom (K – kompozit, A – adhezivni sloj, D – dentin)*

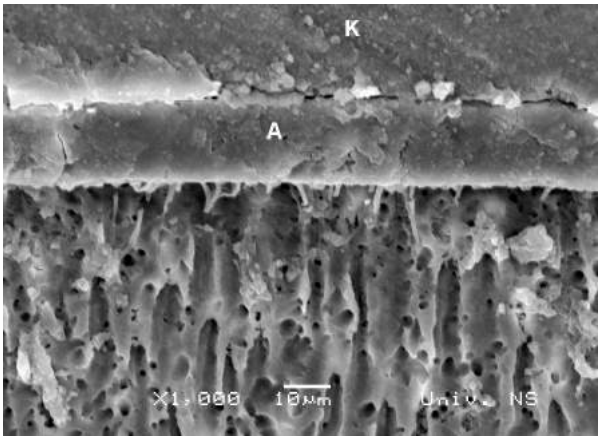

Figure 3. SEM microphotography of acid - NaClO treated specimens for composite system *AdheSE One – Tetric EvoCeram* and sound dentin representing resin-dentin interface (K - composite A - adhesive layer)
Slika 3. *SEM mikrofotografija uzoraka tretiranih kiselinom i NaClO koji prikazuju adhezivnu vezu koju formira AdheSE One – Tetric EvoCeram sa zdravim dentinom (K – kompozit, A – adhezivni sloj)*

Table 2. Hybrid layer thickness µm
Tabela 2. *Debljina hibridnog sloja u µm*

	1	2	3	4	5	6	7	8	9	10
PB/CXM	2.02	3.23	3.53	3.03	1.61	1.92	2.83	4.44	2.49	1.69
AO/TEC	0	0	0	0	0	0	0	0	0	0

PB/CXM – *Prime&Bond NT – Ceram X Mono;* AO/TEC – *AdheSE One – Tetric EvoCeram*

Table 3. Hybrid layer thickness - basic statistics parameters for composite systems
Tabela 3. *Osnovni statistički pokazatelji kompozitnih sistema za debljinu hibridnog sloja*

KS	n	$\bar{x}$	Med.	Min.	Max.	σ	Sk.	Ku.
PB/CXM	10	2.68	2.66	1.61	4.44	0.91	0.62	-0.18

KS - composite system, n - number of specimens, $\bar{x}$ - mean, Med.- median, Min.- minimum, Max.- maximum, , σ- standard deviation, Sk.- skewness, Ku.- kurtosis/*KS − kompozitni sistem, n − broj uzoraka,* $\bar{x}$ *− srednja vrednost, Med. − mediana, Min. − minimalna vrednost, Max. − maksimaln vrednost,* σ *− standardna devijacija, Sk.− skewness, Ku.− kurtozis*
PB/CXM – *Prime&Bond NT – Ceram X Mono*

was taken as a representative for the given specimen [26]. The obtained results are presented in **Table 2**.

The SEM photomicrography showing the sample with adhesive system *Prime&Bond NT – Ceram X Mono* **(Figure 2)** clearly shows the presence of a hybrid layer, while the SEM photomicrography showing a sample with adhesive system *AdheSE One – Tetric EvoCeram* does not identify the hybrid layer (**Figure 3**).

The thickness of the hybrid layer could not be measured for composite system *AdheSE One – Tetric EvoCeram*, so it is not included in the table that represents the basic statistical values (**Table 3**). As shown in **Table 3,** the thickness of the hybrid layer which forms the composite system *Prime&Bond NT – Ceram X Mono* with sound dentin was 2.68 μm.

The SEM analysis of interface showed that the hybrid layer on sound dentin was well formed, with a large number of resin tags and a large amount of lateral branches (**Figure 2**) for samples with a composite system *Prime&Bond NT – Ceram X Mono*, while the presence of the hybrid layer could not be seen in the samples with composite system *AdheSE One – Tetric EvoCeram* and resin tags were poorly identified (**Figure 3**).

The SEM microphotography of samples with *Prime&Bond NT – Ceram X Mono (*PB/CXM) placed perpendicular to the direction of the dentinal tubules (**Figure 2**) shows the composite (K), the adhesive layer (A) that is not penetrated into the acid-etched dentin (D), the hybrid layer is visible as a bright area. Resin tags are large in number with numerous lateral branches.

The SEM microphotography of samples with *AdheSE One – Tetric EvoCeram (*AO/TEC) placed perpendicular to the direction of the dentinal tubules (**Figure 3**) shows the composite (K), thick layer of the adhesive (A) that has not penetrated into dentin. A hybrid layer is not visible. Resin tags are poorly present, and lateral branching is not evident.

Discussion

An ultimate goal in restorative dentistry has always been to achieve a strong and permanent bond between the dental hard tissues and restorations. A chemical bond with the dental hard tissues is formed with glass-ionomer cements and polycarboxylate cements, whereas other restorative materials achieve mechanical or micromechanical bond (amalgam, composite materials).

The study sample consisted only of human teeth-non erupted third molars as a substrate. Having been extracted, the teeth were kept according to the protocol ISO405 [20]. The analysis of adhesive bonds was performed using low vacuum SEM, which is the most commonly used method in similar studies [5].

The smear layer resulting from treating dentin with diamond or carbid burs is compact and thick and compromises the efficiency of self-etching adhesives [21]. The finding that the most important role in the realization of high-quality adhesive bonds is played by wettability and the degree of penetration of the adhesive into dentin, has resulted in the creation of adhesives which effectively penetrate into the demineralized dentin and partially or completely remove the smear layer [22]. Such systems form a hybrid layer, resin reinforced partially demineralized dentin [23].

The absence of a hybrid layer in self-etch adhesives can be explained with their weaker acidity, which results in less demineralization of dentin, and exposes a small number of dentinal tubules, leading to poorer penetration of adhesive into dentin [24]. The results of previous studies suggest that the ability of self-etching primers is weaker in sound dentin than total-etch adhesives [25]. Self-etching adhesive *AdheSE One* shows pH=1.5 and it is one of mild self-etch adhesives (pH between 1 and 2). It has an interaction depth between 1 and 2 μm [26]. Only strong self-etch adhesives, having pH ≤ 1, can form typical resin tags in dentin. Mild self-etch adhesives can hardly form resin tags, they mostly demineralize smear plugs slightly and subsequently infiltrate this area with the resin. The hybrid layer thickness for mild self-etch adhesives is between 0.5 and 1 μm [26]. *Erhardt MCG* at al. examined adhesive *AdheSE One* and found a thin and irregular hybrid layer with small number of resin tags [27].

Mild self-etch adhesives are not efficient enough to dissolve the smear plugs, which close dentinal tubules, and therefore they remain in dentinal tubules as a part of a hybrid complex. That hybrid complex is characterized by sparse resin tags. In this case, the lateral penetration of the adhesive monomer into dentinal tubules does not contribute to the formation of the hybrid layer. On the other hand, in total-etch adhesives, the smear layer affects the penetration of adhesive monomers into dentin because dentinal tu-

bules open after its removal in the etching phase, and promotes the penetration of the adhesive.

Pashley et al. have found that the smear layer in sound dentin reduces the effectiveness of self-etch adhesives in achieving the adhesive bond [23]. A smear layer is a product of burs activity in dentin, and it contains denatured collagen, hydroxyapatite and mineral submicron particles [28]. These structures can interfere with the infiltration of resin monomers, and prevent adequate formation of resin dentin interface [23].

A well-formed hybrid layer and long resin tags with large number of lateral branches are characteristics of adhesives with organic solvent: ethanol or acetone [29]. The organic solvent in the composition of adhesives for wet bonding technique dehydrates acid etched dentin chemically [30]. This leads to the lateral shrinkage of the collagen fibrils, resulting in an increase in the width of interfibrilar spaces and reduction of the hydrophilicity of collagen matrix. Lateral dentinal tubules get filled with organic solvent and the bonding agent easily penetrates into them. In that way, a very well-formed hybrid layer with long resin tags and an expressed lateral branching is obtained. *Prime&Bond NT* contains acetone as a solvent. The use of acetone and ethanol as a solvent in an adhesive is derived from the fact that the comonomers of the adhesive does not dissolve in water. The role of dimethacrylate in the composition of the adhesive is to enhance crosslinking of polymers; they cannot be mixed with water, but are soluble in ethanol and acetone. The total-etch adhesives contain a mixture of the primers (i.e. HEMA) and monomers of the adhesive (i.e. bis-GMA) in a solvent containing a low amount of water. These are applied in two layers. The first layer acts as a primer, and the second acts as an adhesive layer. *Scott* and *Thomlinson* have demonstrated that the organic solvents (ethanol, acetone) remove the watery gel of glycosaminoglycans, thus removing them from the connective tissue [31]. Thus, the collagen fibrils in the acid-etched dentin shrink laterally after the application of an adhesive with organic solvents, and the lateral dentinal tubules are filled with an organic solvent (acetone, alcohol), and adhesive resin penetrates easily into them [32]. This is seen as perfectly formed resin tags in SEM microphotographs.

After acid conditioning of dentin, the smear layer is completely removed, dentin is demineralized and collagen fibrils are exposed. In order to form a high quality hybrid layer, the resin monomers must penetrate into this demineralized zone. However, there is a discrepancy between the depth of demineralization and penetration of resin monomers. It has been found that more effective infiltration of resin monomers is achieved by applying adhesive on a partially wet dentin surface than to a dry one, which is reflected in the measured higher bond strength values [33]. In addition, the application of self-etch adhesives shows discrepancies between the depth of demineralized zone and the penetration of resin monomers because these two processes occur simultaneously.

Phosphoric acid used for total-etch adhesives has pH=0.1-0.4, while the acidity of self-etch adhesives ranges from $pH \leq 1$ to $pH \approx 2$ [23]. Accordingly, dentin demineralization is more evident after the application of phosphoric acid because it completely removes the smear layer and opens dentinal tubules. The composition of adhesives and techniques of their application are also very important. Therefore, adhesives with organic solvents (ethanol, acetone) applied in wet bonding technique form long resin tags with large number of lateral branches [30]. In that way, a wide zone of resin infiltrated dentin is provided, as well as numerous and "branched" resin tags.

The SEM analysis of adhesive interface shows that a hybrid layer has not been observed on specimens with the self-etch adhesives and sound dentin, whereas it has been observed on specimens with total-etch adhesives. Accordingly, the null hypothesis has been rejected stating that there are no important differences in the microstructure of the interfaces between tested adhesive systems.

Conclusion

Total-etch adhesives form a clear zone of resin reinforced dentin (hybrid layer) and numerous and branched resin tags. Self-etch adhesives, due to their weak acidity, are not able to remove the smear layer and form a well-defined hybrid layer and long resin tags. The results of this study indicate that the total-etch adhesives bond better with sound dentin than self-etch adhesives.

In clinical conditions, this means that a better and stronger bond is made by total-etch adhesives. However, self-etch adhesives represent a step forward in the adhesive dentistry because the simplification of clinical procedures reduces the possibility of therapist mistakes. Still they have poorer adhesive interface than total-etch adhesives. Selective etching of enamel margins with phosphoric acid is highly recommended for better bonding of self-etch adhesives. Consequently, total-etch adhesives are still the gold standard in achieving the adhesive bond.

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RISK FACTORS OF THE FIRST STROKE

FAKTORI RIZIKA PRVOG MOŽDANOG UDARA

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Summary
Introduction. This study was aimed at investigating the vascular risk factors associated with the first stroke. It highlighted unfavorable trends in stroke mortality in the region gravitating towards the general hospital in Doboj. **Material and Methods.** The study included all patients hospitalized with the diagnosis of first stroke and their main vascular risk factors were explored, both in terms of their importance in the occurrence of stroke, and in terms of gender and age lines. The research results were statistically processed, analyzed and commented on. **Results.** The most common risk factor for the first stroke included hypertension (70%), smoking (35%), heart diseases (28%), diabetes mellitus (28%), hyperlipoproteinemia (26%), atrial fibrillation (18.5%) and immoderate consumption of alcohol (17%). **Conclusion.** The presence of vascular risk factors in the majority of patients is important, and at least one of them was present in 80% of patients. Alcohol consumption, smoking and hyperlipoproteinemia were significantly more freqeunt in men, and atrial fibrillation was more frequent in women. Arterial hypertension, heart disease and diabetes mellitus were present in both sexes without a significant difference.
Key words: Risk Factors; Stroke; Epidemiology; Age Factors; Sex Factors; Cardiovascular Diseases

Sažetak.
Uvod. U radu su istraživani vaskularni faktori rizika povezani sa prvim moždanim udarom i ukazano je na nepovoljne trendove morbiditeta moždanog udara u regiji koja pripada Opštoj bolnici u Doboju. **Materijal i metode.** U istraživačku studiju su uključeni svi pacijenti sa dijagnozom prvog moždanog udara koji su bolnički lečeni. Kod svih ispitanika su detaljno istraženi glavni vaskularni faktori rizika, kako sa aspekta njihovog značaja u nastanku moždanog udara, tako i sa stanovišta polne i dobne pripadnosti. Dobijeni rezultati su statistički obrađeni, analizirani i komentarisani. **Rezultati.** Najčešći faktor rizika za pojavu prvog moždanog udara je hipertenzija (70%), potom slede pušenje (35%), srčana oboljenja (28%), dijabetes melitus (28%), hiperlipoproteinemija (26%), fibrilacija atrija (18,5%) i neumerena konzumacija alkohola (17%). **Zaključak**. Potvrđena je hipoteza o značajnom prisustvu vaskularnih faktora rizika kod većine obolelih. Najmanje jedan vaskularni faktor rizika bio je prisutan kod 80% ispitanika. Kod muškaraca značajno više zastupljeni su konzumacija alkohola, pušenje i hiperlipoproteinemija, a kod žena češće je prisutna fibrilacija atrija. Arterijska hipertenzija, srčana oboljenja i dijabetes melitus su zastupljeni kod oba pola bez signifikantne razlike.
Ključne reči: Faktori rizika; Moždani udar; Epidemiologija; Starosni faktori; Polni faktori; Kardiovaskularne bolesti

Introduction

Activities in prevention of cerebrovascular (CV) morbidity and mortality, within generally accepted prevention measures, have been directed towards the reduction of vascular risk factors (VRF) by their early detection and timely and successful treatment. In addition, efforts are being made to induce changes in unhealthy and inadequate habits, which are the major etiologic generators of these diseases [1–4].

The main tasks to be accomplished in such studies are to investigate the circumstances in which a man becomes ill and therefore unable to lead the life of good quality as well as the circumstances of the natural course of the disease. Relevant data are to be collected to serve as the basis of any attempt in the future to achieve the reduction of morbidity and mortality [5].

If VFR were absent, the arterial vasculature could be affected by atherosclerosis (AT) up to 60% maximum even in people over 85 years of age. However, the association of smoking, hypertension and diabetes contribute to its development in people even under 42 years of age [6], thus being a pathological phenomenon which could be modified by therapeutic and preventive measures [1, 2]. The same can be said of arterial hypertension (AH), which is the main VRF for stroke [1, 2, 7], as well as of atrial fibrillation (AF), which is responsible for 15–20% of ischemic stroke (IS) and diabetes mellitus (DM), which are independent VRF in the development of both AT and stroke. Data from recent studies indicate that there is an association of dyslipidemia with IS, but not with intracerebral hemorrhage (ICH) [9]. Smoking increases the relative risk (RR) of developing subarachnoid hemorrhage (SAH) over 7 times, and the IS from 2.2 to 2.7 times, while smoking ces-

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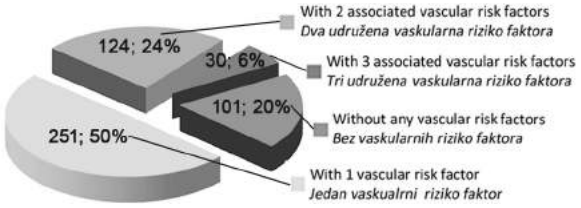
Abbreviations

VRF – vascular risk factors
AT – atherosclerosis
AH – arterial hypertension
AF – atrial fibrillation
DM – diabetes mellitus
IS – ischemic stroke
ICH – intracerebral hemorrhage
SAH – subarachnoid hemorrhage
FS – first stroke

sation significantly reduces this risk [1, 2, 7]. Heart disease and consumption of tobacco and alcohol as well as drug abuse lead to the increased risk of developing stroke at an early age [8]. Moderate consumption of wine (1–2 dl per day), on the contrary, has protective effects, which are more pronounced in women than in men [9–13]. The objectives of this study were to determine the presence of VRF by gender and age, and to analyze them in relation to the frequency and importance in the development of the first stroke (FS).

Material and Methods

The main VRF were studied within this research, which included patients with FS hospitalized at the Department of Neurology of the General Hospital in Doboj, who were divided into groups according to age and gender. The diagnosis was based on history, internist, cardiologist and neurological examinations and findings obtained by relevant supplementary examination method. The research results were statistically processed, analyzed and commented on.



Graph 1. Distribution of patients according to the number of VRF
Grafikon 1. *Distribucija pacijenata prema broju faktora rizika*

Results

The study sample consisted of 506 patients with FS, whose mean age (± SD) was 71.21 ± 9.64 years, ranging from 30 to 94 years. The incidence of VRF is shown in **Table 1**.

It was found that the 405 patients (80%) had at least one VRF ($p < 0.001$), and the AH was the most common variable risk factor.

Special attention was paid to the frequency of VRF in IS and ICH, as well as to their frequency in relation to the gender of the patients. The results are shown in **tables 2, 3** and **4.**

The frequency relative to the number of concomitant VRF is given in **Graph 1**, which shows that the majority of patients had two associated risk factors.

Table 1. Frequency of vascular risk factors
Tabela 1. *Učestalost vaskularnog faktora rizika*

Vascular risk factors/*Vaskularni faktori rizika*	Present/*Prisutan*		Absent/*Odsutan*	
	N	%	N	%
Hypertension/*Hipertenzija*	354	70.0	152	30.0
Smoking/*Pušenje*	178	35.2	328	64.8
Heart disease/*Oboljenja srca*	142	28.1	364	71.9
Diabetes mellitus/*Šećerna bolest*	141	27.9	365	72.1
Dyslipidemia/*Dislipidemija*	131	25.9	375	74.1
Atrial fibrillation/*Atrijalna fibrilacija*	93	18.4	413	81.6
Alcoholism/*Alkoholizam*	87	17.2	419	82.8

Table 2. The frequency of VRF in IS
Tabela 2. *Učestalost vaskularnog faktora rizika kod ishemijskog moždanog udara*

Vascular risk factors/*Vaskularni faktori rizika*	Present/*Prisutan*		Absent/*Odsutan*	
	N	%	N	%
Hypertension/*Hipertenzija*	265	69.9	114	30.1
Smoking/*Pušenje*	136	35.9	243	64.1
Diabetes mellitus/*Šećerna bolest*	118	31.1	261	68.9
Dyslipidemia/*Dislipidemija*	112	29.6	367	70.4
Heart disease/*Oboljenja srca*	107	28.2	272	71.8
Atrial fibrillation/*Atrijalna fibrilacija*	73	19.3	306	80.7
Alcoholism/*Alkoholizam*	63	16.6	315	83.1

Table 3. The frequency of VRF in ICH
Tabela 3. *Učestalost vaskularnih faktora rizika kod intrakranijalnog krvarenja*

Vascular risk factors/*Vaskularni faktori rizika*	Present/*Prisutan*		Absent/*Odsutan*	
	N	%	N	%
Hypertension/*Hipertenzija*	69	78,4	19	21,6
Smoking/*Pušenje*	31	35,2	57	64,8
Heart disease/*Oboljenja srca*	24	27,3	64	72,7
Diabetes/*Šećerna bolest*	19	21,6	69	78,4
Alcoholism/*Alkoholizam*	17	19,3	71	80,7
Dyslipidemia/*Dislipidemija*	14	15,9	74	84,1
Atrial fibrillation/*Atrijalna fibrilacija*	13	14,8	75	85,2

Discussion

In addition to active smoking, abdominal obesity, improper diet and physical inactivity, AH accounts for 80% of total VRF for stroke, 80% of which are responsible for the occurrence of IS and 90% for the occurrence of ICH, as reported by other contemporary authors [9, 15]. It has been found that 28.1% of patients suffer from a heart disease, which is similar to the percent (26%) reported by Argentino et al. [14, 15].

According to the data obtained by the research center from Novi Sad (ISR - 49 NOS), which participated in the study "Monitoring Trends and Determinants of Cardiovascular Disease" (MONICA)

Table 4. Frequency of VRF according to gender
Tabela 4. *Učestalost vaskularnih faktora rizika prema polu*

			Gender/*Pol*		p
			Female/*Ženski*	Male/*Muški*	
Hypertension/*Hipertenzija*	No/*Ne*	N	72	80	1,0
		%	474	52.6	
	Yes/*Da*	N	169	185	
		%	47.7	52.3	
Smoking/*Pušenje*	No/*Ne*	N	210	118	<0,001
		%	64.0	36.0	
	Yes/*Da*	N	31	147	
		%	17.4	82.6	
Heart disease/*Oboljenja srca*	No/*Ne*	N	169	195	0,44
		%	46.4	53.6	
	Yes/*Da*	N	72	70	
		%	50.7	49.3	
Diabetes mellitus/*Šećerna bolest*	No/*Ne*	N	166	199	0,15
		%	45.5	54.5	
	Yes/*Da*	N	75	66	
		%	53.2	46.8	
Dyslipidemia/*Dislipidemija*	No/*Ne*	N	186	189	0,16
		%	49.6	50.4	
	Yes/*Da*	N	55	76	
		%	42.0	58.0	
Atrial fibrillation/*Atrijalna fibrilacija*	No/*Ne*	N	188	225	0,06
		%	45.5	54.5	
	Yes/*Da*	N	53	40	
		%	57.0	43.0	
Alcoholism/*Alkoholizam*	No/*Ne*	N	224	194	<0,001
		%	53.6	46.4	
	Yes/*Da*	N	16	71	
		%	18.4	81.6	

implemented by the members of the World Health Organization (WHO), AH, high cholesterol and elevated blood sugar levels were also significantly present during 1984, 1988 and 1999 [2, 16–19]. Data from other studies have shown that uncontrolled blood pressure levels and blood glucose levels indicate markers of adverse outcome in patients treated with thrombolysis [20–22]. Similar results have been obtained from large study samples for both AF and smoking, particularly for younger age groups [9, 23–26]. A meta-analysis of 32 studies showed that relativ risk was twice and three times higher for developing IS and SAH, respectively, in smokers than in non-smokers [27–29].

Nearly a quarter of patients suffer from DM, and one -fifth of them have the history of a type of DM, mostly type II [30], with evenly matched incidence and higher mortality in the acute stage of stroke [25, 31]. Diet has been marked one of the main reasons for the differences in the prevalence of hyperlipidemia among continental and coastal towns [33], while its high frequency in patients with stroke is often accompanied by an increase in glycaemia [26, 32, 34].

A correlation between stress, alcoholism, obesity and dyslipidemia on one side with the advent of stroke on the other side has been demonstrated [34–36]. Moderate physical activity throughout life significantly increases life expectancy, and the results of the meta-analysis suggest that the risk of stroke in physically active individuals has decreased by up to 25% compared with inactive persons [37].

Conclusion

At least one of the following vascular risk factors is present in 80% of patients, their frequency being: arterial hypertension in 70%, smoking in 35%, heart-diseases in 28%, diabetes mellitus in 28%, hyperlipoproteinemia in 26%, atrial fibrillation in 18.5% and immoderate consumption of alcohol in 17% of patients. The values of the frequency of variable vascular risk factors have been found to be high. Arterial hypertension, heart disease and diabetes mellitus are present in both sexes without a significant difference. Alcohol consumption, smoking and hyperlipoproteinemia are more frequent in men, whereas atrial fibrillation is more common in women.

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PATELLAR TENDON RUPTURE – TREATMENT RESULTS

REZULTATI LEČENJA POKIDANE TETIVE ČAŠICE KOLENA

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Summary

Introduction. Patellar tendon rupture is a rare injury which, if missed, leads to delayed surgical treatment and may result in the loss of the knee joint function. The aim of this study was to report our results of operative treatment of the patellar tendon rupture and point out the significance of timely diagnosis and surgical procedure. **Material and Methods.** This retrospective ten-year study included 20 patients, 15 males and 5 females, their mean age being 42 (20-84) years. Seven participants had an injury on the right side and 13 had an injury on the left side. Thirteen participants had the diagnosis set in the first seven days after the injury. The applied techniques were surgical suture of the tendon, bone-tendon-bone ligamentoplasty using allograft from a bone bank and bone-tendon-bone ligamentoplasty using contralateral autograft, and they were performed in 12, 5 and 3 patients, respectively. The treatment results were assessed by using the Lysholm score, measuring the range of movement in the knee joint and measuring the girth of the thigh 10 cm above the patella. **Results.** The follow-up period after the surgery was 4 years on average (1-10 years) and the average value of the Lysholm score was 83 (27-100). The result was found to be excellent in 11 cases, satisfactory in 5 cases and unsatisfactory in 4. A statistically significant difference ($p=0.0197$ $p<0.05$) was found in the average values of the Lysholm score between the group of patients with risk factors (71.78) and the subjects without risk factors (92.18). A statistically significant difference ($p=0.008$ $p<0.01$) was found in the Lysholm score between the patients with timely diagnosis (91.62) and cases of chronic tendon tear (67). **Conclusion.** Timely diagnosis and early surgical reparation are the basic imperatives in the treatment of this injury. Comorbidity and risk factors are related to a poorer postoperative Lysholm score. The method of choice is early surgical treatment.

Key words: Tendons; Rupture; Treatment Outcome; Patellar Ligament; Early Diagnosis; Reconstructive Surgical Procedures; Risk Factors; Range of Motion, Articular

Sažetak

Uvod. Kidanje ligamenta čašice je retka povreda, čije neprepoznavanje i zakasneli hirurški tretman mogu da dovedu do gubitka funkcije zgloba kolena. Cilj rada je da prikaže naše rezultate operativnog lečenja pokidanog ligamenta čašice i ukaže na značaj pravovremene dijagnostike i hirurške intervencije. **Materijal i metode.** Desetogodišnjom retrospektivnom studijom obuhvaćeno je 20 pacijenata, 15 muškaraca i 5 žena prosečne starosti 42 godine (20−84). Desnostrano kidanje ligamenta je bilo kod sedam, dok je kod 13 ispitanika povreda bila levostrana. Kod 13 pacijenata dijagnoza je postavljena u toku prvih sedam dana posle povrede. Šivenje ligamenta je urađeno kod 12 pacijenata, kod pet pacijenata ligamentoplastika kost-tetiva-kost alograftom uzetim iz banke kostiju, a kod tri pacijenta kontralateralnim kost-tetiva-kost kalemom. Procena rezultata lečenja izvršena je na osnovu Lišolmovog skora, merenja obima pokreta u zglobu kolena i obim natkolenice 10 cm iznad čašice. **Rezultati.** Period praćenja posle operacije je bio prosečno 4 godine (1−10 godina), a prosečna vrednost Lišolmovog skora bila je 83 (27−100). Odličan rezultat postignut je kod 11, zadovoljavajući kod pet, a nezadovoljavajući kod četiri pacijenta. Dobijena je statistički značajna razlika ($p = 0,0197$ $p < 0,05$) između prosečnih vrednosti Lišolmovog skora između grupe pacijenata sa faktorima rizika (71,78) i ispitanika koji nisu imali faktore rizika (92,18). Dobijena je statistički značajna razlika ($p = 0,008$ $p < 0,01$) između vrednosti Lišolmovog skora kod pacijenata čija je povreda pravovremeno dijagnostikovana (91,62) i hroničnih slučajeva kidanja ligamenta (67). **Zaključak.** Pravovremena dijagnostika i rana hirurška reparacija osnovni su imperativi pri lečenju pacijenata sa pokidanim ligamentom čašice. Komorbidno stanje sa faktorima rizika povezano je sa lošijim postoperativnim Lišolmovim skorom. Metoda izbora je rano operativno lečenje.

Ključne reči: Tetive; Ruptura; Ishod lečenja; Tetiva čašice kolena; Rana dijagnoza; Rekonstruktivne hirurške procedure; Faktori rizika; Opseg pokreta zgloba

Introduction

The patellar tendon is the final connection of the extensor mechanism of the knee, connecting the inferior pole of the patella and the tibial tubercle. Technically, it is a ligament (connecting a bone to a bone), but it has historically been referred to as a tendon because the patella is a sesamoid bone [1]. A patellar tendon rupture is the third most frequent injury of the extensor mechanism of the knee, right after patella fracture and quadriceps tendon rupture [2–4].

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Abbreviations
MRI – magnetic resonance imaging
BTB – bone-tendon-bone
ACL – anterior cruciate ligament

A patellar tendon rupture occurs most often at its patellar insertion or at the middle of the tendon [2, 5–8]. In younger patients, this injury occurs because of repeated microtrauma or as a result of taking out medial part of the tendon during anterior cruciate ligament (ACL) reconstruction procedure. However, this injury is a result of degenerative changes in the tendon in older patients [9–11]. Corticosteroid infiltration and systemic diseases are predisposing factors for the tendon rupture. The patellar tendon rupture is diagnosed by symptoms such as pain, palpable infrapatellar defect, inability to extend the knee against gravity, high patella position (confirmed by lateral radiography) as well as by ultrasonography and magnetic resonance imaging (MRI) [12] **(Figure 1)**.

Patellar tendon ruptures are technically difficult to repair and the main goal of the treatment is to reconstruct the extensor mechanism so that it would allow the active knee extension. Since only individual cases or small series up to 30 patients have been studied until now, there is still a dilemma about optimal treatment for this injury [13–17]; therefore, the aim of this study is to show our results of operative treatment of the ruptured patellar tendon and to point out the importance of timely diagnosis and surgical intervention.

Material and Methods

This study has been approved by the Ethics Committee of Clinical Centre of Vojvodina. In the period from January 1, 2003 to December 31, 2013, there were 25 patients with the complete patellar tendon rupture who were operated at the Department of Orthopedic Surgery and Traumatology, Clinical Centre of Vojvodina in Novi Sad. This retrospective study included 20 of those patients. The data were collected by reviewing the patients' medical histories and by a questionnaire. There were 15 male and 5 female patients, their mean age being 42 (20–84) years. One patient had a bilateral patellar tendon rupture. The rupture was on the right side in six cases and on the left side in 13 cases. In 13 cases, the injury was diagnosed during the first 7 days and in 7 cases it was diagnosed after that period. Since the operation was mainly performed in the acute phase, the most frequent technique was suturing the tendon (12 patients). In four cases where the patellar tendon rupture occurred after taking a bone-tendon-bone (BTB) autograft for the anterior cruciate ligament reconstruction, the substitution was made by a BTB allograft taken from the bone bank [18]. In two cases, the reconstruction of the contralateral patellar tendon was also made by using a BTB graft - in one case the rupture occurred after taking a BTB autograft for the reconstruction of the ruptured patellar tendon of the other leg and the substitution was also made by a BTB allograft taken from the bone bank. In another case, the reconstruction of the chronic patellar tendon rupture was made by using the contralateral BTB autograft [3]. In all cases, the knee was immobilized postoperatively for six weeks with a partial weight-bearing allowed. After that period, the patients underwent a three-month rehabilitation program in order to regain the range of motion.

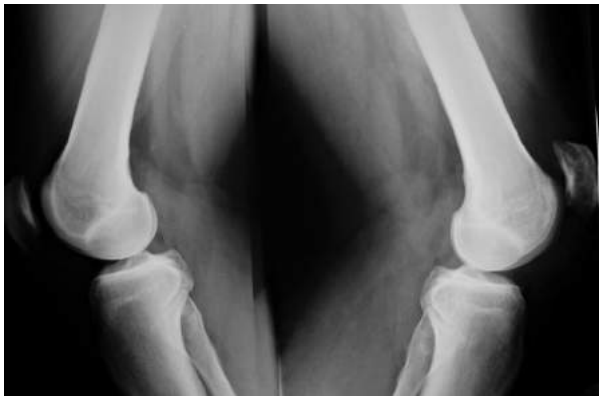


Figure 1. X-rays show the patella alta position on the left knee when compared to the contralateral side. Insall Salvati index: left knee 1.5 (patellar tendon length : patellar lenght) right knee 1.1 (patellar tendon length : patellar lenght)
Slika 1. *Rendgentski snimak pokazuje alta poziciju patele na levom kolenu u poređenju sa kontralateralnom stranom. Insall Salvati indeks: levo koleno 1,5 (dužina patelarne tetive : dužina patele), desno koleno 1,1 (dužina patelarne tetive : dužina patele)*

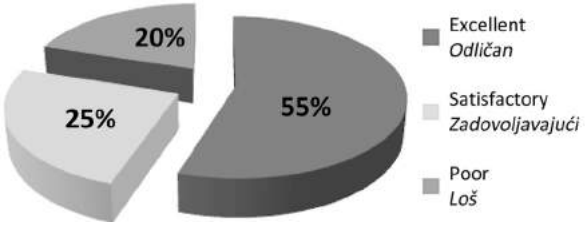
The results were based on the average Lysholm score [19], which takes into account pain, swelling, instability, weight-bearing, climbing stairs, limping and squatting. The result of the operative treatment was rated excellent in the range from 90 to 100 points, satisfactory from 80 to 89 points and poor below 79 points. The range of motion in the knee and the girth of the thigh was measured 10 cm above the patella. The difference in volumes of the left and the right thigh exceeding 2 cm indicated hypotrophy of the quadriceps muscle.

Five patients who did not respond to the invitation or did not want to participate in this research were excluded from the study.

Results

The average follow-up period after surgery was 4 years (1–10 years) and the average Lysholm score was 83 (27–100). An excellent, satisfactory and unsatisfactory result was achieved in 11, 5 and 4 patients, respectively **(Graph 1).**

A statistically significant difference was found ($p=0.0197$ $p<0.05$) between the average Lysholm score of the patients with risk factors (71.78) and the patients without risk factors (92.18) (**Table 1**).



Graph 1. The result of operative treatment of the ruptured patellar tendon based on the average Lysholm score18. Excellent result (90-100 points), satisfactory (80-89 points), poor result (below 79 points)
Grafikon 1. *Rezultat operativnog lečenja pokidane tetive čašice kolena na osnovu prosečnog Lišolmovog skora. Odličan rezultat (90−100 poena), zadovoljavajući (80−89 poena), loš rezultat (ispod 79 poena)*

All four patients with poor results had a risk factor or comorbidity in their medical histories.

A statistically significant difference of the average Lysholm score ($p=0.008$ $p<0.01$) was found in patients whose injury was timely diagnosed (91.62) compared to the cases of chronic patellar tendon rupture (67) where the injury remained unrecognized for several months (**Table 2**).

Fourteen patients (70%) had hypotrophy of the thigh muscles above the patella and six patients had a limited range of motion as well. The limited range of motion was not observed in the knee of 11 patients who had the fixation material extracted. Sixteen patients returned to the activities of daily living without reduction, whereas in four patients these activities were reduced.

Discussion

The average length of the patellar tendon is 40-53 mm [20–23]. The patellar tendon is wider proximally than distally because the fascicles tend to converge toward the midline [24, 25]. Yoo et al. [26] found that the width of the proximal and the distal part was 30 mm and 24 mm, respectively.

Table 1. Demographic data
Tabela 1. *Demografski podaci*

Gender/*Pol*	
– M/*muški*	15
– F/*ženski*	5
Age/*Starost*	42 (20−84)
Side/*Strana*	
– Left/*Leva*	13
– Right/*Desna*	7
Time from injury to diagnosis/*Vreme proteklo od povrede do dijagnoze*	
– First 7 days/*Prvih 7 dana*	13
– More than 7 days/*Više od 7 dana*	7
Risk factors/*Faktori rizika*	
– ACL reconstruction/*rekonstrukcija prednjeg ukrštenog ligamenta*	4
– Reconstruction of the contralateral patellar tendon/*Rekonstrukcija kontralateralne patelarne tetive*	2
– Total knee arthroplasty/*Totalna artroplastika kolena*	3
– Systemic lupus erythematosus/*Sistemski eritemski lupus*	2
– Rheumatoid arthritis/*Reumatoidni artritis*	1
– Diabetes mellitus/*Šećerna bolest*	1
Mechanism of injury/*Mehanizam povrede*	
– Sport injury/*Sportska povreda*	9
– Fall/*Pad*	5
– Spontaneous injury/*Spontana povreda*	3
– Traffic accident/*Saobraćajna nesreća*	2
– Sharp force injury/*Povreda oštrim predmetom*	1
Operative technique/*Operativna tehnika*	
– Suture/*Ušivanje*	12
– Ligamentoplasty using BTB allograft/*Ligamentoplastika pomoću kost-tetiva-kost alografta*	5
– Ligamentoplasty using contralateral BTB autograft/*Ligamentoplastika pomoću kontralateralnog kost-tetiva-kost autografta*	3
Use of crutches/*Upotreba štaka*	6 weeks
Immobilization/*Imobilizacija*	6 weeks
Rehabilitation/*Rehabilitacija*	3 months
Fixation material/*Materijal za fiksaciju*	
– Extracted after 6 months on average (2 months – 2 years) *Izvađen posle 6 meseci u proseku (2 meseca do 2 godine)*	11 patients
– Not extracted/*Nije izvađen*	9 patients

Table 2. Average values of the Lysholm score dependent on the time from the injury to the diagnosis, and on risk factors
Tabela 2. *Prosečne vrednosti Lišolmovog skora u zavisnosti od vremena povređivanja do dijagnoze i faktora rizika*

	Lysholm score *Lišolmov skor*	Statistical significance *Statistička značajnost*
Time from injury to diagnosis/*Vreme od povrede do dijagnoza*		
– First 7 days/*Prvih 7 dana*	91.62	p=0.008
– More than 7 days/*Više od 7 dana*	67	p<0.01
Risk factors/*Faktori rizika*		
– Present/*Prisutni*	71.78	p=0.0197
– Absent/*Odsutni*	92.18	p<0.05

The central third of the patellar tendon is significantly thicker than the medial and lateral thirds [27], and may be affected by continuing sports activity [28, 29]. The average thickness of the patellar tendon in cadavers measured by the MRI was found to be between 3-5 mm [27, 30].

A bilateral patellar tendon rupture is a very rear injury and only 20 cases have been published so far [15]. Since it is often unrecognized, it causes delays in diagnostics and treatment [30]. Siweck and Rao published that 28% cases of the bilateral rupture were misdiagnosed after the injury [2]. We had two patients with the bilateral patellar tendon rupture who had been on long-term hemodialysis due to renal insufficiency. Only one of them came back for a check-up and the result was unsatisfactory because of comorbidities and late diagnosis.

A patellar tendon rupture usually occurs in men under 40 years of age [31, 32], although our patients' mean age was 42. In younger patients, the injury most often occurs during sports activities [33, 34], while landing or stumbling, when the quadriceps muscle contracts eccentrically while the knee is flexed [12]. An unchanged patellar tendon has a substantial strength and the force needed for the rupture is 4366N [35]. The tendon load is maximal at its insertions where collagen fibers are tougher, during active extension when the knee is at an angle of 60 degrees so the rupture occurs at the insertions or in their vicinity, most often unilaterally [2, 12].

The mechanism of patellar tendon rupture is an eccentric overload of the extensor mechanism with a planted foot and flexed knee. Repetitive micro-injuries leading to tendon weakness usually precede the tendon rupture. Ruptures of the patellar tendon can occur secondary to trauma, in conjunction with systemic illnesses, after total knee arthroplasty or ACL reconstruction, as a late complication of tibial nailing, or after local or systemic corticosteroid administration [3].

The patient has a significant pain and is unable to extend the knee actively. A palpable defect is generally present as the patella usually contracts proximally. Exploration reveals that the patellar tendon is disrupted near the inferior pole of the patella. The disruption also involves a large part of both medial and lateral extensor retinaculum. With neglected or chronic patellar tendon ruptures, patients experience weakness, instability, and pain. They result in a loss of active knee extension, quadriceps muscle atrophy, and proximal patella migration. Although the diagnosis is based mainly on clinical examination, MRI and ultrasound examination can be a useful, non-invasive and accurate tool to obtain additional information such as the rupture location, the condition of the tendon, and the appearance of the surrounding tissues [3].

In case of associated systemic illnesses which lead to collagen weakness, such as systemic lupus erythematosus, rheumatoid arthritis, diabetes, chronic renal insufficiency or secondary hyperparathyroidism, the patellar tendon rupture can occur even without a significant trauma [15, 16]. Local or systemic steroid administration affects the sensitivity of the patellar tendon as well [34, 35]. Half of our patients had some of the risk factors.

The rupture of the patellar tendon occurred after total knee arthroplasty in three patients. Disruption of the extensor mechanism after total knee arthroplasty is an infrequent but catastrophic complication after total knee arthroplasty with the prevalence of 0.17% to 2.5% [36, 37]. Prevention is important in order to avoid problems during primary total knee arthroplasty and to identify those patients who are at risk preoperatively (obesity, history of corticosteroid use, stiffness, previous extensor mechanism complications, osteolysis, previous osteotomy, and patella baja). This includes the use of appropriate extensile exposures when necessary to avoid damage. If it occurs, however, the treatment is reconstruction rather than repair. Allograft tissue provides the best means for reconstruction. With proper surgical technique that includes full tensoning of the allograft, acceptable functional outcome can be achieved. On the other side, results of direct repair of extensor mechanism failure are dismal.

Results of direct repair of extensor mechanism failure are dismal. Failure rates have been reported to exceed 90% using a variety of techniques [38, 39]. Allograft tissue provides the best means to reconstruct the disrupted patellar tendon adequately [40, 41]. The options for allograft reconstruction include an Achilles tendon bone block allograft or a whole extensor mechanism allograft. Achilles ten-

don allografts are indicated in patients with an intact patella and patella component, which can be mobilized to within 2 to 3 centimeters of the joint line. It should be noted that they might also be used in patients with a chronically disrupted quadriceps tendon for which there is extreme retraction that could not be reached with a whole extensor mechanism allograft.

Bone-patellar tendon-bone remains the most common graft material for anterior cruciate ligament reconstruction. A rupture of the patellar tendon after harvesting a BTB autograft occurs very rarely [42, 43]. Patellar tendon rupture after ACL reconstruction may occur during the first month after the operation, usually as a result of trauma [43], or it may occur much later, 7 months to 10 years after the procedure, as a result of a very strenuous physical activity (strong kick or high jump). In our three patients, the rupture of patellar ligament occurred after 10 months on average (7–12) during the jump and in one patient in a car accident 60 months after ACL reconstruction. One patient received corticosteroids due to the pain in the top of the kneecap. Etiology of the patellar tendon rupture after ACL reconstruction is multifactorial: devascularization of the tendon during graft harvesting will result in a avascular degeneration [44] and the reason may be also mechanical when the donor tendon might be weaken even more than by one half when the central third of it is removed during graft harvesting [43]. Lairungruang at al. [35] compared the ultimate load bearing capabilities of the normal patellar tendon (4365.59N) to the patellar tendon after its central third was removed (2226.58N) and concluded that taking out the central third of the patellar tendon reduced both its cross-section area and ultimate load to one half.

The aim of repairing the patellar tendon ruptures is the restoration of the muscle-tendon complex to its original position as well as of the quadriceps function, preservation of the reconstructed tendon blood supply, splinting of the patellar tendon and preventing degenerative changes of the patella. The most common surgical treatment of the acute patellar tendon rupture is suturing which was done in 12 of our patients. This method provides lesser morbidity, better preservation of the ligament integrity, faster regaining of the range of motion and quicker overall recovery compared to other techniques. Marder and Timmerman [8] reported excellent results in 15 patients with acute patellar tendon rupture which had been treated with suture. Early surgical treatment imposes itself as an imperative in treatment of patellar tendon rupture [2]. In this study, better postoperative results were achieved in cases of early operative treatment compared to late operative treatment of the rupture. Operative treatment of obsolete ruptures leads to contracture of the quadriceps muscle with fibrous adhesions which additionally complicates surgical intervention and recovery as well as the functional outcome thus causing patients' dissatisfaction [2]. In these cases, the surgical substitution is done by using autograft [2, 45, 46], allograft [1, 47] or synthetic materials [2, 48]. The reparation is often protected with a wire [13, 49] or external fixation [2] and some form of postoperative immobilization is recommended [45]. The wire reduces the load on the reconstructed ligament and enables early rehabilitation but additional surgery is required in order to extract the wire. In our patients, the knee was postoperatively immobilized in extension for 6 weeks [2, 14] followed by three months of physical therapy.

We used the Lysholm score for the assessment of operative treatment results [19]. The average value of 83 in our study is most similar to the result reported by Enad and Loomis [49]. Frequent complications of the operative treatment are reduced mobility of the patella, low lying patella, limited flexion of the knee, persistent pain and muscle weakness [14]. Our most frequent complication was hypotrophy of the quadriceps muscle, which could be explained by insufficiently aggressive physical therapy. On the other hand, an aggressive physical therapy could lead to the patellar tendon re-rupture so the physical therapy must be balanced.

Besides small size of our sample, one of the shortages of our study was the inability to do control X-rays and MRI scans because of the technical reasons so we could not correlate the length of the patellar tendon between the injured and the uninjured knee. A histopathology analysis of the ruptured tendon could provide answers to some unresolved questions about etiology and pathogenesis of this complex injury. Some future studies could take into account some other factors which could potentially affect the treatment outcome such as length, aggressiveness and type of physical therapy.

Conclusion

Patellar tendon ruptures can have a significant effect on the athletic and nonathletic patient. The diagnosis can be made acutely based on careful history and physical examination. Predisposing medical conditions and activity level may present as risk factors. Upon diagnosis, immediate orthopedic referral is necessary to avoid costly delays in definitive surgical repair. The impact of the injury to the patient may be long-standing, even after operative treatment. Contemporary surgical and rehabilitative techniques give the best opportunity for restoration of functional activity.

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PSYCHOLOGICAL ASPECTS OF PEDIATRIC ANESTHESIA

PSIHOLOŠKI ASPEKTI PEDIJATRIJSKE ANESTEZIJE

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Summary
Surgery and anesthesia cause a significant emotional stress in both parents and children. Since the consequences of this stress develop immediately after surgery and can last even when the hospital treatment is over, the role of the anesthesiologist is to ensure psychological as well as physiological well-being of the patient. In order to reduce emotional stress induced by anesthesia and operation, the anesthesiologist has to understand certain developmental phases that children go through and to identify situations which a child could potentially see as a danger or a threat. This can usually be achieved by careful preoperative assessment and by administering preoperative sedation. During the preoperative visit to the patient, the anesthesiologist can evaluate the levels of anxiety of both parents and children as well as assess the child's medical condition.
Key words: Pediatrics; Anesthesia; Child Behavior; Child; Stress, Psychological; Child Psychology; Preoperative Care; Anxiety; Fear; Risk Factors; Parents; Premedication

Sažetak
Hirurgija i anestezija izazivaju značajan emocionalni stres kod dece i roditelja. Budući da se posledice ovog stresa javljaju neposredno posle postoperativnog perioda, ali se mogu zadržati i dugo nakon što prođe bolničko lečenje, jedan od zadataka pedijatrijskog anesteziologa jeste da obezbedi psihološku i fiziološku dobrobit za pacijenta. Da bi smanjio emocionalni stres anestezije i operacije, anesteziolog mora da razume razvojne odrednice i faze dečje psihologije i da predvidi situacije koje bi dete moglo doživeti kao opasnost i patnju. To se često može postići pažljivim preoperativnim razgovorom i preoperativnim davanjem sedacije. Preoperativnu posetu pacijentu anesteziolog može iskoristiti kako za procenu zdravstvenog stanja deteta, tako i za procenu nivoa anksioznosti i kod roditelja i kod deteta.
Ključne reči: Pedijatrijska anestezija; Ponašanje deteta; Dete; Psihološki stres; Dečija psihologija; Preoperativna priprema; Anksioznost; Strah; Faktori rizika; Roditelji; Premedikacija

Preoperative Anxiety Definition, Frequency and Consequences

A great number of children undergo surgery every year and it is estimated that up to 70% of these children experience significant fear and anxiety before being operated on [1, 2]. Preoperative anxiety is defined as a subjective feeling of tension, nervousness, worry and loss of sleep associated with an increased autonomic nervous system activity [3]. Children may look scared and/or agitated, breathe deeply, tremble, stop talking or playing and/or start to cry. Other children may become nauseous, wet themselves, have increased motor tone and/or attempt to run away from the operating room staff [4].

Based on children's behavior and physiological parameters, the induction of anesthesia appears to be the most stressful moment for the child during the perioperative period [3, 5]. It has been proved that intravenous induction is more stressful for children than inhalation induction [5, 6]. It is presumably due to the pain which the child experiences during the placement of peripheral intravenous line, as well as the pain during the application of an anesthetic (propofol) [7].

In addition to the fear of being separated from their parents, children are afraid of pain, loss of control, sense of insecurity due to "going to sleep" and unfamiliar uniformed faces who surround them in an unknown environment [2, 4]. Younger children are more concerned about being separated from their parents, while older children are more worried about anesthesia and surgery itself [2, 8].

Stress and anxiety experienced by children during the induction of anesthesia are associated with the child-related and environment-related factors. The child-related factors include their age, developmental stage, previous experience with medical procedures, the child's temperament, as well as the parental anxiety. The environment-related risk fac-

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tors are the interaction with medical staff, brightness, level of noise made by medical staff as well as the preparation of the operating room instruments and the number of medical staff communicating with the child [3].

Three most common factors affecting the outcome of surgery are postoperative pain, nausea and vomiting and preoperative anxiety [3, 9]. Increased preoperative anxiety has been proved to be associated with increased postoperative pain, higher consumption of analgesics, general anxiety and sleeping problems [1, 2, 10, 11]. Anxiety on induction of anesthesia is also associated with emergence distress and postoperative behavioral problems [2, 4]. Children who are extremely anxious before the operation are at 3.5 higher risk of having negative postoperative behavioral patterns in comparison with those who showed lower anxiety levels. Some of the most common maladaptive behavioral patterns are general anxiety, crying during the night, wetting themselves, anxiety on separation from the parents, inadequate eating, apathy, drawing into themselves and irritability [2]. Preoperative anxiety triggers a stress response, which is associated with higher corticosteroid blood level, which increases susceptibility to infection, thus prolonging the process of recovery [2, 12, 13]. Although it has been reported that the incidence of postoperative behavioral changes reduces in time, these changes persist up to 6 months after surgery in about 20% of children and up to a year in 7.3% of children. Since they could potentially have long-term negative effects on the child's development, it is very important to understand psychological problems associated with operation and anesthesia [3, 4].

Identification of Children at Risk

The first step in psychological preparation of children who will undergo surgery is identification of children who are at a particularly high risk of developing extreme anxiety and fear of surgery. Risk factors that affect the behavioral responses of children during the preoperative period are their age, temperament, developmental stage, their parents' anxiety, various demographic characteristics as well as the previous experience of the child with medical procedures [1, 5, 8, 14].

Children between 1 and 5 years of age have been identified to be at the highest risk of developing significant preoperative anxiety [8, 14]. At this age, children are particularly vulnerable because they are both too young to be independent of their parents and old enough to recognize the parent's absence. Considering the fact that they are not aware of what is happening exactly, their major fear is to be separated from their parents by an unknown person. Although younger children may not have the ability to anticipate potential dangers or painful situations during the induction of anesthesia, children over 6 years of age may anticipate the pain and fear of "going to sleep". Older children rely on different techniques in order to cope with the stress, including verbal (questioning) and cognitive (learning about medical equipment or what doctors do). This helps them relieve their anxiety [15].

Children who had bad experience with medical procedures and illness in the past are at a higher risk of developing high anxiety during the preoperative period and they cooperate poorly during the induction of anesthesia [5]. Repeated surgeries do not represent a risk factor themselves [8].

Several studies have shown that children who are shy and inhibited by temperament feel fear and anxiety of higher levels on the day of surgery compared with other children. Conversely, children who have a more socially adaptive temperament are less anxious when being prepared for surgery [15].

A child's predisposition towards anxiety before surgery is strongly affected by the behavior of the parents. Parental anxiety affects the child's stress response in two ways. Firstly, worrying parents are less capable of responding to their child's needs although parents can generally relieve the stress response of their child. In this case, the child's distress may be further increased by the parents' anxiety. Another pattern in which parental anxiety can affect a child's response reflects the genetics of parental disposition to being overanxious [15].

Preoperative anxiety in children can be managed by psychological (preoperative preparation programs, parental presence at the induction of anesthesia) or pharmacological approach, or both.

Psychological Approach
Preoperative Preparation Programs

There are different preparation programs including playing, tour of the operating room, video program explaining what the child will go through at the day of surgery, conversation with the psychologist and written material adjusted to the child's age [5]. Their efficacy depends on how and how often they are conducted (just once or several times), as well as on the child's age [8, 14]. Children of and over 6 years of age benefit most if they participate in the program more than 5 to 7 days before surgery and benefit the least if the program is performed only one day before surgery [14]. This longer interval between the preparation and the surgery is needed for the older children to have adequate time to process new information acquired during the preparation program. Interestingly, there may be a negative effect of a preparation program on younger children. This could be the consequence of the inability of children under 3 years of age to separate fantasy from reality [14].

Designing a preparation program for children who have already been hospitalized is particularly challenging. Standard preparation programs have been proved to be inadequate for these children because they can often remind them of negative emotions associated with the previous surgery, and thus sensitize them. Alternative psychological programs, such as extensive individualized trainings for coping

with stress, combined with a practical situation, are more helpful for these children [14].

Program must be created according to the individual needs of every child, taking into account the child's age, previous experience with medical care and temperament of the child [5].

It is necessary for both the parents and the children to be included in the preoperative preparation. Multiple studies have suggested that the parents become very anxious when their children have to undergo surgery and this has been identified as a major risk factor for the increase preoperative anxiety in children [, 5, 8, 14]. Parents experience preoperative anxiety due to the separation from their child and the child's suffering from pains; they worry about the surgery outcome and have a feeling of guilt in addition to financial stresses. Mothers are more prone to anxiety than fathers [16]. Parents who undergo a preoperative preparation program or those who have viewed a video with factual information about anesthesia show a lower level of preoperative anxiety on the day of surgery, but not during the induction of anesthesia, after surgery, in the intensive care unit and during a two-week postoperative recovery [17].

Parental Presence

The presence of parents during the induction of anesthesia is sometimes an alternative to premedication with sedatives, although its influence on relieving child's anxiety remains controversial [18]. Potential benefits from parental presence include a reduced need for sedatives, reduced parental anxiety and stress due to being separated from their child before surgery, as well as better compliance of the child [4, 19]. However, most of the studies dealing with this issue have not established any benefit from the parental presence during the induction of anesthesia [2]. In addition, it has been found that the induction itself lasts longer if the parents are present and children of anxious parents are even more anxious in the presence of their parents [4, 18, 19]. On the other hand, several studies have identified the children who may benefit from parental presence during the induction of anesthesia. Those are older children who are less active and impulsive, as well as children whose parents are calm and appreciative of preparation programs [18].

A great number of studies have found that most of the parents prefer to be present during the induction of anesthesia regardless of the child's age because they believe that their presence helps their child [8, 19]. More than 80% of parents choose to be present in the operating room when returning for a second operation regardless of whether they were present the first time [20]. Although current evidence does not suggest that the parental presence alleviates anxiety in either children or parents, the presence of parents during the induction of anesthesia is associated with increased parental satisfaction [2, 4, 21].

Research in this area has been focused so far on the question whether the parent should be present during the induction of anesthesia or not. However, more concern should be given to what parents should actually *do* during the induction rather than simply to their presence [5, 18].

Pharmacological Approach - Premedication

Midazolam is a short-acting benzodiazepine, which is most often used in premedication of anxious children due to its sedative, anxiolytic and amnesic effect. It has been proved to reduce anxiety in children in preoperative period, but it does not delay recovery and hospital discharge [2, 5, 22]. Many controlled randomized studies have found that midazolam is superior in reducing preoperative anxiety and increasing compliance of children during the induction of anesthesia when compared to preparation programs and parental presence during the induction of anesthesia [18, 21]. However, some authors have verified an increase in postoperative anxiety in children. This paradox can be explained by the influence of midazolam on explicit memory due to which children are unaware of the fact that the operation is over [23, 24]. Furthermore, if the child has not experienced the induction of anesthesia as negative, but just does not remember it, then another operation can be felt as a new and disturbing experience [5, 25].

Clonidine is an alpha 2-adrenergic agonist that has analgesic properties in addition to its sedative ones, therefore, it is increasingly being used in premedication. It has been proved that when given nasally or orally as a premedicant, it acts as an anxiolytic, reduces the requirement for volatile anesthetics, and increases perioperative hemodynamic stability and postoperative analgesia [2]. Almenrader et al. have shown that orally administered clonidine is superior to orally administered midazolam because children ingest it more easily, premedication is more efficient, it reduces agitation upon emergence and increases parents' satisfaction [26]. In addition, clonidine does not cause amnesia, and sedation thus induced resembles physiological sleep, which is not the case with midazolam [2].

Alternative Ways of Affecting Anxiety and Behavioral Changes

Music

A number of studies have shown that music can reduce anxiety in children, increase compliance and reduce the need for sedatives. The most probable mechanism of action is distraction [27]. Kain et al. have come to an interesting conclusion that the reduction in sensory stimuli (dimmed light, only one person communicating with the child in the operating theatre), combined with background music, alleviates anxiety in children during the induction of anesthesia [28]. The same authors have shown that interactive music therapy can be useful during the separation from parents and when entering operating theatre; however, they failed to prove its efficacy in reducing children's anxiety [29].

Clowns

Golan et al. have studied how the presence of specially trained clowns before surgery affects children's behavior and concluded that clowns significantly reduce preoperative anxiety, compared to the control group and the group which received premedication. However, upon application of a facial mask for inhalation induction of anesthesia, the presence of clowns did not prove efficient [30]. The Italian authors found that the children were significantly less upset during the induction of anesthesia when they were accompanied by two clowns and parents in the preoperative room and in the operating theatre compared with children premedicated with midazolam or children who were accompanied only by parents [25]. Clowns can make the induction of anesthesia smoother and more pleasant, which makes them an important alternative to midazolam, which causes amnesia for the event. As indicated previously, if children did not find the induction of anesthesia a traumatizing experience, without remembering it, future operations can be more stressful for them [5, 25].

Hypnosis

Hypnosis is the altered state of mind based on dissociation, with focused but directed attention which differs from sleep. A study conducted by French authors has proved that hypnosis, as a technique of premedication, is more efficient in reducing preoperative anxiety in children than midazolam, particularly during the induction of anesthesia. Hypnosis makes children relaxed and able to take active participation during the induction, leaving them with a pleasant memory, which is significant for possible future operations. Given that hypnosis makes the separation of children from their parents stress free, it can also reduce anxiety of parents and increase their satisfaction. Last, but not least, hypnosis reduces incidence of behavioral changes during the first two weeks after surgery [31].

Acupuncture

Acupuncture originates from China and has been gaining on popularity in the western world of medicine during recent decades, despite the lack of strong scientific evidence.

Wang et al. have shown that acupuncture of certain points on the ears reduces preoperative anxiety in 30 minutes in adults scheduled for elective surgery. This method is easy to use, relatively cheap and has minimal side effects [32].

Given that anxiety in parents who are present during the induction of anesthesia is related to increased anxiety in children, acupuncture was evaluated as treatment of anxiety in parents too. Wang and Kain had applied acupuncture in the mothers of children who underwent surgical intervention and concluded that ear acupuncture together with the presence of mothers during the induction of anesthesia reduced anxiety in children and increased their compliance [33]. Wang also proved that parents were less anxious after acupressure of Yintang point than the control group after acupressure of sham points (which do not have any effect on anxiety) [34]. Acupuncture could easily become an integral part of treatment of preoperative anxiety in children because it requires minimal equipment, with minimal expenses, it is simple to apply, it has relatively quick onset of effect and practically no side effects.

Video Games

Video games are widespread in the modern society. Children can immerse themselves so much in playing video games that they become unaware of their surroundings and they disregard verbal and tactile stimuli. A prospective randomized controlled study showed that the children between 4 and 12 years of age who played a video game holding it in their hands were significantly less anxious during the induction of anesthesia than the children whose parents were present in the operating theatre. This method is cheap, easy to implement and efficient in stress reduction during the induction of anesthesia in children of both sexes [35].

Smartphones

A recent study performed by the Korean authors was aimed at using smartphones to reduce preoperative anxiety in children. The authors concluded that children who had used a phone application before surgery were significantly less anxious compared to the children who received standard premedication with midazolam. When smartphones were used in combination with a low-dose midazolam, the level of anxiety was significantly lower than in other two groups. The authors believe that low-dose midazolam converts anxiety to curiosity in children and thus increases their compliance. Smartphones are widely present today and their contents can be adjusted to the individual needs of a child [36].

Conclusion

Preoperative period can be very stressful for children. Fear and anxiety during this period are related not only with the imminent discomfort for both children and parents, but also with negative consequences on the postoperative behavior and clinical recovery of the child. There are a lot of possibilities to reduce preoperative anxiety in children. Some of these interventions are widespread and their efficacy is well known, while some are still being evaluated. It is important to understand psychological problems related to operation and anesthesia in order to help children and parents to cope with perioperative stress.

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REASONS FOR AND FREQUENCY OF *OFF – LABEL* DRUG USE

RAZLOZI I UČESTALOST OFF – LABEL PRIMENE LEKOVA

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Summary

Introduction. The application of drugs in accordance with the marketing authorization issued by the regulatory authority is considered *on-label* use, while *off-label* drug use frequently occurs in medical practice. It includes the application of drugs beyond approved indications, for unapproved age group, with different dosage regimens or different administration route. Medical specialists frequently prescribe an *off-label* drug in pediatrics, neonatology, geriatrics, psychiatry and oncology. Some countries have established registers of *off-label* drugs and guidelines for their prescribing and administration. The aim of the paper is to review practices in *off-label* drug use in order to satisfy the attitude of regulatory bodies and professional associations regarding the *off-label* use of drugs. **Material and Methods.** The sources of information used are articles published in scientific journals and information from the official websites of regulatory agencies. **Results and Discussion.** The most common reasons why physicians decide to prescribe *off-label* drugs are primarily the absence of drugs for a particular indication or those for a particular age group. In their daily work, doctors prescribe drugs for an *off-label* use based on their own or other colleague's experience. There is no general agreement on *off-label* use of drugs at the national or international level, but more and more doctors' associations and regulatory bodies approve *off-label* drug use in compliance with certain scientific and legal requirements. **Conclusion.** *Off-label* drug use has its place in practice and it has been widely accepted by the medical community and by itself it is not a violation of the standards of healthcare. *Off-label* use is common in our country and worldwide, and it is necessary to establish a registry for *off-label* drug use.

Key words: *Off-Label* Use; Drug Prescriptions; Physician's Practice Patterns; Registries

Sažetak

Uvod. Primena leka u skladu sa dozvolom za promet koju je izdao regulatorni organ predstavlja *on-label* primenu, dok se u praksi često sreće i *off-label* primena lekova, koja podrazumeva primenu leka mimo odobrenih indikacija, za neodobrenu starosnu grupu, sa drugim režimom doziranja ili drugačijim načinom primene. Lekari često propisuju *off-label* lekove u pedijatriji, neonatologiji, gerijatriji, psihijatriji i onkologiji. Neke zemlje imaju registre upotrebe *off-label* lekova i vodiče za njihovo propisivanje i primenu. Cilj rada je bio da se prikažu iskustva iz prakse u *off-label* primeni lekova. **Materijal i metode**. Izvori podataka su radovi objavljeni u naučnim časopisima i zvaničnim internet stranicama regulatornih tela. **Rezultati i diskusija**. Razlozi zbog kojih se lekari odlučuju za *off-label* propisivanje lekova su nedostatak lekova za određenu indikaciju ili za određenu starosnu grupu. U praksi, lekari propisuju lekove za *off-label* primenu na osnovu vlastitog ili iskustva drugih kolega. Nema jedinstvenog stava o *off-label* primeni lekova kod nas i u svetu ali sve više udruženja lekara i regulatornih tela odobrava *off-label* primenu lekova uz poštovanje određenih stručnih i zakonskih uslova. **Zaključak**. Primena *off-label* lekova ima svoje mesto u praksi i široko je prihvaćena među lekarima, te nije u suprotnosti sa zdravstvenim standardima. *Off-label* primena je zastupljena kod nas i u svetu i neophodno je formirati registre za *off-label* primenu lekova.

Ključne reči: *Off-label* primena; Primena lekova; Lekarsko iskustvo; Registri

Introduction

Administration of drugs in compliance with the marketing license specifying the formulation, dosage and age-category, issued by a relevant authority is referred to as *on-label* use. However, the practice of *off-label* prescribing is very common. It implicates the use of a medication in a manner not listed in the approved prescribing guidelines with respect to indications, age-category, and dosage regimen or administration route. *Off-label* drug use is to be distinguished from the application of unlicensed and thereby unregistered drugs. Unregistered drugs are those that have not been evaluated or approved by a relevant authority responsible for putting the drug in the market. This category in-

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Abbreviations

AIDS – Acquired Immune Deficiency Syndrome
ALIMS – Medicines and Medical Devices Agency of Serbia
EBM – Evidence Based Medicine
EU – European Union
FDA – Food and Drug Administration
USA – United States of America

cludes drugs undergoing the registration procedure and/or clinical trials, particular *ex-tempore* preparations intended for individual patients, modified forms of registered drugs in view of their formulation or strength (e.g. the preparation of a suspension from capsules or tablets, the preparation of a topical product from a peroral preparation, modification of the preparation to the one with different pharmacokinetic profile, etc.), repackaged drugs (the drugs that are removed from their original container and placed into another container during storage or dispensing process), chemicals used for the treatment of particular diseases [1].

Are there Legal Regulations relating to *Off-Label* Prescription and Promotion of Drugs?

A treatment is commonly defined as a discipline that includes preventive, diagnostic and therapeutic measures in line with relevant legislation, which are primarily aimed at improving, recovering and maintaining of health. However, medicine is often described not as a science, but as an „art of healing" – literally translated from Latin „*ars medicinae*". Therefore, as artists tend to resist censorship, so doctors tend to fight against some legislative decrees that seem to them as a barrier to their freedom of prescribing [2]. Undoubtedly, enforcement of certain legal guidelines is inevitable in order to provide safe and effective health protection.

Are Doctors Granted Freedom in Prescribing Drugs?

European Medicines Agency (EMA), Food and Drug Administration of the United States of America (FDA) and other national regulatory authorities, as well as the Medicines and Medical Devices Agency of Serbia (ALIMS) are responsible for ensuring the quality, safety and effectiveness of the drug put on the market and its compliance with the approved guidelines. However, such authorities do not generally regulate the administration of drug in everyday practice. Thus, doctors are entitled to freedom in prescribing drugs. Such prescription-freedom must be in accordance with fundamental postulates of medicine – a doctor's responsibility and care for the patient's well-being. Doctors must keep in mind their professional liabilities and responsibilities towards relevant national legislation and obey medical ethical principles. In line with novel scientific accomplishments, doctors should prescribe an *off-label* drug only if this *off-label* prescribing (according to their professional judgment) is the safest and most effective therapeutic option for the patient [3].

The aforementioned facts clearly indicate that the *off-label* practice of drug prescribing is legal and very common in many countries worldwide. This also pertains to opioid analgesic drugs (morphine, methadone, pethidine, etc.), the marketing of which is governed by special regulations. It is a worldwide known fact that the lack of adequate registered and approved (*on-label*) therapy makes the *off-label* prescribing inevitable. Even Hungary, being one of the countries in which *off-label* prescription had not been permitted, initiated the process of official legal recognition of the *off-label* drug prescribing [4, 5]. According to the data from the available international literature, it is evident that *off-label* prescribing is legitimate [6]. The question that inevitably arises is when the *off-label* prescribing can be considered an appropriate approach. Regrettably, a universal answer does not exist. Doctors are entitled and responsible to estimate what could be considered the "appropriate" *off-label* application in each individual case.

Legal Regulations and Criteria for *Off-Label* Drug Prescription in the European Union, the United Kingdom of Great Britain, the United States of America and in our Region

Certain standards for *off-label* prescribing are regulated by relevant legislation and medical and health-related bodies in the majority of countries.

Different opinions on this issue could be summarized as following:

1. It is frequently emphasized that *off-label* drug prescribing is justifiable under certain specific circumstances when convincing clinical evidence for its application is available. If an *on-label* drug is likely to produce a similar effect for particular indication as an *off-label* drug, the doctor should undoubtedly choose the registered one, i.e. an *on-label* drug.
2. Professional standards and guidelines must be followed. *Off-label* prescribing should be based on scientific evidence, except in case of extreme emergency, when no alternative is available.
3. Each *off-label* treatment should guarantee a high level of respect of the patients' needs and rights and written consent to the treatment should be obtained. Although standards vary substantially among the relevant authorities, it is generally believed that doctors are obligated to inform their patients about the nature and details of suggested therapy (i.e. to emphasize that the drug is *off-label* and not registered for this particular indication), to explain clearly their reasons for suggesting the treatment, potential adverse reactions, risks and benefits. In addition, they must mention available alternatives for the treatment. Ideally, such information should be communicated to the patient personally, in private conversation. Afterwards,

the doctor should ask and obtain the written consent from the patient.

4. The doctor is obligated to keep clear, accurate and legible records on the application and effects of the drug, including the lists of all prescribed drugs and the reasons for their prescribing. It is of paramount importance in order to provide adequate monitoring of the effects of *off-label* prescribed drugs and obtain an overview of the extent and effectiveness of such treatment [6].

Legal Regulations Pertaining to *Off-label* Drug Promotion

Contrary to drug prescribing, which is regulated by somewhat more flexible regulations, promotion of drugs is strictly regulated by national laws. Strict regulatory restrictions on drug promotion, i.e. advertising, come from the fact that drug advertising is a powerful tool that might result in massive adverse impact on public health if inadequately applied. To prevent such negative effects on human health, *off-label* promotion is declared illegal in all countries worldwide. However, it is to be emphasized that, whereas promotion of *off-label* drug is distinctly prohibited, providing information on *off-label* application is not [6].

Legal Regulations in the European Union

The European regulations governing the marketing of medicines do not offer a universal definition for "appropriate application of the *off-label* drugs", yet defining the number of situations where *off-label* prescribing is allowed:

– products currently undergoing clinical trial
– exceptions from European Union (EU) Directive and Regulation (e.g., compassionate use for terminally ill patients)
– *off-label* use under the individual decision of a treating doctor while applying appropriate procedure to protect patients' health [7]

In the majority of EU member countries, the patient's right is to obtain information about available alternative treatments to the one proposed by their treating doctor, that is, available *on-label* therapies when their doctor has suggested an *off-label* treatment option. Besides the aforementioned circumstances pertaining to the EU as a whole, Ethics Committees of each individual member state provided the opinion on the *off-label* drug application and declared the binding (or not binding) regulations on the prescription thereof [7].

Legal Regulations in Great Britain

Off-label prescribing is legal and accepted in Great Britain. This concept is regulated by *Good practice in prescribing and managing medicines and devices* of the British Medical chamber that represents the core guidance for drug prescribing for all registered doctors. This Guidance, issued in 2006, states the principles that must be followed by doctors when prescribing drugs. The Guidance indicates that a doctor may prescribe medicines for the purpose other than the one they were registered for. Besides a wide range of circumstances when *off-label* prescribing is possible, the Guidance emphasizes that it is most likely in pediatric practice. When prescribing medicine outside the terms of their license the doctor has to:

– assess whether an off-label drug will better meet the specific needs of the patient than the licensed therapeutic alternative
– assess whether there is sufficient evidence on the safety and effectiveness of relevant *off-label* medicine or experience on its application. In some cases, the information provided by the manufacturer might be insufficient, thus, more information should be provided from other sources.
– take full responsibility for *off-label* prescribing and monitoring of the patient's care, and follow up treatment, or ensure that arrangements are made for another suitable doctor to do so (in case of hospitalized patients)
– keep clear, precise and legible records on all prescribed medicines; indicate the reasons for prescribing an *off-label* drug in case of not complying with common practice [8, 9]

The Guidance also addresses the issue of patient's being informed about the use of drugs within or outside the terms of their license. Accordingly, if an authoritative guidance supports the *off-label* drug application, the patient does not have to be alerted about the drug being or not being used in line with its original license. The doctor should give the patient sufficient information about the therapy that he considers relevant and important. However, if the patient or his caregiver (parents, family members, etc.) expresses any concern about *off-label* prescribed drug, the doctor must provide the explanation for his decision. Such explanation may be supported by written information, e.g. the brochure about the application of unregistered drugs or application of registered drugs beyond their proposed use in pediatric patient population published by the Royal College of Pediatrics and Child Health. On the other hand, if there is not enough supporting evidence relying on authoritative prescribing practice, the doctor should explain the reasons for prescribing an *off-label* medicine. The same applies to drugs not yet registered but whose administration is indispensable.

Legal Regulations in the United States of America

In the United States of America (U.S.A.), *off-label* prescribing is not prohibited by any federal regulation. The discretion of doctors and other healthcare-team members who are licensed for prescribing drugs (pharmacists and specially trained and qualified nurses) to prescribe products off label is recog-

nized. The FDA approves a product for marketing, yet it does not have the legal authority to regulate the prescribing practice of the medicine. That is, the *off-label* prescribing practice is beyond the authority of this regulatory body. According to the official statement of the FDA dated April 1982, once a product is approved and registered for marketing in the U.S.A., doctors are legally entitled to prescribe it for indications beyond the registration limit and age categories, as well as to prescribe doses or administration routes other than those included on the label. *Off-label* drug prescribing must rely on the doctor's professional assessment of the effectiveness and safety of such drug application. The FDA considers that *off-label* drug administration is justified and rational in some instances and that it reflects therapeutic approaches reported in the relevant medical literature [9].

Legal Regulations Pertaining to *Off-label* Prescribing and Promotion in Serbia and Neighboring Countries

Similar to the neighboring countries, the issue of *off-label* drug prescribing in Serbia has not been addressed in relevant legislation. Although the *off-label* prescribing practice is evident from the data on everyday medical practice, the ALIMS has not yet publicly communicated any official data. Contrary to Great Britain where the registry of *off-label* drugs applied in pediatrics or neonatology is available, there are neither regulations regarding the *off-label* drug prescribing nor relevant registries of *off-label* medicines in our country. Moreover, promotion and advertising of *off-label* medication is not regulated, i.e. directly prohibited by any law or subordinate legislation except for the general prohibition on advertising and promotion of drugs other than over-the-counter drugs (OTCs). The provisions of the Law on Medicines and Medical Devices indirectly indicate that *off-label* promotion is not legal. Advertising of a prescription drug to professional community is allowed under conditions stipulated in the license, and in accordance with the previously approved summary of product (drug) characteristics [10].

Reasons for *Off-label* Drug Administration

One of the major reasons why doctors choose *off-label* prescribing is the unavailability or absence of licensed, effective and safe therapeutic options for particular conditions and diseases. It is particularly evident in some rare conditions, carcinoma (because of resistance of malignant cells towards the range of medicinal substances), infectious diseases (human immunodeficiency virus (HIV)/*Acquired Immune Deficiency Syndrome* /(AIDS)], complex psychiatric disorders, etc. Sometimes, *off-label* prescribing is the ultimate choice of doctors, particularly after the approved treatment options have failed. Absence of therapeutic alternatives for specific patient populations (newborns, children, pregnant or lactating women, the elderly, patients with severe kidney or liver diseases, etc.) often results in *off-label* drug prescribing to unapproved patient population in spite of potential contraindications stated in the Summary of Product Characteristics (SmPC) or Patient Information Leaflet (PIL). Children, pregnant women and the elderly are often excluded from clinical trials for a number of legal, ethical or practical reasons, thus, a wide range of drugs is neither approved nor specifically intended for such populations. Consequently, *off-label* prescribing is often practiced in pediatric, geriatric and obstetric practice. Another common reason for prescribing medicines outside the limits of their original license is convincing evidence on their effectiveness and safe application in particular situations. Positive and encouraging results of randomized clinical studies often represent a starting point for considering the *off-label* drug as a therapeutic option. In that respect, doctors may take into consideration novel developments in the field of medicine and pharmacy when prescribing medicine beyond the approved indications, contraindications, recommended dose and dosage regimen, administration route or age category. Doctors' decisions on off-label prescribing are often justified by the clinical and scientific facts relying on Evidence-Based Medicine (EBM). The EBM concept represents "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients", that is, "integrating individual clinical expertise with the best available external clinical evidence from systematic research" [11, 12]. This very definition of EBM encourages some doctors to administer *off-label* drugs if such administration is appropriate in given circumstances. Having in mind the fact that information on drugs is widely available to patient population, it is not surprising that patients and their families often initiate the *off-label* prescribing. Obviously, it occurs most commonly in terminally ill patients or patients with degenerative diseases, who desperately seek any information about potentially effective treatment option. Easily accessible information on the effects of an *off-label* medication is not necessarily supported by sound and valuable scientific evidence. Thus, insufficiently valid results of particular studies might often be misleading for the patients and their families with regard to therapeutic effectiveness of particular *off-label* medication. One should bear in mind that, even when the patient initiates the *off-label* prescribing, the doctor is the one to take the responsibility for prescribed therapy. Thus, the doctor should decide about the best available therapeutic option for the patient while providing the patient's consent for its application.

Prevalence of *Off-label* Drug Prescribing

Off-label drug prescribing is very common in medical practice. Most frequently, drugs are prescribed outside their licensed indications or to different age categories. Studies have revealed that *off-label* prescribing is more common by special-

ists than by general practitioners [13, 14]. Psychiatric and malignant diseases are often associated with *off-label* prescribing, which is not surprising having in mind that unknown etiology and factors influencing disease progression require highly complex approach to the treatment and selection of an effective therapy. Administration of drugs outside their original license is evident in obstetrics, psychiatry as well as in treatment of some infectious diseases (particularly AIDS).

Off-label prescribing is common in pediatrics practice, which is due to the specific age of the patients. The most commonly prescribed *off-label* drug categories include drugs used in the therapy of cardiovascular diseases, anticonvulsive drugs, antipsychotics, antidepressants and antiasthmatics. The extent of *off-label* prescribing of particular drugs is best illustrated in the following example. Fentanyl, a powerful, rapid-acting opiate analgesic is registered in American market for the treatment of severe pain in patients with carcinoma. However, available data indicated that only 1% of Fentanyl prescriptions were issued by oncologists in the first half of the 2006. It was established that 80% of the drug was prescribed *off-label* predominantly to treat migraine and back pain. In 2006, a study aimed at investigating the prevalence of off-label prescribing to outpatients was published in the U.S.A. [15, 16]. That research encompassed 160 mostly prescribed drugs in the U.S.A. The rates of *on-label* and *off-label* prescribing were investigated, as well as the existence of sound scientific justification for their *off-label* prescribing. The obtained results revealed that as many as 20% of drugs registered and licensed in the U.S.A. were prescribed *off-label*. The research revealed that 50-90% of drugs prescribed as "*off-label"* and "*unlicensed"* and used in pediatric and neonatological practice had never been evaluated for application in children and newborns [14, 17, 18]. The research revealed that the rates of *off-label* medications ranged from 62% (pediatric departments), 80% (primary pediatric practice) to even 88% (neonatology hospital departments) in the period 1990-2010. Numerous studies conducted in various therapeutic fields, among different age groups and geographic regions indicated that the newborns are the population most commonly treated with medications that are beyond the license for this particular age group. According to these studies, the percentage of children who have received at least one *off-label* or unregistered drug ranges between 36%–92% at pediatric departments, 80%–97% at neonatology department and 11%–37% in primary health care [19–26]. *Off-label* prescribing is very common in oncology. According to available data, particular antineoplastics are more frequently associated with unlicensed and *off-label* drug prescribing than with the licensed one. It has been estimated that 50–75% of drug administered in oncology practice in the U.S.A. are prescribed *off-label* today.

A study conducted in the U.S.A. in 1991 revealed that one third of the drugs administered to oncology patients were prescribed *off-label*, while more than a half of the patient received at least one drug beyond its licensed indication. Another study done in 1997 with 200 participating oncologists, members of the American Society of Clinical Oncology, revealed that 60% of members prescribed drugs outside the relevant license [17, 26].

Conclusion

Doctors' freedom in prescribing *off-label* drugs is associated with substantial advantages. It enables an innovative approach in clinical practice, particularly in cases when approved therapeutic options are unsuccessful. In other words, *off-label* drug prescribing offers possibilities of adopting novel evidence-based treatment practices. On the other hand, such policies facilitate patients' early access to potentially valuable medication. The fact that *off-label* prescribing often represents the only available therapeutic option for specific patient groups or patients with rare diseases is an important advantage of this approach. However, the drawbacks of *off-label* prescribing practice should not be neglected. Potential problems associated with the *off-label* drug prescribing include the following:

a) adverse reactions associated with *off-label* drug prescribing

b) increased responsibilities of health care providers in view of patient's well-being

c) impossibility to compensate health care expenses because of *off-label* drug use

d) promotion of *off-label* drugs by the manufacturers

Major drawback of the *off-label* drug use is an increased probability of adverse effects of the drug. It is attributed to the fact that safety and effectiveness of an *off-label* drug have not been confirmed. Thus, implementation of more precise legislation defining appropriate prescribing and application of *off-label* drugs as well as stipulating the responsibilities of all parties participating in such therapeutic approach is highly demanded in our country. Creation and regular update of a registry of off-label drugs applied in daily healthcare practice is of vital importance.

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^{18}F-FLUORIDEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY/ COMPUTED TOMOGRAPHY IMAGING: ARTIFACTS AND PITFALLS

POZITRONSKA EMISIONA TOMOGRAFIJA/KOMPJUTERIZOVANA TOMOGRAFIJA SA ^{18}F-FLUORODEOKSIGLUKOZOM: ARTEFAKTI I GREŠKE U INTERPRETACIJI NALAZA

Jasna MIHAILOVIĆ, Emil MATOVINA and Katarina NIKOLETIĆ

Summary

^{18}F-fluorodeoxyglucose, being a radiolabeled glucose analogue, is a marker of glucose metabolism indicator. Since glucose uptake is increased in malignant tumors, its major application is in oncology. However, an increased ^{18}F- fluorodeoxyglucose uptake is found in various benign tumors, granulomatous diseases, tuberculosis, inflammation, infection. A healing process may be interpreted as a false positive finding. In contrast, some types of renal cell cancers and lymphomas, neuroendocrine tumors, colonic mucinous adenocarcinomata, hepatocellular carcinomas, prostate cancer, and carcinoid tumors have low ^{18}F-fluorodeoxyglucose avidity which may give a misleading false negative result. In addition, an increased ^{18}F-fluorodeoxyglucose uptake in the bone marrow may be seen in oncologycal patients following various types of therapy. Besides the advantages of hybrid positron emission tomography–computed tomography imaging, this dual-modality scanning may produce their own specific artifacts due to different causes, such as metallic implants, respiratory motion, contrast medium and truncation. Proper patient preparation is required to minimize the potential artifactual uptake patterns that make reporting difficult. It is important to learn about proper quality control, imaging and reconstruction and to be familiar with potential artifacts and pitfalls for the accurate interpretation of ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography.

Key words: Fluordeoxyglucose F18; Positron-Emission Tomography; Tomography, X-Ray Computed; Artifacts; False Positive Reactions; False Negative Reactions; Neoplasms; Radiopharmaceuticals; Diagnostic Errors

Sažetak

^{18}F-fluorodeoksiglukoza radio-obeleženi je analog glukoze i predstavlja indikator metabolizma glukoze. Usled toga što je nakupljanje glukoze povećano u malignim tumorima, najveća primena ovog radiofarmaka jeste u onkologiji. Međutim, povećano nakupljanje ^{18}F-fluorodeoksiglukoze može biti prisutno i u brojnim benignim tumorima, granulomatoznim oboljenjima, tuberkulozi, inflamaciji, infekciji i procesima zarastanja tkiva; pa može doći do pogrešnog tumačenja nalaza (lažno pozitivni). Nasuprot tome, neki tipovi karcinoma bubrežnih ćelija, limfoma, neuroendokrini tumori, mucinozni adenokarcinomi debelog creva, hepatocelularni karcinom, karcinom prostate i karcinoidi imaju nizak stepen nakupljanja ^{18}F-fluorodeoksiglukoze što može pogrešno biti interpretirano kao lažno negativni rezultat. Pored toga, povećano nakupljanje ^{18}F-fluorodeoksiglukoze u kičmenoj moždini se može naći i kod bolesnika nakon određenog terapijskog protokola. Pored brojnih prednosti, hibridni imidžing može dovesti do specifičnih artefakata usled brojnih uzroka: metalni implatati, pokreti disanja, kontrastna sredstva i skraćenje slike (*truncation*). Pravilna priprema pacijenta za snimanje je neophodna radi smanjenja potencijalnih artefakata koji otežavaju očitavanje nalaza. Radi validne interpretacije ^{18}F scintigrafije važno je dobro ovladati procesima kontrole kvaliteta, snimanja i rekonstrukcije, kao i o mogućim artefaktima i zamkama.

Ključne reči: Fluordeoksiglukoza F18; PET; CT; Artefakti; Lažno pozitivni rezultati; Lažno negativni rezultati; Neoplazme; Radiofarmaceutici; Dijagnostičke greške

Introduction

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography–computed tomography (PET/CT) imaging is a novel hybrid imaging that simultaneously provides anatomical (morphologic) data, and functional (metabolic) data in the organ being studied. The adequate and valid PET/CT interpretation requires correct understanding of the physiological biodistribution of the injected tracer. Since ^{18}F-FDG is a glucose analogue with a similar metabolic pathway, it also behaves as a glucose metabolism indicator. Elevated serum glucose levels compete with radioalabeled ^{18}F-FDG for uptake in neoplasms and in normal tissue. Due to increased glucose uptake in malignant tissue, the major application of ^{18}F-FDG PET/CT is a powerful metabolic imaging tool in oncology [1, 2].

However, ^{18}F-FDG is not taken up only by malignant tumors. Sometimes, the normal pattern and variants of ^{18}F-FDG uptake in some organs or tissues may produce a false interpretation (e.g. stom-

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Abbreviations

18F-FDG 18F	– fluorodeoxyglucose
PET/CT	– positron emission tomography–computed tomography
CT	– computed tomography
HGF	– hematopoetic growth factors
G-CSF	– granulocyte colony-stimulating factor
MAR	– metal artifact reduction

ach, intestines, bowel, brown fat, urinary tract etc.) [2]. Kubota et al. have reported that 29% of ^{18}F-FDG uptake is by non-tumoral tissue [3]. Neutrophils and activated macrophages also show an increased ^{18}F-FDG accumulation, which results in an increased its uptake in various benign processes, such as granulomatous diseases, tuberculosis, inflammation, infection and healing processes [3, 4]. In contrast, not all neoplasms are associated with an increased ^{18}F-FDG uptake. Thus, some types of renal cell cancers, lymphomas, neuroendocrine tumors, colonic mucinous adenocarcinoma, hepatocellular carcinoma, prostate cancer, and carcinoid tumors have low ^{18}F-FDG avidity that might potentially give false negative result [5].

Patient Preparation for PET/CT

The proper preparation of patients and collecting of their data as well as medical history are important in order to avoid pitfalls in reporting. At our institution, patients are provided with written instructions a week before their examination. They should have a 4 hour-fasting period prior to their examination and are asked to limit physical activity on the day prior to PET/CT. Example of a patient who did not fast before the PET/CT exam is shown in **Figure 1a**.

The abstinence from beverages with sugar and no exercises 24 hours prior to examination are recommended. On admittance, the patients are checked for their blood glucose level (appropriate range is 120-150 mg/dL) and an intravenous line for tracer application is inserted. It is a general policy not to perform PET/CT if blood glucose level exceeds 150 mg/dL in order to avoid obtaining false negative results. The patient has to drink water for good hydration and diuresis, which may limit artifacts from the renal excretion system and decrease the bladder radiation exposure. One hour prior to imaging, ^{18}F-FDG is injected (the dose is calculated according to the patient's weight; approximately 8.14 MBq/kg). The patients are placed in a quiet room and instructed not to talk or move in order to minimize skeletal muscle uptake. To improve the delineation of the intestinal tract, 1000 mL of positive oral contrast agent is also administered orally to the patients one hour prior to examination. The injection room should be kept at warmer temperatures to avoid possible brown fat activation [6, 7].

Before scanning, the patients should empty their bladder and remove all metallic objects. A head and arm support should be used to make the patients more comfortable during the examination. Before ^{18}F-FDG administration, the patients should be questioned about their medical history in details, especially about the presence of dental or metal implants. It is important to provide the exact date and extent of prior surgical procedures (site of biopsy, site and type of any stoma) and/or treatments (chemotherapy, external radiation therapy, bone marrow stimulating factors) to avoid false positive findings. Recent trauma or recent falls, recent diagnostic imaging procedures such as whole body scintigraphy (WBS) computed tomography (CT), magnetic resonance imaging (MRI) prior PET/CT, as well as prior laboratory results (tumor markers) should also be noted [6, 7].

Adequate quality control, imaging, and reconstruction are essential for optimal PET/CT interpretation. If any motion of the patient appears during the scanning, the technologist should be trained to note and record it. In case when the patients are large and overweight, increased time for acquisition and transmission scan should be considered to obtain better image quality. In general, a standard body PET scan starts from the skull base to the upper thighs. However, in the patients with melanoma, the scans should include the head and neck region and the extremities. In the patients with lymphoma, a brain scan may also be included [6, 7].

Physiological ^{18}F-FDG uptake in brown adipose tissue appears to be the most frequent in young patients and females. It is located predominantly in the head and neck region, supraclavicular regions, around large mediastinal vessels, axillae, perinephric regions, and in the intercostal spaces along the thoracic spine. It is usually multifocal intense, bilateral and symmetric (**Figure 1b**). It has been reported that brown adipocytes specifically take up ^{18}F-FDG and are initially activated in the thermogenesis response to cold. Glycolysis in brown fat is markedly increased via the sympathetic innervation. On the other hand, increased catecholamine levels in circulation in anxious patients may also have a role in stimulating the brown fat ^{18}F-FDG metabolism. In some patients, premedication with benzodiazepine can prevent brown fat activity on a repeated study [8, 9].

Head and Neck

Physiologically, the brain is a site of high ^{18}F-FDG uptake due to its marked glucose utilization, especially in the gray matter. In fact, the glucose is the only source of energy in the brain; it has been reported that the brain accounts for 20% of total body glucose metabolism in the fasting state [8]. A low-to-moderate ^{18}F-FDG uptake is present in the tonsils and at the tongue base due to physiologically active lymphoid tissue of the Waldeyer's ring. An increased ^{18}F-FDG accumulation in tonsils is often seen during the winter time following respiratory infections [10, 11]. The salivary glands (pa-

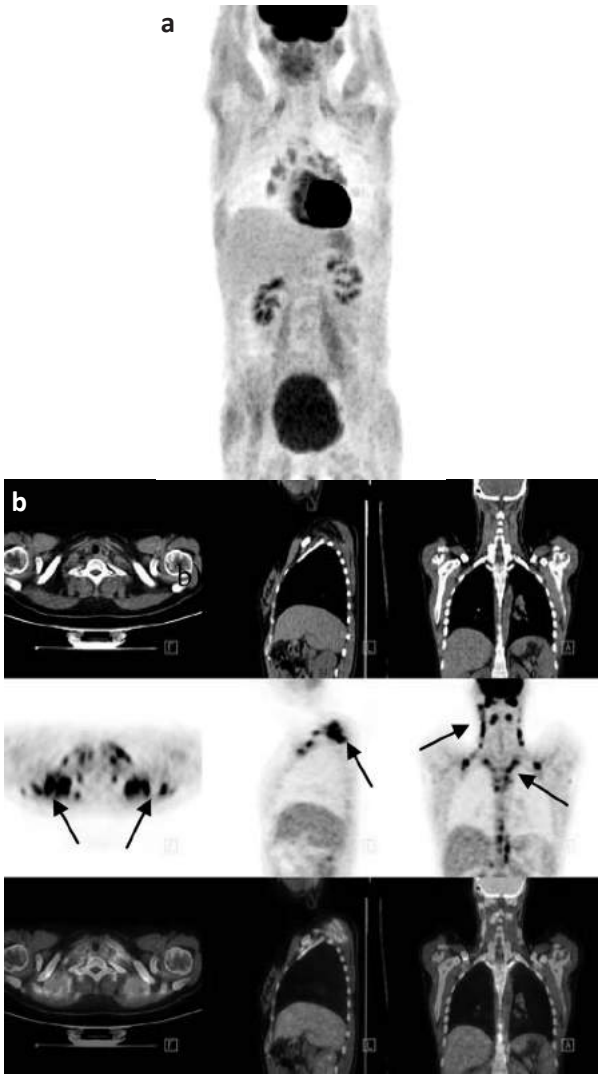

Figure 1. a) Maximum Intensity Projection (MIP) image shows intense ^{18}F-FDG uptake in muscles of patient who did not fast prior to examination; **b)** Physiological ^{18}F-FDG uptake in brown adipose tissue in 20-year old female; (rows, from top to bottom in transversal, sagittal and coronal planes: CT images, PET images, fused PET/CT images)
Slika 1. a) *PET snimak u projekciji maksimalnog intenziteta pokazuje povećano nakupljanje fluorodeoksiglukoze u mišićima pacijenta koji nije gladovao pre pregleda;* ***b)*** *Fiziološko nakupljanje fluorodeoksiglukoze u mrkom masnom tkivu kod dvadesetogodišnje pacijentkinje (redovi, od gore prema dole: CT, PET I PET/CT snimci u transverzalnoj, sagitalnoj i koronalnoj projekciji)*

rotid, submandibular and sublingual glands) show a variable intensity of tracer uptake, from low to intense. The laryngeal uptake is usually negligible appearing as a shape of an inverted V [11]. However, a focal unilateral increased ^{18}F-FDG uptake may be caused by an overactive muscle if contralateral vocal cord paralysis is present [12].

A normal thyroid gland demonstrates only a minimal tracer uptake and it is very subtle, varying from no tracer accumulation to mild intensity. An incidental, increased ^{18}F-FDG activity in the thyroid is reported in 2% of PET/CT scans. A diffuse, increased uptake is usually seen in Graves' disease, in hypothyroid patients treated with L-thyroxine therapy and in Hashimoto thyroiditis. An asymmetric, focal uptake in the thyroid may be associated with autonomous functioning thyroid nodules or thyroid cancer and should require further diagnostic examinations [13, 14].

Thorax

The myocardial uptake in normal subjects is heterogeneous and variable, ranging from no uptake to very intense. However, in patients with cancer, the interpretation may be difficult since paracardiac lymph nodes may not be seen due to the increased cardiac ^{18}F-FDG activity. To obtain better images, an examination should be performed in the fasting state (during this period the myocardium utilizes fatty acids to produce energy) which consequently results in a reduced myocardial uptake [15].

In young children, physiologic thymic activity is mainly seen as an increased ^{18}F-FDG activity in the anterior upper mediastinum in a shape of "inverted Y" [16, 17] (**Figure 2**). Granulomatous processes such as tuberculosis and sarcoidosis also present as ^{18}F-FDG avid regions. An increased ^{18}F-

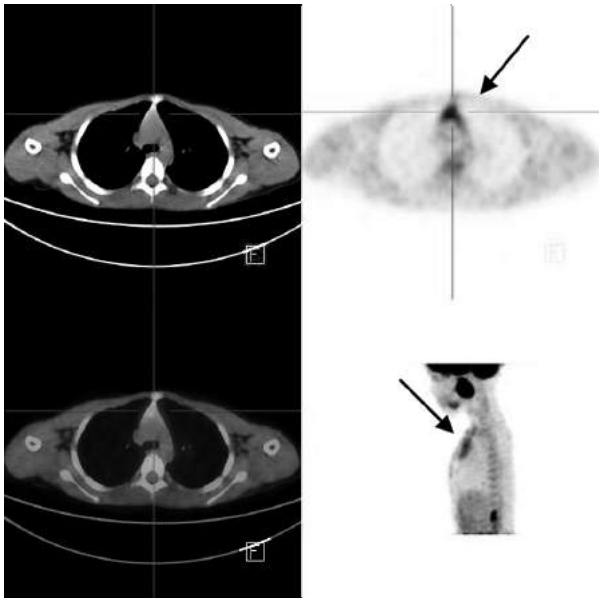

Figure 2. Physiologic intense FDG activity in thymus in a 7-year old patient (arrows on PET, transversal image and MIP sagittal image)
Slika 2. *Fiziološka intenzivna aktivnost fluorodeoksiglukoze u timusu sedmogodišnjeg pacijenta (strelice na transverzalnom PET snimku i sagitalnom preseku MIP)*

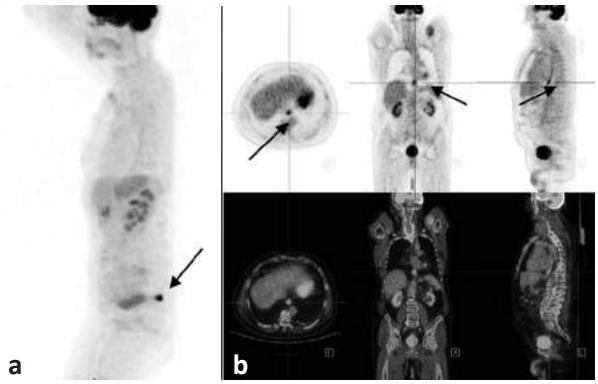

Figure 3. a) Female with prior history of breast carcinoma; polyp identified in the sigmoid colon; Maximum Intensity Projection (MIP) sagittal image; **b)** Hypermetabolic activity in patient with esophagitis (arrows on PET images; transversal, coronal and sagittal planes)
Slika 3. a) *Pacijentkinja sa karcinomom dojke; akcidentalno detektovan polip na sigmoidnom kolonu; MIP snimak u sagitalnoj projekciji* ***b)*** *Hipermetabolička aktivnost u bolesnika sa ezofagitisom (strelice na PET snimcima; transverzalna, koronalna i sagitalna projekcija)*

FDG uptake is associated with the lactating breasts and breasts in pre- and postmenopausal women under hormone replacement therapy [6].

Gastrointestinal Tract

The origin of ^{18}F-FDG uptake in digestive system is unknown. Several causes have been suggested, including active smooth muscle, metabolically active mucosa, swallowed secretions or colonic micro-bacterial uptake [18]. Infrequently, an ^{18}F-FDG activity in the esophagus may be shown as a mild linear uptake anterior to the spine, and it is caused by swallowing saliva and smooth muscle metabolism. A focal, increased esophageal activity is suspicious for malignancy. The gastric uptake varies, from faint to intense. A J-shape of gastric activity is usually seen physiologically in the left upper abdomen. An ^{18}F-FDG activity in the colon differs from subtle heterogeneous to mild, focal segmental or diffuse pattern. Inflammatory benign disease in colon such as candidiasis may show high ^{18}F-FDG uptake. In addition, some benign tumors may also show high focal accumulation of ^{18}F-FDG such as, for example, adenomatous polyps in the colon (**Figure 3a**). An increased gastric ^{18}F-FDG uptake may be also influenced by infection with Helicobacter pylori [19]. A diffuse hypermetabolic activity in the esophagus and the stomach may be influenced by a chronic benign disease (**Figure 3b**).

The activity in the cecum and the right colon is normally increased comparing to the remaining colon due to the presence of normal ^{18}F-FDG avid lymphocyte cells. Therefore, these scans should be reviewed in the sagittal and rotating images to exclude a possible misinterpretation of physiologic ^{18}F-FDG uptake. An ^{18}F-FDG activity in the liver, as well as in the spleen, is usually negligible and homogeneous. Sometimes, an overlapping bowel loop may be interpreted as a focal liver lesion and give a false positive result [1].

Some benign conditions such as infectious mononucleosis may also cause an increased ^{18}F-FDG uptake in the spleen [1, 5]. Since the spleen is an active site for the extramedullary hematopoesis, a diffuse spleen enhancement of ^{18}F-FDG uptake represents in patients receiving hematopoietic growth factor (HGF), such as granulocyte colony stimulating factor (G-CSF) and erythropoietin [20, 21].

Genitourinary System

Since ^{18}F-FDG is cleared primarily through the renal system, an activity is usually seen in renal calyces, ureters, and bladder. Sometimes, a congenital urinary malformation, such as horseshoe kidney, congenital pelvic kidney or transplanted kidney, may simulate malignancies, as well as a focal ureter activity due to the urine retention [1].

A moderate ^{18}F-FDG testicular activity is physiological and generally inversely associated with age [22]. An increased ^{18}F-FDG activity has been reported during menstruation (**Figure 4**) due to the elevated activity in the uterus and associated with fibroids. An increased ^{18}F-FDG uptake in females is also seen in the ovary during ovulation, in corpus luteal cysts and in follicular ovarian cysts. According to the literature, the best time for PET/CT examination in women in reproductive age should be within a week before or a few days after the menstrual period [23].

Skeletomuscular System

An ^{18}F-FDG uptake in the bone marrow is usually faint and diffuse, less than the liver activity and predominantly seen in vertebral bodies [1].

The muscle activity is usually presented as a linear, symmetric mild to moderate ^{18}F-FDG up-

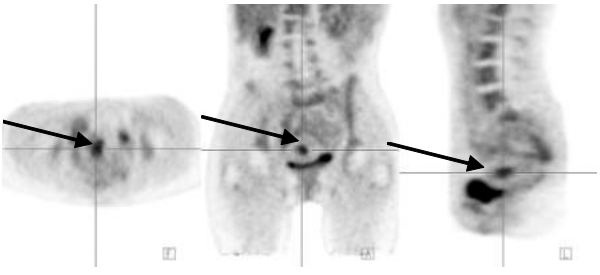

Figure 4. Increased FDG uptake in pelvic region; in the endometrium during menstrual period (arrows on PET images; transversal, coronal and sagittal planes)
Slika 4. *Povećano nakupljanje fluorodeoksiglukoze u endometrijumu u toku menstrualnog perioda (strelice na PET snimcima u transverzalnoj, koronalnoj i sagitalnoj projekciji)*

take. If diabetic patients received insulin for glucose control prior to ^{18}F-FDG injection, it may exaggerate the physiological uptake in muscles seen as focal and unilateral tracer activity [24].

If there is any muscle activity during the ^{18}F-FDG uptake phase (after the tracer injection), an increased ^{18}F-FDG activity may be seen. An increased ^{18}F-FDG activity has been seen in the extra-occular muscles if the patient did not have their eyes closed during a quiet resting period. If there is a tongue activity, ^{18}F-FDG uptake is usually related to the genioglossal muscles. For exapmle, the increased ^{18}F-FDG accumulation in the masticatory muscles (masseter and pterygoid muscle) can indicate that patient has been chewing a gum [6]. The intense usage of skeletal muscle is based more on glycolysis to meet the energy demands. Therefore, an intense exercise prior to the PET/CT examination (weight-lifting) or an active skeletal muscle contraction during the ^{18}F-FDG injection or during the uptake phase (30 minutes following the ^{18}F-FDG injection) may show a high ^{18}F-FDG activity in the muscles. It usually causes an increased symmetric uptake in the trapezius, paraspinal muscles, thoracoabdominal wall muscles and abdominal rectus muscle. The pectoral muscles usually show an increased ^{18}F-FDG uptake after heavy bench pressing. An increased activity in the diaphragm and intercostal muscles may be seen due to hyperventilation in patients with pulmonary disease and labored respiration. In young patients, a physiological generalized muscle uptake may be seen. Administration of muscle relaxant (diazepam 30 min prior to ^{18}F-FDG injection) is sometimes recommended for muscle suppression and relaxation [1].

Therapy Related Artifacts

The uniform diffuse ^{18}F-FDG avid bone marrow may be seen after chemotherapy if PET/CT is performed during the bone marrow recovery (the first 2–4 weeks after the completion of chemotherapy) [24]. An increased diffuse ^{18}F-FDG activity in the bone marrow may be seen also in the patients receiving HGF such as erythropoietin, G-CSF, and granulocyte macrophage colony-stimulating factor (GM-CSF) [20, 21, 25].

There is a precise period after the treatment of oncologic patients before PET/CT should be performed. An increased ^{18}F-FDG activity may persist for several weeks or months after various treatments. Bone marrow flare presents as adiffuse generalized uptake involving the axial and appendicular skeleton consistent with a recent chemotherapy response. Post cytokine therapy (including GCSF) in patients is usually seen as prominent marrow and splenic hyperplasia [20, 21, 25]. Thus, PET/CT may be performed in 4–6 weeks after the completion of chemotherapy and 3 months after the external beam therapy. Patients with Hodgkin's disease after chemotherapy may occasionally present with a ^{18}F-FDG avid thymus as a result of "thymic rebound hyperplasia" [26].

In addition, increased accumulation of ^{18}F-FDG may be seen in postoperative healing scars induced by an inflammatory process. Therefore, waiting for 6–12 months after the surgery before performing the ^{18}F-FDG study is advised [1].

Attenuation-Correction Artifacts

Attenuation correction artifacts on PET/CT images are influenced by the increased density of highly attenuating objects (metallic hardware or high-Z materials: hip prosthesis, metallic stents, dental devices, pacemakers and contrast-enhanced vessels).

In fact, PET/CT attenuation correction software creates artifactual overestimation of activity since CT transmission data are used for attenuation correction. This creates "overactivity" of the metallic objects which are photopenic, making them appear hypermetabolic on the attenuation-corrected PET images [7, 24]. A dental artifact is shown in **Figure 5.** Several different techniques have been proposed with the aim to eliminate or decrease the artifacts caused by metallic implants on both CT and PET/CT images. There have been a few attempts to reduce these artifacts without the use of algorithmic mathematical metal artifact reduction (MAR) approaches, so called implicit methods [27, 28]. However, most of these techniques are MAR techniques which are based on various mathematical algorithms (explicit MAR methods) [29, 30]. However, these artifacts are easily recognized and assessed by comparing the attenuation-corrected images with the uncorrected images [31].

If dense intravenous contrast materials are present in blood vessels during the PET/CT scan, they might cause linear artifacts on attenuation corrected PET images. Barium or iodine-based oral contrast agents are also highly attenuating structures at CT energies and tend to produce attenuation-corrected artifacts on PET images. This artifact appears most frequently as an overlap of physiological and false bowel activity [6]. In these cases, the non-attenuation-corrected images as well as the attenuation-corrected images should be compared. In addition, negative or water-based oral contrast agents with densities less than 400-500 Hounsfield units (HU) are recommended

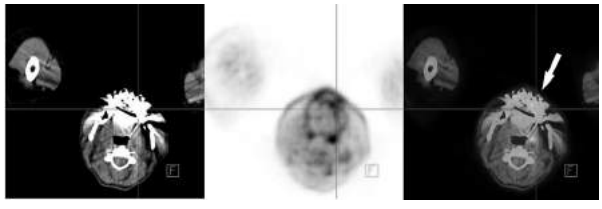

Figure 5. Patient with a history of unknown primary tumor shows an artifact due to dental prosthesis
Slika 5. *Snimak pacijenta sa istorijom nepoznatog primarnog tumora pokazuje artifakt zbog zubne proteze*

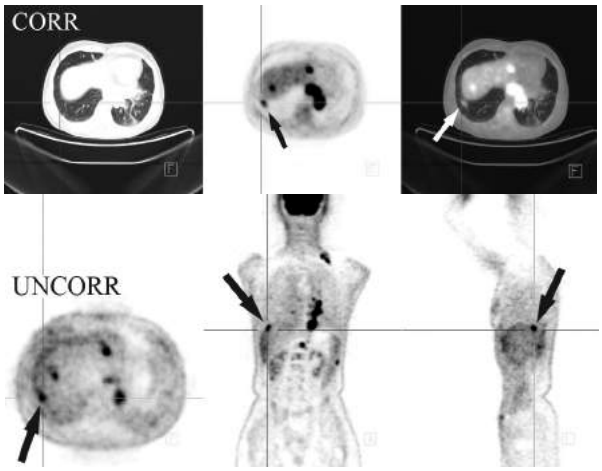

Figure 6. Misregistration influenced by diaphragmatic motion; hypermetabolic foci in the liver dome appear to be located in the lung base. PET and corrected image in transversal plane (arrow), PET and fused PET/CT images (arrows); Uncorrected PET images; transversal, coronal and sagital planes (arrows)
Slika 6. *Zbog pokreta dijafragme, čini se da su hipermetabolički fokusi u kupoli jetre locirani u bazi pluća. Korigovani PET snimak u transverzalnim ravima, PET i fuzionisani PET/CT snimci (strelice); Nekorigovani PET snimci; transverzalne, koronalne i sagitalne ravni (strelice)*

since they should not usually produce significant attenuation-correction induced artifacts [32, 33].

Motion

A misregistration of the PET data with the CT data occurs most frequently due to a change in the patient's position between CT and PET acquisition. This will produce artifacts in the attenuation correction process. A misregistration usually appears in the head and limbs where the movement is the most frequent. It may also appear at the diaphragm (diaphragmatic artifact) influenced by a respiratory motion and a movement of adjacent anatomical organs above and below the diaphragm. Mismatches of different breathing patterns in combined PET/CT scanning cause PET artifacts and anatomic localization artifacts following CT-based attenuation correction. On the one hand, the CT scan is usually acquired during a specific stage of the breathing cycle (at maximum inspiration which is the typical protocol for a standalone thorax CT scan), while on the other hand, due to long acquisition time of PET scan, it is acquired while the patient is breathing freely (the final image is an average of many breathing cycles). Artifacts appear because there is a mismatch between the anatomy of the thoracic and abdominal organs acquired at the maximum inspiration and the anatomy when averaging over many respiratory cycles during PET scan of the chest. It may produce an attenuation-corrected image where hypermetabolic foci in the liver dome may appear as located in the lung base [34–36] (**Figure 6**).

In contrast, FDG non-avid lesions in the lung base may appear to be located in the areas where the activity of the liver dome or superior aspect of the spleen is superimposed due to a diaphragmatic motion. The degree of lesion motion is dependent of the location; lower lung lesions can move more than the apical lesion. Respiration may also produce a blurred lesion and increase the lesion size, which will consequently cause underestimation of standardized uptake values (SUV). Therefore, when this type of misregistration is recognized, it is important to study in particular the non-attenuated-corrected PET images to determine the relationship of focal uptake with the normal uptake in the liver. PET/CT artifacts due to respiratory motion may be eliminated if a respiratory gating protocol is available [34–36]. Some authors suggest a limited breath hold protocol. Patients should maintain breathing during the entire scan while breath holding in normal expiration for the time the CT takes to cover the lower thorax and liver (less than 15 seconds) [7]. Others recommend instructing the patient to breathe gently throughout both components of the PET/CT study [5].

The patient's movements should be minimized by giving a strict instruction not to move during the study and to empty the bladder prior the acquisition, and by placing them in a comfortable position for the examination [5].

Truncation

In obese patients and in patients positioned with their arms down, some parts may extend outside the axial field of view of the CT scanner (50 cm in diameter). However, the axial field of view of the PET scanner is larger (about 60 cm in diameter) comparing to CT, which results in missing data for the CT-based attenuation-correction leading to both artifacts of the corrected PET images and biased activity concentrations. Modern systems with integrated novel algorithms corrects the truncation errors and reduce bias in the attenuation corrected PET images [37].

Conclusion

^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography imaging combines the advantages of physiological and anatomical imaging correlating a sensitive method of demonstrating the tissue metabolism with the anatomical localization. The sensitivity of the fluorodeoxyglucose imaging can produce pitfalls and artifacts since not only are benign and malignant tumors imaged, but other increased tissue metabolisms including infections can be visualized as well. With experience, the variations in fluorodeoxyglucose uptake due to normal physiological processes can be recognized and a misinterpretation of a disease process avoided. It is

also important to pay attention to technical factors such as registration, attenuation correction, and problems with motion in order to avoid artifacts. With due care and extensive knowledge of the metabolism of fluorodeoxyglucose, artifacts and pitfalls in positron emission tomography–computed tomography can be avoided thus making this technique an excellent means of imaging disease particularly in oncology.

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CASE REPORTS
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SOLITARY SYNOVIAL CHONDROMATOSIS AS A CAUSE OF HOFFA'S FAT PAD IMPINGEMENT

SOLITARNA SINOVIJALNA HONDROMATOZA KAO UZROK UKLJEŠTENJA HOFINOG MASNOG JASTUČETA

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Summary

Introduction. Synovial chondromatosis is a benign disease of synovial membrane usually affecting knee, elbow and shoulder joints. It rarely appears as a solitary formation and exceptionally within Hoffa's fat pad. **Case Report.** We report a case of solitary synovial chondromatosis within Hoffa's fat pad as a cause of its impingement in a female patient aged 63. At first, the patient had anterior knee pain with limited extension of the knee. Standard radiogram showed only mild patellofemoral osteoarthritic changes. Magnetic resonance of the knee showed ovoid solitary formation within Hoffa's fat pad repressing its superior part between the kneecap and distal femur. Histopathological examination confirmed a case of extra-articular synovial chondromatosis. The tumorous mass was extracted surgically en bloc. **Conclusion.** Solitary synovial chondromatosis is an uncommon cause of Hoffa's fat pad impingement and anterior knee pain in elderly female patients and can easily be misinterpreted as a different diagnosis.

Key words: Chondromatosis, Synovial; Adipose Tissue + pathology; Joint Diseases; Knee Joint; Female; Middle Aged; Radiography; Magnetic Resonance Imaging; Surgical Procedures, Operative; Diagnosis

Sažetak

Uvod. Sinovijalna hondromatoza je benigno oboljenje koje obično zahvata zglobove kolena, lakta i kuka. Retko se pojavljuje kao solitarna formacija i izuzetno unutar Hofinog masnog jastučeta. **Prikaz slučaja.** Prikazujemo slučaj solitarne sinovijalne hondromatoze unutar Hofinog masnog jastučeta kao uzrok njegovog uklještenja kod pacijentkinje stare 63 godine. Pacijentkinja je prvo imala bol u prednjem delu kolena sa ograničenom ekstenzijom kolena. Standardni radiogram je pokazao samo blage artrotične promene. Magnetna rezonancija kolena pokazala je solitarnu jajastu formaciju unutar Hofinog masnog jastučeta koja je potiskivala njegov gornji deo između čašice i distalnog dela butne kosti. Patohistološki pregled je potvrdio slučaj ekstraartikularne sinovijalne hondromatoze. Tumorozna masa je hirurški odstranjena u celosti. **Zaključak.** Solitarna sinovijalna hondromatoza je neuobičajeni uzrok uklještenja Hofinog masnog jastučeta i bola u prednjem delu kolena kod starijih pacijentkinja i lako se može zameniti pogrešnom dijagnozom.

Ključne reči: Sinovijalna hondromatoza; Masno tkivo + patologija; Oboljenja zglobova; Zglob kolena; Žensko; Srednje godine; Radiografija; MRI; Operativne hirurške procedure; Dijagnoza

Introduction

Synovial chondromatosis (SC) is a benign synovial membrane disease of unknown etiology [1]. The knee is the most commonly affected joint followed by the elbow and the hip [2]. It usually affects males between 30 and 50 years of age, being two to four times more common in men than in women [2, 3]. A great majority of patients present with a multilocular process within a joint followed by the presence of multiple cartilaginous loose bodies. Solitary cases are rare, and according to the available information, only two within Hoffa's fat pad (HFP) have been reported [3]. Histologically, this disease is described as metaplasia of histiocytes [3]. It can be intra- or extra-articular, primary or secondary, intrinsic or extrinsic one [3, 4]. In most of the cases, it affects only one joint, but can also be found in multiple joints, bursa

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Abbreviations
SC − synovial chondromatosis
HFP − Hoffa's fat pad
MRI − magnetic resonance imaging

or tendon sheath. An idiopathic or primary form is less common than the secondary one. The frequency of its appearance is 1 per 100.000 people per a year. SC can be diagnosed by magnetic resonance imaging (MRI) and arthroscopy with biopsy [3, 4]. The confirmed diagnosis of chondromatosis is an indication for extraction or synoviectomy [4]. Even after the complete extraction of all cartilaginous loose bodies and radical synoviectomy, chondromatosis can reappear. Cases of malignant transformation to chondrosarcoma have also been reported, but such an outcome is very rare [5, 6].

The aim of this study was to show a rare pattern of appearance of synovial chondromatosis within Hoffa's fat pad in a 63-year-old female patient as a cause of Hoffa's fat pad impingement, as well as to point out diagnostic and treatment procedures.

Case Report

A 63-year-old woman was examined by a doctor after she had had pain in the anterior aspect of the right knee for a year. The pain increased with physical activity and disappeared with rest. Her symptoms were similar to those of patellofemoral osteoarthritis. The range of flexion of the affected knee was full, without clinical signs of joint laxity. The full extension was painful with the pain located just laterally from the patellar tendon. The pain started to develop at the last 20 degrees of extension. The Hoffa's clinical sign was positive. A plain radiogram showed only mild osteoarthritic changes of patellofemoral joint accompanied with calcifications of Hoffa's fat pad. MRI showed well-circumscribed tumefaction within HFP of heterogeneous, predominantly hypodense T1/T2 signal. Diameters of tumefaction were 3x3, 2x4.5 cm. The tumefaction invaginated under the transverse intermeniscal ligament to the zone of the front horn of lateral meniscus, being in close contact with the anterior tibial intercondylar eminence. The tumorous mass was associated with a mild HFP edema. The superior part of HFP was repressed between the kneecap and distal femur. There was no erosion of bony structures, no loose bodies within the knee joint and no other pathological findings of the synovial membrane. Mild degenerative changes could be seen on both menisci, but without a rupture. The ligaments of the knee were intact (**Figure 1**).

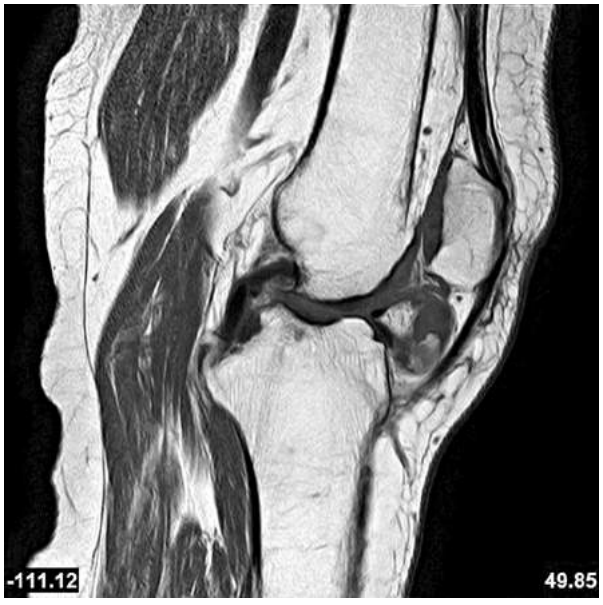

Figure 1. Sagittal T1-weighted MRI of the right knee
Slika 1. *Sagitalna T1 sekvence desnog kolena*

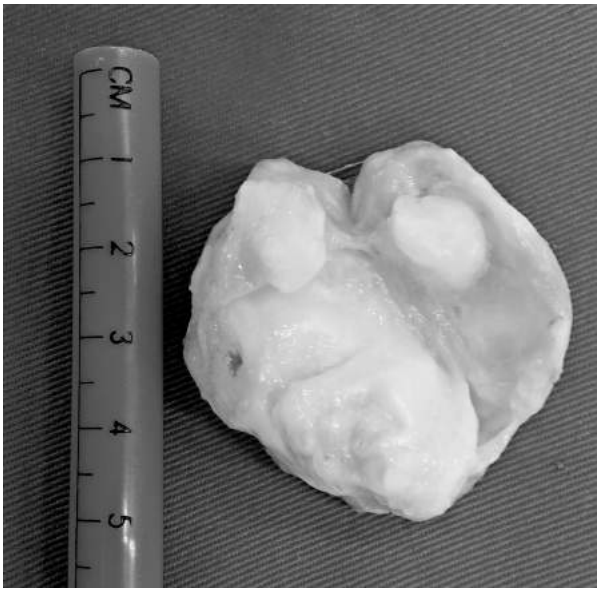

Figure 2. Tumorous mass extracted en bloc
Slika 2. *Tumorska masa odstranjena u celosti*

Arthroscopic treatment was abandoned due to the size of tumorous mass which could not be extracted through standard portals. The tumorous mass was surgically removed en bloc (**Figure 2**) through a small lateral parapatellar incision and sent to histopathological analysis that confirmed the diagnosis of SC with zones of ossification and myxomatose stromal degeneration.

The operation was performed under general anesthesia with use of tourniquet. After the operation, full weight bearing was allowed. On the first control after 10 days, the operated knee was painless with a mild swelling. The sutures were extracted and the patient continued with her usual daily activities without any restrictions. On the second control after one month, the patient was without previous symptoms with preserved and full range of movements.

Discussion

Hoffa's fat pad is an intracapsular structure of the knee that is routinely visualized on magnetic resonance images of the knee [1, 6].

Hoffa's fat pad is situated behind the patellar tendon, under the inferior pole of patella, above the proximal pole of tibia, with the joint cavity behind it. It is attached to the periosteum of tibia and anterior horns of menisci [2, 3, 7]. It can be a cause of anterior knee pain due to pathological changes caused by trauma, inflammation and tumors. SC can be a cause of HFP impingement between the kneecap and distal femur.

Hoffa's fat pad disorders can be classified into two groups: intrinsic disorders (originating from the fat pad tissue) and extrinsic ones (caused by pathological changes of the surrounding structures). The most common intrinsic HFP disorders are Hoffa's disease, intracapsular chondroma, nodular synovitis, shear injuries, posttraumatic and post surgery fibrosis. The most common extrinsic disorders that can be projected into infrapatellar fat pad are meniscal and ganglion cysts, "Cyclops" lesions following anterior cruciate ligament reconstruction and synovial disorders [1, 3, 8]. Practically any synovial proliferating disorder could have an infrapatellar fat pad involving potential. SC is just one among many. The others are synovial proliferations due to rheumatoid arthritis, septic arthritis, synovial disorders associated with hemosiderin deposition, synovitis associated with primary osteoarthritis and inflammatory intestinal disorders [1, 3]. MRI has a potential to differentiate between all of the disorders listed above and to determine whether the disorder is an intrinsic or extrinsic one [6, 7].

Synovial chondromatosis is usually associated with severe pain, palpable nodules, swelling, crepitations, stiffness and locking. In our case, the patient complained of anterior knee pain during extension and occasional swelling of the knee. The anterior knee pain in older population can also be attributed to osteoarthritis of patellofemoral joint, especially with the positive findings on radiogram. Detailed anamnesis and clinical examination are necessary to make the correct diagnosis. In the case reported here, a tumorous mass situated just beneath the patellar tendon was the main reason for MRI and consequently for surgical treatment. Histopathological examination is also required as there is no uniform MRI appearance of SC [2]. However, there are three patterns in SC development described by Kramer in his classification based solely on MRI criteria. Pattern A (intra-articular homogeneous nodul isointense to muscle on T1-weighted and hyperintense on T2-weighted images), pattern B (the same as the pattern A but with foci of signal representing calcifications) and pattern C (the same as the pattern B but with foci of signal representing ossifications). According to Kramer's classification, the presented case follows the pattern C of SC development. The classification by Milgram considers radiographic and histological features, also suggesting three types of SC. Each of the described types is one stage of SC. The first type represents an early stage in which there are no intra-articular loose bodies and no obvious synovial disease. The second type is intermediate stage with synovial-based and loose masses combined. The third stage is the most severe and is presented by many intra-articular loose bodies without synovial involvement [2, 9]. The presented case can be described as Milgram type 1.

In case reported by Osti and al. [3], the affected patient is a man in the sixth decade of life. MRI and histopathological findings were almost identical as in our case and could also be classified as Kramer C and Milgram 1. However, that patient had more severe clinical symptoms with limitation of flexion, more intense pain and swelling. The symptoms were present for 6 months. Calcifications within HFP were visible. After the initial arthroscopic treatment, SC of HFP reappeared and was treated by open technique. The fact that our patient was a woman in the seventh decade of life with clinical symptoms of HFP impingement makes our case unique.

There are three possible outcomes after the successful surgical treatment of isolated SC. The cartilaginous mass can reappear as in the case reported by Osti and al. [3]. This way of development is possible but not probable. Opposite to that, Coolican [4] and Jeffreys [9] reported series of patients with multilocular SC of the knee treated arthroscopically. In their series, the recurrence rate was very low. The second outcome is also improbable, and that is a recurrence with malignant alteration to chondrosarcoma. Several cases of malignant alteration have been reported [2, 9], but all associated with multilocular and long-stand cases of the disease. The third and the most probable scenario is the complete recovery of the patient without recurrence [6–9]. Surgical treatment can be performed either with open or arthroscopic surgery, although arthroscopical treatment is with lower complication rate [10].

Conclusion

Solitary form of synovial chondromatosis within Hoffa's fat pad can be an extremely rare cause of Hoffa's fat pad impingement and the anterior knee pain in elderly female patients. A detailed clinical examination, magnetic resonance imaging and histopathological examination are required to make the correct diagnosis.

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POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN ECLAMPTIC PATIENTS: NEURORADIOLOGICAL MANIFESTATION, PATHOGENESIS AND MANAGEMENT

POSTERIORNI REVERZIBILNI ENCEFALOPATSKI SINDROM KOD BOLESNICA SA EKLAMPSIJOM: NEURORADIOLOŠKA MANIFESTACIJA, PATOGENEZA I ZBRINJAVANJE

Marija S. KUTLEŠIĆ[1], Ranko M. KUTLEŠIĆ[1] and Goran P. KORAĆEVIĆ[2]

Summary

Introduction. Eclampsia is one of the most serious complications of hypertensive disorders of pregnancy, defined as the occurrence of one or more convulsions superimposed on preeclampsia. Besides the ordinary course of the disease, ranging from a mild to a severe form, with culmination in eclamptic seizures, there is a significant percent of cases where eclampsia starts unexpectedly, without typical premonitory symptoms and signs, which makes it difficult to prevent. **Neuroradiological Characteristics and Pathogenesis of Eclampsia.** Neuroradiological signs of eclampsia are described as posterior reversible encephalopathy syndrome, and are manifested by nausea, vomiting, headache, visual disturbances, altered mental status, convulsions and coma, together with characteristic findings on computed tomography or magnetic resonance imaging scan of the head, indicating the presence of vasogenic brain edema. The topic of this article are possible mechanisms of the development of posterior reversible encephalopathy syndrome in pregnancy and modalities of acute treatment of this emergency state. **Management of Eclampsia.** Magnesium sulphate is nowadays the drug of choice for the treatment and prevention of eclamptic seizures. Labetalol is considered to be the agent of choice in the treatment of hypertensive emergencies of pregnancy, followed by hydralazine, nifedipine, nicardipine, urapidil, nitroglycerin and sodium nitroprusside (in most refractory cases). Angiotensin converting enzyme inhibitors and angiotensin blocking drugs are contraindicated in pregnancy. Captopril and enalapril are allowed during lactation. **Conclusion.** Posterior reversible encephalopathy syndrome in eclamptic patients is completely reversible if adequate diagnosis is promptly made and intensive treatment immediately administered.

Key words: Posterior Leukoencephalopathy Syndrome; Eclampsia; Neurologic Manifestation; Tomography, X-Ray Computed; Magnetic Resonance Imaging; Signs and Symptoms; Disease Management; Pregnancy Complications; Hypertension, Pregnancy-Induced; Female

Sažetak

Uvod. Eklampsija je jedna od najozbiljnijih komplikacija hipertenzivnih poremećaja u trudnoći; definiše se kao postojanje jedne ili više konvulzija superponiranih na preeklampsiju. Pored uobičajenog toka bolesti, koji se kreće od blage do teške forme i kulminira eklamptičnim napadima, postoji i značajan procenat slučajeva gde eklampsija počinje neočekivano, bez tipičnih prodromalnih simptoma i znakova, što otežava sprečavanje njene pojave. **Neuroradiološke karakteristike i patogeneza eklampsije.** Neuroradiološki znaci eklampsije su opisani kao posteriorni reverzibilni encefalopatski sindrom, i manifestuju se nauzejom, povraćanjem, glavoboljom, poremećajima vida, izmenjenim mentalnim statusom, konvulzijama i komom, praćenim karakterističnim nalazima na kompjuterizovanoj tomografiji ili prikazu magnetne rezonancije glave, ukazujući na prisustvo vazogenog edema mozga. U ovom članku razmatramo moguće mehanizme razvoja posteriornog reverzibilnog encefalopatskog sindroma u trudnoći i načine lečenja ovog urgentnog stanja. **Tretman eklampsije.** Danas magnezijum-sulfat predstavlja lek izbora za tretman i prevenciju eklamptičnih napada. Labetalol se smatra lekom izbora za lečenje hipertenzivne krize u trudnoći, posle njega slede hidralazin, nifedipin, nikardipin, urapidil, nitroglicerin i natrijum-nitroprusid (kod najrefraktornijih slučajeva). Inhibitori angiotenzin konvertujućeg enzima i lekovi koji inhibiraju angiotenzin su kontraindikovani u trudnoći. Kaptopril i enalapril su dozvoljeni tokom laktacije. **Zaključak.** Posteriorni reverzibilni encefalopatski sindrom kod pacijentkinja sa eklampsijom je kompletno reverzibilan ako se postavi promptna dijagnoza i odmah preduzme intenzivni tretman.

Ključne reči: Posteriorni leukoencefalopatski sindrom; Eklampsija; Neurološke manifestacije; CT; MRI; Znaci i simptomi; Zbrinjavanje bolesti; Komplikacije u trudnoći; Trudnoćom indukovana hipertenzija; Žensko

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Abbreviations

PRES – posterior reversible encephalopathy syndrome
MRI – magnetic resonance imaging scan
ADC – apparent diffusion coefficient
DWI – diffusion weighted imaging
BP – blood pressure
BBB – blood brain barrier
MgSO4 – magnesium sulphate
ACE – angiotensin converting enzyme

Introduction

Eclampsia is one of the most serious complications of hypertensive disorders of pregnancy [1–3]. It complicates one in 100 - 1700 pregnancies in developing countries and one in 2000 - 3450 pregnancies in the western world [4, 5]. Preeclampsia/eclampsia is responsible for 10–18% direct obstetric deaths [6–10].

The disease is defined as the occurrence of one or more convulsions superimposed on preeclampsia [1]. Neurologic symptoms include nausea, vomiting, occipital or frontal headache, blurred vision, cortical blindness, altered mental status, convulsions and coma [10–16]. Diagnostic parameters of hypertensive disorders of pregnancy are well defined [1, 6, 7, 12, 17–20], but clinicians should be aware of the existence of atypical forms of preeclampsia, with symptoms ranging from mild hypertension with or without proteinuria to severe hypertension with/without proteinuria and/or end organ damage [2, 5, 6, 12, 21]. Hypertension is considered to be the hallmark of the diagnosis of eclampsia; nevertheless, patients may be normotensive in even 16-30% of cases [3, 15]; severe hypertension was found in 47% of eclamptic patients [10, 15].

The ordinary course of the disease goes from a mild to a severe form of preeclampsia, culminating in eclamptic seizures. However, according to recent data, eclampsia starts unexpectedly, without premonitory symptoms and signs of preeclampsia in up to 20% of cases [4].

Eclampsia can be complicated by several serious conditions, such as cerebral hemorrhage or stroke, pulmonary embolism, acute renal or liver failure, disseminated intravascular coagulopathy (DIC), syndrome of hemolysis, elevated liver enzymes and low platelet count (HELLP), abruptio placentae, temporary or permanent neurologic abnormalities and cognitive impairment later in life [4, 5, 10, 15, 22–24]. Perinatal morbidity and mortality is high (5.6 – 18%), related to severe growth restriction and prematurity.

Neuroradiological Characteristics and Pathogenesis of Eclampsia

Neuroradiological signs of eclampsia are described as Posterior Reversible Encephalopathy Syndrome (PRES). PRES, as a relatively new neuroradiological entity, was described by Hinchey et al. in 1996 [25]. The authors connected it with hypertensive encephalopathy, autoimmune diseases, sepsis, renal insufficiency, transplantation, exposure to immunosuppressants and eclampsia [3, 12, 25–31]. PRES is a transient state, manifested by the abovementioned clinical signs and symptoms, together with characteristic findings on computed tomography (CT) or magnetic resonance imaging scan (MRI) of the head [2, 4, 11–13, 15, 29, 30, 32]. The widespread application of MRI has allowed more precise recognition of PRES [26]. It typically shows bilateral focal regions of signal intensity alterations, indicating the presence of brain edema [4, 13, 27, 31]. In vast majority of cases it is vasogenic edema, presented by high signal intensity on T2 weighted imaging and fluid attenuated inversion recovery (FLAIR), increased apparent diffusion coefficient values (ADC) and hypointensity or no change of intensity on diffusion weighted imaging (DWI) [2, 3, 13, 33, 34]. An increased DWI signal combined with a decreased ADC and a decreased or normal FLAIR, indicates the presence of cytotoxic edema, which used to be seen in much lower percent of eclampsia cases [26].

There are two opposing hypothesis trying to explain the brain edema formation in PRES [4, 5, 11–13, 28, 33, 34]. According to the prevailing, *forced dilatation theory*, a rapid rise in blood pressure (BP), which exceeds the upper limit of cerebral autoregulation, leads to the blood brain barrier (BBB) dysfunction, cerebral vasodilatation and local hyperperfusion, manifested by vasogenic edema present in 93–100% of eclamptic women. *Vasospasm theory*: severe hypertension promotes cerebral overregulation, vasoconstriction, ischemia, infarction and cytotoxic edema.

Although vasogenic edema is far more common, autopsy findings have shown the predominance of cytotoxic edema, infarction and hemorrhage in the subcortical white matter in women who died from eclampsia. The explanation might be that vasogenic brain edema occurs in the first, reversible stage of the disease, which, if not promptly treated, progresses to cytotoxic edema, ischemic damage and hemorrhage with worse prognosis [2, 3, 12, 15, 29, 32].

The fact that PRES in an eclamptic patient can develop without a significant rise in BP and in cases where upper limit of autoregulation is not reached, makes this issue even more controversial [2, 3, 5, 11, 13, 28, 29]. We have to keep in mind, however, that it could be the case of "relative hypertension" when BP rises from a low baseline level (as in the young women with average BP levels of 90/60 mm Hg out of pregnancy) [13]. In addition, even normal pregnancy causes a decrease in the small brain vessel resistance when BP is elevated, which promotes enhanced BBB permeability and edema formation [11]. During pregnancy, autoregulation of cerebral blood flow (CBF) is shifted to the lower range of pressures; in preeclampsia/eclampsia this is even more pronounced [5, 11].

One more crucial factor for PRES formation is present in eclampsia- *endothelial damage* [13, 28]. From what we know so far, immunological intolerance between the fetal and maternal tissues develops in susceptible women (the presence of risk factors). This leads to abnormal trophoblast invasion of uterine blood vessels and to placental ischemia. Abnormal placentation provokes excessive production of reactive oxygen species, abnormal nitric oxide and lipid metabolism, excessive inflammatory response, activation of leukocytes, platelets and complement cascade, predominance of procoagulant and antiangiogenic factors, which all together lead to vascular endothelial damage and dysfunction [1, 6, 8, 21, 23, 28, 35–39]. All organ systems are affected, and so is cerebral vasculature. The enhanced BBB permeability per se is sufficient to provoke seizure activity. The passage of albumin into interstitial space and the presence of proinflammatory cytokines (such as tumor necrosis factor (TNF)), or aquaporines (AQP4), can lower the seizure threshold and also provoke seizure itself [5, 11].

Parieto-occipital brain region is affected in 94-98.7% of cases, but other parts might be involved as well: the frontal lobe in 77–78.9%, the temporal lobe in 64-68%, and the cerebellum in 53% of cases [3, 12, 13, 27, 29]. The predominant involvement of posterior brain was explained by the findings of less dense sympathetic innervation that makes vertebrobasilar system more susceptible to the breakthrough of the autoregulation limits. There is also an increased capillary density in the posterior brain region with an increased possibility of transcapillary filtration and edema formation [5].

PRES usually resolves in several days if prompt, aggressive management of seizures and BP is initiated [12, 15, 17]. Definitive therapy for preeclampsia/eclampsia is the delivery, especially removal of the placenta, as the placenta is the central organ in the pathogenesis of hypertensive disorders of pregnancy [3, 6, 10, 21].

Management of Eclampsia

During or immediately after a convulsive episode, cardiovascular and respiratory support, treatment of seizure, prevention of maternal injury and aspiration have the priority in the management [40].

The drug of choice for treatment and prevention of convulsions is magnesium sulphate ($MgSO_4$) [1, 4–6, 10, 13, 14, 24, 40, 41]. As an N-methyl-D-aspartate (NMDA) receptor antagonist, magnesium acts as an anticonvulsant. It reduces cerebral endothelial permeability and protects BBB as a calcium antagonist. Magnesium also acts as a vasodilator (the effects on systemic vasculature are more pronounced than on cerebral circulation) and a tocolytic agent [5, 28, 42].

Therapy starts with 4 - 6 g of $MgSO_4$ iv over 15 – 20 min (loading dose), followed by a continuous infusion of 1 - 2 g/h [6]. Side effects could be nausea, headache, and weakness. Overdose leads to the depression of neuromuscular transmission and the loss of deep tendon reflexes, respiratory depression and cardiovascular arrhythmias and collapse. Urine output, magnesemia, tendon reflexes and respiratory function should be monitored during the treatment. The first sign of magnesium toxicity is the loss of patellar reflexes. At that point, $MgSO_4$ should be discontinued and, if necessary, an antidote given (1 g of calcium gluconate over 2 min) [7, 13]. In cases of refractory seizures, therapy should be more aggressive and traditional anticonvulsant agents added (pentobarbital, phenytoin).

The next step in management of eclampsia should be the reduction of BP.

One of the challenges of treating hypertensive disorders in pregnancy is to decide *when to start using antihypertensive medications*. In case of mild to moderate hypertension, there is no evidence of obvious benefit of antihypertensive treatment in outcomes, preterm birth, and neonatal death [18, 19, 36]. However, there is no doubt in case of severe hypertension-therapy should immediately be initiated for the benefit of the mother [18, 23, 41, 42]. According to the opinion of the American College of Gynecology and Obstetrics (ACOG) Committee expressed in 2011 "*Acute onset of severe systolic (more than 160 mmHg), or severe diastolic (more than 110 mm Hg) hypertension, or both, in pregnant women, persisting more than 15 min, is considered hypertensive emergency*" [43]. Hypertensive emergency is a life threatening condition with evidence of target organ damage, in which therapy must be started within one hour [10, 27, 41, 44, 45]. Severe systolic hypertension is the most important predictor of cerebral complications [43].

Another important question is *what level of BP to target* in order to prevent and treat severe hypertension and its possible complications on the one hand, and avoid (iatrogenic) hypotension with cardiac, cerebral and fetoplacental hypoperfusion in a patient who might be intravasculary volume depleted, on the other hand. In such a case, continuous infusion of short-acting titratable antihypertensive agent is the best choice [45]. The immediate goal is to reduce MAP by 25% over 30 – 60 min and to reach 160/110 mmHg during the next 2 to 6 hours [44]. The long-term goal is to keep BP at 140-150/90-100 mmHg, because lower levels of arterial pressure could jeopardize uteroplacental circulation and fetal wellbeing as well as coronary and cerebral circulation of the mother in preeclampsia/eclampsia [12, 17, 20, 24, 30].

The choice of antihypertensive agent in pregnancy and lactation is limited because of their possible impact on fetal/neonatal development.

Labetalol is nowadays the antihypertensive agent of choice in treatment of severe hypertensive disorders of pregnancy [9, 42]. This is α1 and non-selective β-blocker (β-effect being 7 times more pronounced than α-effect is). Labetalol decreases systemic vascular resistance (SVR) without reducing

peripheral blood flow, so it does not affect uteroplacental perfusion [9, 18, 45]. It reduces myocardial oxygen consumption by slowing the heart rate. The following side effects have been reported: dizziness, nausea, vomiting, postural hypotension, bronchospasm, fetal bradicardia. Labetalol is contraindicated in patients with asthma and heart failure [9, 27, 44, 45]. Treatment begins with 20 mg iv bolus given over 2 min. If there is no response, doses of 20-80 mg could be repeated every 10-15 min. Maximum cumulative dose is 300 mg [19, 45].

Hydralazine, a peripherial arteriolar dilator, is recommended in boluses of 5-10 mg every 10 – 20 min to a maximum cumulative dose of 30 mg [9, 20]. Hydralazine is unsuitable for the first line treatment of hypertension in pregnancy due to its delayed onset of action, prolonged duration (up to 12 hours), unpredictable hypotensive effect, reflex tachycardia, and increased intracranial pressure [9, 42–45].

In spite of being an oral agent, *Nifedipine* has been used in hypertensive emergencies, and proved to be as effective as hydralazine, but with a fewer side effects [9, 20]. It induces arteriolar dilatation and decreases the afterload without a reduction in the uteroplacental blood flow by blocking the calcium entry into the cells [42]. Acting as a selective renal arteriolar dilator, it increases urinary output. Its side effects are headaches, facial flushing, and tachycardia [9]. Short-acting nifedipine preparations or sublingual application could provoke sudden, uncontrolled reduction of BP, with cerebral, renal or myocardial ischemia. In order to avoid such events, sustained-release nifedipine tablets are recommended [18, 42, 45, 46]. In cases of simultaneous use of nifedipine and $MgSO_4$ there is a possible danger of potentiating neuromuscular blocking effects; however, this has not been observed in large randomized trials [9, 19, 23, 42].

Nicardipine, a parenteral calcium channel blocker, strong cerebral and coronary vasodilator, reduces cardiac and cerebral ischemia [9, 44]. Its most frequent side effect is headache. Initial infusion rate is 5 mg/h; it could be increased every 5 min by 2.5 mg/h, to maximum of 15 mg/h [13, 45].

Urapidil blocks α1 receptors in arterioles and veins, provoking vasodilatation without reflex tachycardia or increased intracranial pressure (ICP). Its side effects include hypotension, palpitations, headaches, weakness, and fluid retention [9, 42].

Nitroprusside, a potent vasodilator that reduces both pre and afterload with the rapid onset of action (30 sec) and duration of 3 min [9, 44]. It should be used with extreme caution in pregnancy, only in most complicated, refractory cases and as short as possible because of its toxicity and close monitoring is required in intensive care unit. Nitroprusside should not be administered in patients with ICP [18, 23, 45].

Nitroglycerin, being mostly venodilatator, reduces preload and cardiac output (CO), so it is effective in patients with pulmonary edema or acute coronary syndrome. Its side effects are headaches, reflex tachycardia, and hypotension. The onset of action is in 2 min, half life 1 – 4 min. Infusion regime starts with 5 ug/min and can be doubled every 5 min, to maximum of 100 ηg/min [9, 44].

Diuretics are avoided because of volume depletion in majority of hypertensive patients, except in cases of pulmonary edema, congestive heart failure or renal failure [19, 42].

Angiotensin converting enzyme inhibitors and angiotensin receptors blocking drugs are a very effective group of medications, but, unfortunately, contraindicated in pregnancy [9, 17, 23]. They can be used in cases refractory to other agents, when its benefit surpasses the risk [9]. Captopril and enalapril are allowed during lactation [9, 23, 46].

Conclusion

Eclampsia, one of the most serious complications of hypertensive disorders of pregnancy, can occur without prodromal signs or elevation in blood pressure in up to 20% of cases.

Neurological (headache, blurred vision, cortical blindness, nausea, vomiting, altered mental status, seizures, and coma) and radiological signs on magnetic resonance imaging scan (presence of bilateral focal regions of brain edema - predominantly vasogenic) in patients with eclampsia are described as posterior reversible encephalopathy syndrome.

Posterior reversible encephalopathy syndrome is completely reversible if adequate diagnosis is promptly made and intensive treatment immediately undertaken.

Magnesium sulphate is the anticonvulsive agent of choice.

Labetalol is considered to be the agent of choice in treatment of hypertensive emergencies of pregnancy. Hydralazine, urapidil, nicardipine, nifedipine, nitroglycerine and sodium nitroprusside (in most refractory cases) are recommended as well. Angiotensin converting enzyme inhibitors and angiotensin blocking drugs are contraindicated in pregnancy. Captopril and enalapril are allowed during lactation.

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HISTORY OF SPORTS MEDICINE IN EAST EUROPEAN COUNTRIES

ISTORIJA SPORTSKE MEDICINE U ISTOČNOEVROPSKIM ZEMLJAMA

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Summary
The purpose of this article is to provide a historical background of medicine, science and sports with the focus on the development of modern sports medicine in European countries, with an accent on Eastern European countries that have a long sports medicine tradition. The development of modern sports medicine began at the end of 19th and the beginning of 20th century, and it has been associated with social and cultural changes in the world of medicine, science and sports. Advanced medical knowledge, skills and practices, and the progress of scientific achievements enabled sports people to improve their performance level. Increased popularisation and commercialisation of sports have resulted from urbanization and city lifestyle, leading to the lack of physical activity and increased psychological pressure. In addition, the growing need and interest in sports and successes in professional sports have become a symbol of international recognition and prestige for the nations.
Keywords: History of Medicine; Sports Medicne; Europe, Eastern; History, 19th Century; History, 20th Century; Health Promotion

Sažetak.
Ovim radom prikazuje se istorijat razvoja sportske medicine kao nauke i sporta u evropskim zemljama sa posebnim osvrtom na zemlje Istočne Evrope. Prvi zapisi o sportskoj medicini, kao savremenoj disciplini datiraju s kraja 19. i početka 20. veka i usko su povezani sa društvenim i kulturnim promenama u svetu medicine, nauke i sporta. Unapređenjem medicinskog znanja, veština i prakse i napretkom naučnih dostignuća, otvoreno je novo poglavlje u medicini, a popularizacija i komercijalizacija sporta su rezultat urbanizacije i gradskog načina života, što je dovelo do nedovoljne fizičke aktivnosti i porasta psihološkog pritiska. Potreba i interesovanje za sportom porasli su sa uspesima u profesionalnom sportu − sportski rezultati ubrzo postaju simbol međunarodnog priznanja i prestiža.
Ključne reči: Istorija medicine; Sportska medicina; Istočna Evropa; Istorija 19. veka; Istorija 20. veka; Promocija zdravlja

Introduction

Modern sports medicine may be defined as an organized application of medicine and science in the study of sports and their institutionalization in the form of professional associations, research establishment, scientific conferences and journals [1]. It is primarily based on healthcare of sports professionals and recreationally active individuals in order to diagnose, treat and prevent disease or other damage to the body and mind, as well as to promote health. The development of modern sports medicine began at the end of the 19th and the beginning of the 20th century, and it has been associated with social and cultural changes in medicine, science and sports. Advanced medical knowledge, skills and practices, and the progress of the scientific achievements enabled sportsmen to improve the level of their success. Modern sports medicine has changed and rapidly progressed since the Second World War. Urbanization and city lifestyle have led to the lack of physical activity and increased psychological pressures on the one hand, but have increased the popularization and the commercialization of the sport on the other hand. In addition, the growing need and interest in sports and successes in professional sports have become a symbol of international recognition and prestige

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Abbreviations

BC	– before Crist
FIMS:	– The International Federation of Sports Medicine/ Fédération Internationale de Médécine du Sport
EFSMA	– European Federation of Sports Medicine Associations
BSMA	– Sports Medicine Association of the Balkans
DDR	– Deutsche Demokratische Republik
FKS	– Research Institute for Physical Education and Sports
USSR	– Union of Soviet Socialist Republics
SMAS	– The Sports Medicine Association of Serbia
AIMS	– Association Internationale Médico-Sportive

for the nations. The purpose of this article is to give a historical background of medicine, science and sports with the focus on the development of modern sports medicine in European countries with special emphasis on Eastern European countries with long sports medicine tradition.

Origins of Link between Sports, Medicine and Science

The origins of sports medicine can be found in the times of ancient Egyptians, Greeks and Romans. The Egyptian Imhotep described the diagnosis and treatment of 200 diseases in 2600 before Crist (BC). Hippocrates (460–370 BC) is the earliest known physician, recognized as the father of medicine. He dissociated medicine from magic, religion and philosophy, and established medicine as a profession, based the practice of medicine on objective observations and emphasized the physician/patient relationship [2–4]. Today his postulate is more relevant than ever: "All functional parts of the body will do well, stay healthy and age more slowly if moderate demands are made on them. In passivity, however, they age faster and are prone to diseases." It can also be proved that the contemporary Greek medicine was as closely linked to the training and competitions of ancient athletes as modern sports medicine is to present-day athletes [5]. Galen (Anno Domini 131-201), a Greek physician to gladiators and Roman Emperor Marcus Aurelius, was the first physician who documented his medical observations and is known as the founder of experimental medicine. At the beginning, the physiologists were interested in study of the human organism and its performance, discovering the natural laws that regulate the function of the human body. The scientific insight into the human athletic potential was a source of interesting physiological data. Since Galen's time, doctors have been treating not only sports injuries, but have also been instructing and preparing athletes [1–4].

It was not before the 17th and 18th centuries that far-sighted doctors and scientists referred to this wealth of ancient knowledge again, which at last became the subject of scientific research [4]. Girolamo Mercuriale (1530-1606) was an Italian physician, being the most famous for his work *De Arte Gymnastica*, which is now considered the first book of sports medicine with the principles of physical therapy. The development of sports in Europe increased the development of physiology, and vice versa. Pierre-Jean-Georges Cabanis (1757-1808), a French doctor and physiologist, provided a systematic description of the human organism and its sources of energy. Jan Evangelista Purkyne (1787-1869), a Czech anatomist and physiologist, presented the idea of favorable effect of body training for human health. Nathan Zuntz (1847-1920), a German physiologist and a pioneer of modern altitude physiology and aviation medicine, published studies in biology of the athlete: metabolism, respiration, circulation, nutrition, muscular work and altitude physiology [1–3].

Modern Era of Sports Medicine

In their efforts to promote prevention, therapy and rehabilitation, doctors found permanent allies in the fast developing gymnastics and sports movements after the revival of the Olympic Games starting in 1894 [5]. This was a great incentive for sports medicine, which created a demand for a greater change in the approach to health and sports. August Bier (1861-1949) and Arthur Mallwitz (1880–1968), both German doctors, organized the first lectures in sports medicine at the Berlin University in 1919. Arthur Mallwitz is considered the founder of modern sports medicine. August Bier was also a director of the *Akademie für Sport und Leibeserziehung* (*Academy for Exercise and Physical Training*) in Berlin, latter called *Hohenlychen Hospital*, which became the first sports medicine clinic in Germany. Its director Karl Gebhardt (1897–1948) became the first professor of sports medicine in Berlin, who expanded Bier's methods, adopting an academic approach to sports medicine and awarding degrees [1, 2].

At the same time, Arlie V. Bock (1888-1984) was a researcher at the Harvard Medical School, United States of America, and a pioneer in the field of blood research, especially in the relation with exercise physiology. Archibald V. Hill (1886-1977), an English physiologist, won the Nobel Prize in physiology in 1922 for explaining the production of heat and mechanical work in muscles based on high-performance athletics [1, 2].

The First German Congress of the Scientific Investigation of Sports and Physical Education, with 60 participants, was organized in Oberhof, Germany in 1912. The Congress topics were: "The Importance of Physical Education with Hygienic View", "Woman and Physical Ability", "The Impact of Regular Exercise on the Cardiovascular System", etc. At the same time, the German Committee for Scientific Research of Sports and Physical Education was constituted [1, 2]. This was the first national organization of sports medicine in the world. Sports medical organisations were founded in other countries decades later [5]. The expression "sports doctor" was used officially the first time in Berlin, Germany in 1913, and Arthur Mallwitz was ap-

pointed the first doctor, the specialist in the new area of the medical science called sports medicine. The First World War (1914-1918) interrupted the development of sports medicine in Germany for more than 10 years, and France came with the first post-war sports medicine news [1, 2].

By the end of the 19th century, parallel to the Industrial revolution, which had provided the motive and means for creation of new tools and mechanism that would make life better, specific equipment and support devices started to emerge. These devices and equipment enabled the next phase in the development of medical support to sports people and development of health care for amateur and professional athletes. The first manual ergometer, measuring physical work, was constructed in 1883. Six years later, the first treadmill was promoted and first bicycle-ergometer was represented at the World Exhibition of Technical Achievements in Paris, France in 1896. When the Scotsman Douglas constructed gasbag in 1911, it could be accessed to complex analysis of the metabolic changes in the human body under the influence of defined physical effort and determining physical working capacity based on samples of exhaled air. This and other new inventions made it possible to study human organism reaction to physical efforts and to determine its physical ability. During the first modern, renewed Olympic Games, doctors, mainly former athletes, who took care of health and physical ability of sports national teams, first became interested in new developments. The first sports medical laboratory for anthropological, functional and radiological examinations, managed by Arthur Mallwitz, was established during the First International Hygiene Exhibition, organized in Dresden, Germany in 1911. During that exhibition, which was open for six months, the visitors could check their physical ability based on parameters obtained before and after exercises under medical supervision [1, 2]. Jiri Kral, a Czech medical doctor, founded the first Institute for Sports Medicine affiliated to the Medical Faculty of Charles University in Prague, Czech Republic in 1945. Among other research projects, the first wireless transmission of heart frequency and cardiologic observations during sports events were studied at this Institute [2]. Technological inventions and healthcare support measures have resulted in the discovery of possibilities of human body and methods of how to make the body and mind keep up with growing physical and psychological efforts induced by competitions and ever-lasting motive always to perform better. The link between sports, science and medicine became stronger.

Today, the sports science may be defined as a scientific discipline applied to the theory and practice of athletic performance [2]. Parts of modern medicine fields of science and practice, as well as modern sports medicine, are clinical practice, healthcare science, biomedical research, medications, surgery, medical devices, as well as alternative medicine and psychotherapy. The application of new techniques, methods and modern medical equipment help to further develop sports medicine. New machines, which promote health and ensure the safety of athletes, have contributed to the development of sports medicine and its important and unavoidable role in life of professional athletes as well as everyday health driven exercise practices of individuals all over the world.

Association and Cooperation within Sports Medicine

The Second German Sports Medicine Congress was organized in 1924 in Berlin, Germany, whose name was changed into the German Medical Association for the Promotion of Physical education. At the 4th Congress of German Association, which was held in Berlin, Germany in 1927, Walter Schnell, the president of the Association, invited sports medicine doctors from 12 countries to discuss international cooperation and establishment of an international organization of sports medicine. Association Internationale Médico-Sportive (AIMS) was established in Sent Moritz, Switzerland in 1928. Its first president was Wilhelm Knoll from Switzerland, and Arthur Mallwitz from Germany became the first secretary general. The main aims of the association were to exchange information and experience related to research and practical aspects of sports medicine. This event is considered the official date of launching sports medicine as new medical disciplines. In the same year, during the 9th Summer Olympic Games held in Amsterdam, the Netherlands, the First AIMS International Congress of Sports Medicine was organized with participation of 286 physicians from more than 30 countries. They had the opportunity to study many of the athletes taking part in the Games by collecting anthropometric, cardiovascular, physiological and metabolic data. The first statute determined three directions of AIMS action: promotion of scientific researches in the field of biology, psychology and sociology of sport, promotion of medical research projects associated with athletes' training and competition, and organization of international sports medicine congresses. AIMS changed its name into the International Federation of Sports Medicine (Fédération Internationale de Médécine du Sport - FIMS) during the 3rd International FIMS Congress in Chamonix, France in 1934. The FIMS started mostly as a European organization, but later, during 1960s until 1980s, it included countries from all five continents. Today, the FIMS includes continental and national sports medicine associations, multinational groups and individual members. It is the biggest federation of national medical associations in the world, which includes hundreds of thousands of medical doctors and other professionals from different fields of sports medicine. The primary aims of FIMS are to promote scientific research and development of sports medicine all over the world, and to help athletes to achieve optimal com-

petition ability by improving their genetic potential, health, nutrition, quality of medical protection and training. It organizes courses, international congresses and publishes scientific information related to sports medicine in specific scientific journals, and keeps and promotes the contacts with sports medicine specialists throughout the world. During the Second World War (1939-1945), no sports activities were organized. The revival of FIMS started after the Second World War. During the 20th century, the FIMS congresses were organized throughout Europe. For example, the 7th International FIMS Congress was organized in Prague, Czechoslovakia in 1948, the 10th International FIMS Congress was in Belgrade, Yugoslavia in 1954, and the 12th International FIMS Congress and the 30th Anniversary of FIMS was in Moscow, Union of Soviet Socialist Republics (USSR) in 1958. Since 1963, the FIMS has organized FIMS European Congresses, besides the international ones, which changed their name into the FIMS World Congress at the 16th FIMS World Congress in Hannover, Germany in 1966. The 1st FIMS European Congress was organized in Prague, Czechoslovakia in 1963. Since the 1980s, the FIMS has developed relations with other institutions and countries throughout the world. The first joint meeting of FIMS and the World Health Organization (WHO) was organized in Cologne, Germany in 1994. In 2003, the FIMS celebrated 75 years of its existence in all five continents. For example, the Bone and Joint Decade World Network Conference was held in Berlin, Germany, and the 7th IOC Olympic World Congress on Sports Sciences in Athens, Greece. The FIMS ambassador had his tour through Eastern European countries, Slovakia and Serbia and Montenegro in 2004. The last 32nd FIMS World Congress was held in Rome, Italy in 2012.

The European Federation of Sports Medicine Associations (EFSMA) was founded in Porto, Portugal in 1997. Its first president was Norbert Bachl from Austria, Fabio Pigozzi from Italy was the first secretary general, and today Dr Nenad Dikic is the representative of Sports Medicine Association of Serbia. The goals of EFSMA are to establish sports medicine as a specialty in Europe, to develop and coordinate training and teaching of sports medicine at the relevant educational institutions, to create a pan-European forum to coordinate activities between European societies of sports medicine and sports science facilities, to promote the importance of physical activity and exercise for the prevention, treatment and rehabilitation after illness and injury, to exchange scientific results and experiences in the field of sports medicine and to work on joint research projects, creation of licensed sports medicine centers, and promotion of ethical principles in sports medicine.

Modern Sports Medicine in Eastern Europe

In most countries of Eastern Europe, medicine and sports had their own parallel history of development. The key role in connecting these two branches and making the scientific link between them was to establish movements, associations and institutions for physical education and gymnastics that were part of the state public-health system. When it comes to the development of modern sports medicine in Eastern Europe, one organization played a significant role in promoting sports medicine and spreading the spirit of physical education in Eastern Europe. The name of this youth sport movement and gymnastics organization was The Sokol. The Sokol was a youth sport movement and gymnastics organization first founded by Miroslav Tyrs and Jindrich Funger in Prague, Czech in 1862. It was the first physical education organization in the Austro – Hungarian Empire at the time of political freedom in the 1860s, with more than 2000 members in 1863, and over a million members in the period between the two world wars. It had a versatile program based on physical, moral and intellectual training of the nation. The Sokol found its base in the German gymnastic movement *Turnverein* founded by Friedrich Ludwig Jahn in 1811. Miroslav Tyrs (1832-1884), a Czech art historian, sports organizer and founder of the Sokol movement, introduced new gymnastic exercises and its terminology. Sokol gymnasiums were built as sports and cultural centers. The movement units organized regular training of all age groups, sports competitions, cultural events, excursions and youth camps, active discussions and exhibitions. The Sokol festival (SLET), held for the first time in 1882, represented a mass gymnastic festival. The Sokol movement started to be popular in most of the Slavic countries, such as Poland, Serbia, Bulgaria, Russia (Ukraine, Belarus), Slovenia, Croatia, etc. It established the base for the 20th century development of widely accepted approach to make sport activities become more science with a specific purpose than mere leisure or entertainment activity [6, 7].

During the FIMS's Congress of Sports Medicine held in Romania in 1969, the Turkish representative Dr Necati Akgn proposed the establishment of the Sports Medicine Association of the Balkans (BSMA). The BSMA was established in 1971 with the representatives from the Balkan countries that linked all the sports doctors from Bulgaria, Greece, Romania, Turkey and Yugoslavia. The 1st Balkan Congress of Sports Medicine was organized in Athens, Greece in 1972. Today, the Association consists of the Sports Medicine Association of Albania, Bulgaria, Cyprus, Greece, Macedonia, Romania, Moldova, Serbia and Turkey. Unfortunately, due to the large number of annual conferences in the field of sports medicine and a lot of historical and political reasons, the BSMA Executive Committee decided to freeze its activities, and focus on work under the auspices of the European Federation of sports associations. In 1995, the Balkan Congress of Sports Medicine was organized in Belgrade, and the last, 15th Balkan Sports Medicine Congress was organized, in Bucharest,

Romania in 2008. Germany is considered the cradle of sport medicine worldwide. In 2012, they celebrated a hundred years of organized sports medicine in Germany. Although the terms "sportarzt" and "sportmedizin" were not used in German before the last century, their area of concern and their issues are among the oldest in medicine [5]. Turbulent German history of the 20th century, however, shaped the development of sport medicine and gave it different 45 years of development in Western and Eastern part. After the Second World War, about 60 percent of the sports facilities in Eastern Germany were shattered or used for other purposes, such as emergency and refugee lodgings, and agrarian facilities. Nevertheless, sports-medical curricula were set up by various facilities of physical education for sport students and trainers in 1946. In the same year, Friedrich Wilhelm University in Berlin included sports-medical teaching as "sport biology" and began teaching it. In 1950, the Ministry of Health created a department of sports medicine, and right afterwards issued a decree on the physical examination for acquisition of a sport medal. Thus, the necessity for doctors with sports-medical engagement arose and sports-medical examinations as a paid "additional activity" were introduced. Also in 1950, a decade-old demand that "every doctor (be) a sports doctor" was reaffirmed by Arno Arnold. He believed that sports medicine should be a mandatory examination subject in the study of medicine. This created a pathway for the introduction of lectures in sports medicine or sports-related topics as a part of other subjects at the six medical university faculties in the Deutsche Demokratische Republik (DDR) and three medical academies (Erfurt, Dresden and Magdeburg) starting in the late 1950s. German College of Physical Culture (Deutsche Hochschule für Körperkultur – DHfK) was founded in 1950, with the Sports Medicine Department right from the start. The Department was in charge of the sports medical teaching of sport students and the monitoring of students' health. In 1961, the Institute for Sports Medicine was founded as well as the Faculty of Natural Sciences and Sports Medicine in 1962. The Rehabilitation Centrum Kreischa (near Dresden) was affiliated to the Institute in 1962. This Centrum evolved into the Central Institute for Sports Medical Services in 1968. In Leipzig, as well as in Kreischa, there were courses and advanced seminars in sports medical areas with national and international participants. Sports medicine was taught there primarily by doctors with sports-medical qualification in out- and in-patient health services and university facilities. The Research Institute for Physical Education and Sports (FKS) was founded in 1969 to meet the high-performance sports goals of the DDR effectively. It was a combination of the research facility and the major part of the Institute for Sports Medicine of the German University for Physical Education in Leipzig. The FKS was the only institution for high-performance sports research in the DDR and employed more than 600 people until it was closed down in 1990. As a result of this effective practical work at the FKS, sports type specific ergometers were introduced in all types of sports by 1974. Among these were the current channel in swimming and the tiltable treadmill for cross-country skiing. With the establishment of the Sports-medical Consultation Centers in 1952, and the introduction of the specialist in sports medicine in 1963, the sports medicine management system became a centralized state organizational structure. Until the end of the 1950s, county sports doctors from health services used to give advice to those going in for sports and to examine them. However, since 1970, they have been assigned clearly defined responsibilities in order to facilitate high-performance sports system. The county sports doctors became responsible especially for the extensive care of young aspiring athletes enrolled in the training centers. Every activity in high-performance sports was kept strictly secret. Since the leaders of the political party and sports directors recognized the significance of athletic achievement for the international reputation, they spared no expense to uphold and boost the impressive success of DDF sports on the world stage. The preparations in some sports for the Olympic Games in 1971 in Munich included particular or "supportive measures" as doping was euphemistically called. Still, the DDR and its sports managers had always officially recognized the Anti-Doping Charta. Doctors were not forced to perform measures determined by the Sports Leagues, but anyone who refused could be certain of being judged unsuitable for employment in high-performance sports. These activities casted a shadow over a very successful state sports medicine works done in the past. At the end (1990), there were about 1800 people employed in the Sport Medical Department and 350 of them were specialists for sports medicine. At the end of 1990, the Sports Medical Department as the central institution was closed by the Federal Ministry of Finance for all of Germany although some of the doctors and well-known university teachers strongly opposed that decision [8].

In the USSR, the term "vrachebnyi kontrol" (medical supervision) was sometimes used instead of the term sports medicine [9]. Modern sports medicine started to develop in the countries of the former Soviet Union at the end of 19th century. Ivan Mikhaylovich Sechenov (1829-1905), the father of Russian physiology, explained how the alveolar pO_2 changed with barometric pressure. At the end of 19th century, Russian army doctors made comprehensive examinations of the fitness of soldiers at high altitude and of procedures for improving acclimatization [10]. The development of sports medicine in the USSR was closely related with N. A. Semashko, V. V. Gorenevskii, B. A. Ivanovskii, I. M. Sarkizov-Serazini, V. N. Moshkov, I. A. Kriach-ko,

S. P. Letunov, R. E. Motylianskaia, and others [9]. These individuals laid the scientific foundation of sports medicine as an integral part of the Soviet system of public health, physical culture, and sports. In the Soviet Union, sub-departments, laboratories, and departments of sports medicine were organized in the 1920s and 1930s at scientific research institutes and educational institutes of physical culture. Dispensaries and stations for medical supervision of all categories of physical culturists and athletes were established in the 1940s. There were more than 300 dispensaries and about 1500 stations in 1975. The Federation of Sports Medicine of the USSR was organized in 1946 and became a member of the FIMS in 1952. It was represented at international congresses on sports medicine sponsored by the FIMS. The All-Union Society of Medical Supervision and Kinesitherapy of the Ministry of Public Health of the USSR were founded in 1961, and the Kiev Scientific Research Institute of Medical Problems in Physical Culture and Sports was founded in 1967. Laboratories (groups) on different aspects of sports medicine were created in the 1970s at many scientific research institutes of the Academy of Medical Sciences of the USSR. Research in sports medicine was coordinated by the Commissions for Medical Problems in Sports and in Physical Culture [9]. As an educational discipline, sports medicine was a part of the curricula at institutes of physical culture, medical institutes, and pedagogical higher educational institutions with departments of physical education.

Bulgaria started its first formal institution for physical education in 1942 as Higher school for physical education. Today, the same school exists under the name the National Spots Academy "Vassil Levski". Its role in establishing the basis for development of methodology and multi-disciplinary approach to sports in Bulgaria was significant. The school had four departments: 1.Health sciences - anatomy, biology, anthropology, general physiology and physiology of physical exercises, general hygiene and hygiene of physical exercises, first aid, correctional gymnastics and massages; 2. Physical education - history of physical education, theory of physical exercises, methods in physical exercises (including practice); 3. General education - general knowledge of Bulgaria (in the field of Bulgarian language and literature, ethics, Bulgarian history, culture and geography), common psychology and psychology of physical exercises at different ages, common pedagogy and education by means of physical exercises; 4. Organization of physical training - modern organization of physical training in the world, law matters concerning the organization of physical training, concept of organized camps, summer sports activities, children playgrounds, fairs, competitions etc., construction and equipping of facilities for exercising, knowledge of exercise equipment and apparatus.

In 1967, Higher school for physical education was divided into the Sports-pedagogical faculty and the Faculty for mass health and healing physical culture. Twelve departments replaced the old four ones, including general hygiene and hygiene of the physical exercises, medical surveillance, study of the physical development of the human body, and anthropometry. This was the beginning of an important work to be done in the next decades aimed at providing professional support to Bulgarian athletes in the field sports medicine.

The development of sports medicine in former Yugoslavia began when a group of doctors started up an organized health control of athletes, and hygienic control of sports facilities in Belgrade in 1930. In 1936 the first sports outpatient department was opened within the Clinic for Internal Medicine at the Medical Faculty University in Belgrade, under the leadership of Prof. Dr. Vojislav Arnovljević. The first doctor from Yugoslavia, Vojin Smodlaka, was sent to specialize Sports Medicine in the Center of Sports Medicine at the Academy of Physical Culture in Berlin in 1937, and as early as 1940, Sports Medicine was introduced as an optional course, led by Dr Smodlaka, at the Faculty of Medicine in Belgrade. After the Second World War, in 1945, teaching of sports medicine was introduced at the Federal Institute of Sports Culture in Belgrade (today – Faculty of Sport and Physical Culture), and the Department of Sports Medicine was established within the Medical Association of Serbia. Soon afterwards, in 1952, the Institute for Sports Medicine was founded within the Yugoslav Institute for Physical Culture and Sports Medicine in Belgrade. A year later, in 1953, the Sports Institute of Vojvodina (today – the Regional Institute for Sports and Sports Medicine) was established in Novi Sad. The Sports Health Care Center was opened in Belgrade in 1957. In 1965, the Section of Sports Medicine was established in Novi Sad within the Society of Physicians of Vojvodina, a part of Serbian Medical Society. Today, the Section of Sports is a part of Serbian Medical Society, and since 2011 its president has been Dr. Ivan Lukic from Vojvodina. The crowning moment in the development of sports medicine in Serbia was the graduation of the first specialist. Medical doctor Miodrag Petrovic passed the exam in sports medicine in 1966, thus paving the way for generations of sports medicine specialist who supported enormously the success of Yugoslavian athletes during the 1970s and 1980s. In 1970, the Institute for Sports Medicine was founded at the Medical Faculty University of Belgrade. Three years later the symposium "Athlete's heart" was organized in Novi Sad. In 1975, our karate player and doctor of medicine Prof. Dr. Vladimir Jorga became the head of the World Karate Federation established by the Health Commission (Medical Board), and six years later an international symposium of sports medicine "Medical and Biological Characteristics of Karate Training" was organized in Belgrade. In 1977, the Congress of International Federation of Sport Medicine was organized in Belgrade. The Sports Medicine Associa-

tion of Serbia (SMAS) was founded in 1995 as an association of specialists in sports medicine, doctors of other specialties, as well as other experts engaged in health care and improvement of physical abilities of participants in sports and recreation in the territory of the Republic of Serbia. Its first president was Prof. Dr. Slobodan Živanić. The goals of SMAS are education through training courses in fields of sports medicine, wide publishing activity and organization of regular conferences in the field of sports medicine and sports science as well as dietary supplements. The main objectives are to develop and promote technical and scientific practices in the field of sports medicine and sports science, to provide adequate healthcare to all athletes, to protect professional interests and rights of doctors and medical staff involved in sports medicine, to educate in the field of sports medicine, to issue certificates and licenses, to publish technical and scientific articles and to cooperate with other national associations of sports medicine.

The SMAS is a member of the Sports Association of Serbia (SSS), Olympic Committee of Serbia (OKSCG), British Association of Sports Medicine (BSMA), EFSM, and FIMS. The SMAS organized the 1st Serbian Congress of Sports Science and Sports Medicine in Belgrade in 2003, and the 1st Congress about dietary supplements in 2007 [11]. These congresses have been held every two years so far.

Conclusion

Regarding physical health, sports system is trying to deal with the lack of physical activities**,** which is present among the population in most of the so-called developed countries. The main concerns of modern sports medicine are healthcare of active sporting and exercising population, prescribing exercise as therapy in chronic diseases, and prevention of chronic disease caused by sedentary life style by health promotion. It demands sports-specific knowledge and expertise of health care professionals, researchers and educators from different disciplines, especially of doctors, as sports medicine specialists and leaders of sports medicine team. Physical examination, medications, drugs and other substances, such as special instruments and equipment, are used to prevent, diagnose, treat or cure the illness or other damage of the human body, and to promote health. Current national tasks are to motivate the population to participate in physical activity and promote sports, since health related problems and diseases based on sedentary behavior are rising as well as costs in the health care system. The authors of this article indirectly tried to show that the achievement of doctor's success has never been easy, but it is worthwhile.

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IN MEMORIAM
IN MEMORIAM

Dr IGOR BITENC
(1925-2014)

Dr Igor Bitenc – A great man has gone

Earlier this year, on January 5, a dear friend and great benefactor Dr Igor Andrej Stevo Bitenc left us at the age of 90. The name of Dr Bitenc will remain inscribed in gold letters in orthopedic circles of the former Yugoslav republics. We owe him our eternal gratitude for being the creator and founder of study tour scholarship for young orthopedic surgeons from the area of the former Yugoslav Republics to the famous orthopedic centers in Canada.

Dr Igor Bitenc was born on July 3, 1925 in Ljubljana. At the age of 2, he began his interesting and dynamic way of life, having moved with his family first to Austria, and then to Germany, Switzerland and Belgium a few years later. The Bitenc family settled in Belgrade for a while, where he attended "Boys' Grammar School of King Alexander I" in the period from 1935 to 1940. He enrolled in the University of Vienna in 1946 to study medicine and graduated in 1951. Even during his studies, he showed great interest in surgery working at the Traumatology Clinic in Vienna with the famous Professor Lorenz Böhler and then at the Second Medical University Clinic, also in Vienna. The road to trauma continued in Bregenz, Austria, where he was a postgraduate trauma student from 1951 to 1953. During his last year of postgraduate studies, he immigrated to Canada.

He performed compulsory medical service at the General Hospital in Sherbrooke, after which he started his residency in orthopedic surgery in 1954. He spent the first part of residency at the Royal Victoria Hospital, and the second one at the Hospital for Crippled Children (Shriners Hospital for Crippled Children), both in Montreal. After the completion of the specialization in 1958, he opened his private practice and began working as a clinical assistant at the Royal Victoria Hospital in Montreal as well, where he was the chief of trauma service for some time. He transferred his knowledge and practical experience to the students of the "McGill" University in Montreal as a teacher of surgery, where he was appointed associate professor in 1968.

Dr Bitenc was a recognized member of a large number of associations such as the Austrian Traumatology Association, Association of Orthopaedic Surgeons State of Quebec, the Canadian Medical Association, Canadian Association of Orthopaedic Surgeons, International Association of Orthopaedic and Traumatology (SICOT) and others. At the IX Congress of the Yugoslav Association of Orthopaedics and Traumatology (JUOT), which was held in October 1986 in Novi Sad, he was appointed honorary member of JUOT. On the day of his birthday, July 3, 2002 he was appointed honorary member of the Slovenian Orthopaedic Association. His career of orthopedic surgeon was finished in 1973, when he retired and moved to the city of Victoria on Vancouver Island, where he lived until his death on January 5, 2014.

Dr Igor Bitenc never forgot the country of his origin. He used to spend 7 days on Lake Bled almost every year, and enjoyed hiking should his health permitted it.

The idea to start a scholarship was born precisely because of this attachment to the former Yugoslavia. The first concrete proposal came as early as 1984. Dr. Bitenc offered Prof. Dr. Želimir

Mikić, the President of the Yugoslav Association of Orthopaedic and Traumatology (JUOT) at that time, to provide young orthopedic surgeons (coming from different Yugoslav republic each year) with a scholarship to visit the largest orthopedic centers in Canada from his personal funds.

He wanted this fund to be called the "Anica Bitenc Scholarship" (Anica Bitenc Traveling Fellowship) after his late mother, who had died on September 19, 1980. At the meeting of JUOT, which was held on November 17, 1984 in Novi Sad, Presidency officially established the "Anica Bitenc Scholarship". As it was agreed, the scholarship was to last for 3 weeks, during which young orthopedic surgeons from Yugoslav republics would visit several orthopedic centers in Canada, ending this traveling fellowship by attending the annual meeting of the Canadian Orthopaedic Association. The first fellow from the former Yugoslavia was Dr Ranko Bilic. He traveled to Canada the following year, i.e. 1985. This generous gesture of Dr Bitenc did not arouse the admiration of the Yugoslav orthopedic community only. The President of the Board of Directors of the Foundation, Dr Paul Wright said: "On behalf of the Canadian Orthopaedic Foundation I would like to thank Dr Igor Bitenc for his charity. This is the greatest gift that has been so far received by the Foundation and we are very pleased that we will thus be able to provide a permanent continuation of this important project." The last President of the Board of Directors of the Canadian Orthopaedic Foundation, Dr. James P. Waddell said: "On behalf of the Canadian Orthopaedic Foundation, I invite the surgeon community to celebrate the life of Dr Bitenc. I admire Dr Bitenc for his generosity and commitment to giving back. We are honoured to carry out his legacy."

Fellowship provided by this Foundation was not used during the war years (1992 to 1996). It was resumed in 1997, but only for young orthopedic surgeons from Slovenia, Croatia and Macedonia in the first years that followed. To our great satisfaction, since 2003 Serbia has again been given the opportunity to use the funds of "Anica Bitenc Scholarship", and from that year, the representatives of national orthopedic associations of Serbia, Slovenia and Croatia have been sent to Canada. From 1985 to 2014, 24 young orthopedic surgeons had the honor and pleasure to be Fellows of the Foundation and those from Serbia were Dr Goran Ercegan (1986), Dr Zoran Blagojevic (1989), Dr Dragan Savic (2003), Dr Alexander Lesic (2006), Dr Vladimir Harhaji (2009) and Dr Nemanja Slavkovic (2012).

Dr Igor Bitenc in 2007, said: "When I raised the "Anica Bitenc Scholarship", colleagues from Yugoslavia had many complications to travel and thus acquire new knowledge from colleagues in other countries. While this situation has changed in recent years, I believe it is still important to help surgeons from Slovenia, Croatia and Serbia, and provide them with the opportunity to learn from their colleagues from abroad. "

Shortly after the death of Dr Igor Bitenc, Mrs. Cynthia Vezina, Communications Manager for the membership of the Secretariat of the Canadian Orthopaedic Association, sent us the following letter: "It is with deep regret that I inform you of the Dr. Igor Bitenc's recent death. We received notification through his power of attorney that he died on January 5th, 2014. This fellowship endowment will continue. He made arrangements with his estate to ensure that Anica Bitenc fellowship will continue on for several more years. Dr. Bitenc will be sorely missed by our society and his Canadian colleagues. He was a true gentleman and I will personally miss him very, very much. "

All those who had the privilege to be recipients of "Anica Bitenc Scholarship" returned from Canada enriched with new knowledge, experience and contacts. Whenever his health permitted, Dr Igor Bitenc attended the annual meeting of the Canadian Orthopaedic Association, where some of us had the honor to meet personally this benefactor, noble soul and a big heart. Death of Dr Igor Bitenc is undoubtedly a great loss for both the Canadian and former Yugoslav orthopedic communities. The name of this kind and noble man will be pronounced with great respect by many generations of orthopedic surgeons to come.

Prof. Dr. Želimir Mikić
Prof. Dr. Goran Ercegan
Prof. Dr. Dragan Savić
Doc. Dr. Vladimir Harhaji

Prof. dr DUŠAN MRATINKOVIĆ (1933−2014)

Profesor Dušan Mratinković rođen je 1933. godine u Petrovčiću od oca Dimitrija sveštenika i majke Ljubice. Ratne godine je proveo u Sremu sa majkom i sestrom Svetlanom, bez oca koji je bio u zarobljeništvu. Gimnaziju je završio u Zemunu, a nakon velike mature upisao je Stomatološki fakultet Univerziteta u Beogradu. Nakon završenih studija, prvo zaposlenje dobio je u Sremskim Karlovcima gde je i živela porodica Mratinković. Posle nekoliko godina prešao je u Dom zdravlja Novi Sad. Godine predanog rada u Domu zdravlja na Bulevaru a potom u Zavodu za stomatologiju na poznatoj adresi, JNA 4, afirmisale su profesora Mratinkovića kao stručnog, veštog i nadasve omiljenog lekara kako kod kolega stomatologa tako i kod brojnih pacijenata. U tom periodu je specijalizirao iz oblasti Bolesti usta i zuba i odbranio magistarsku tezu.

Upravo ta grupa lekara Doma zdravlja, odnosno Zavoda za stomatologiju, kojoj je po svemu pripadao i profesor Dušan Mratinković, činila je osnovu nastavnog kadra Odseka za stomatologiju Medicinskog fakulteta u Novom Sadu. Naime, odlukom Saveta Medicinskog fakulteta u Novom Sadu, februara 1976. godine doneta je odluka o formiranju Odseka za stomatologiju, dok je 1978. godine otvorena Klinika za stomatologiju Vojvodine u ulici Hajduk Veljkova 12, gde se nalazi i danas. Prof. dr Dušan Mratinković je bio član kolektiva Klinike za stomatologiju, tadašnjeg Instituta za stomatologiju, od prvog dana osnivanja. Vreme provedeno u nastavi, od asistenta do profesora na Medicinskom fakultetu u Novom Sadu, dodatno je afirmisalo profesora Mratinkovića kod brojnih generacija studenata i specijalizanata. Postavio je predmet Bolesti zuba i držao teoretsku i praktičnu nastavu na pretkliničkim i kliničkim predmetima osnovnih studija stomatologije i istovremeno bio mentor i član Ispitne komisije iz specijalističke oblasti Bolesti usta i zuba. Bio je učesnik višegodišnjeg multicentričnog projekta u kojem su učestvovali svi stomatološki fakulteti i odseci na području Jugoslavije pod pokroviteljstvom Svetske zdravstvene organizacije − *Oral health in SFR Yugoslavia in 1986*. Značajan doprinos razvoju stomatologije u Vojvodini ostvario je kroz aktivnosti u okviru Stomatološke sekcije Društva lekara Vojvodine Srpskog lekarskog društva. Stručno znanje je nesebično delio sa mlađima uz malo reči a više dela. Bio je dugogodišnji načelnik Odeljenja za bolesti zuba, član Uprave zadužen za zdravstvo a jedno vreme i direktor Klinike za stomatologiju Vojvodine.

Malo je reći da je bio omiljen, uvek spreman da pomogne, pun razumevanja podjednako i za sestre i kolege, kao i za studente i specijalizante. Stručnost i kolegijalnost su osobine koje su krasile profesora Mratinkovića za sve vreme rada na Klinici za stomatologiju Vojvodine. Njegovo ime je bilo sinonim za uspešnu terapiju i najkomplikovanijih slučajeva iz oblasti endodoncije. Ostaće u sećanju kolegama, pacijentima i brojnim generacijama studenata i specijalizanata koji su ga poznavali i učili od njega.

Prof. dr Ljubomir Petrović

Štampu ovog časopisa ”Medicinski pregled”
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UPUTSTVO AUTORIMA

Časopis objavljuje sledeće kategorije radova:

1. Uvodnici (editorijali) – do 5 stranica. Sadrže mišljenje ili diskusiju o nekoj temi važnoj za Časopis. Uobičajeno ih piše jedan autor *po pozivu*.

2. Originalni naučni radovi – do 12 stranica. Sadrže rezultate sopstvenih originalnih naučnih istraživanja i njihova tumačenja. Originalni naučni radovi treba da sadrže podatke koji omogućavaju proveru dobijenih rezultata i reprodukovanje istraživačkog postupka.

3. Pregledni članci – do 10 strana. Predstavljaju sažet, celovit i kritički pregled nekog problema na osnovu već publikovanog materijala koji se analizira i raspravlja, ilustrujući trenutno stanje u jednoj oblasti istraživanja. Radovi ovog tipa biće prihvaćeni samo ukoliko autori navođenjem najmanje *5 autocitata* potvrde da su eksperti u oblasti o kojoj pišu.

4. Prethodna saopštenja – do 4 stranice. Sadrže naučne rezultate čiji karakter zahteva hitno objavljivanje, ali ne mora da omogući i ponavljanje iznetih rezultata. Donosi nove naučne podatke bez detaljnijeg obrazlaganja metodologije i rezultata. Sadrži sve delove originalnog naučnog rada u skraćenom obliku.

5. Stručni članci – do 10 stranica. Odnose se na proveru ili reprodukciju poznatih istraživanja i predstavljaju koristan materijal u širenju znanja i prilagođavanja izvornih istraživanja potrebama nauke i prakse.

6. Prikazi slučajeva – do 6 stranica. Obrađuju *retku* kazuistiku iz prakse, važnu lekarima koji vode neposrednu brigu o bolesnicima i imaju karakter stručnih radova. Prikazi slučajeva ističu neuobičajene karakteristike i tok neke bolesti, neočekivane reakcije na terapiju, primenu novih dijagnostičkih postupaka ili opisuju retko ili novo oboljenje.

7. Istorija medicine – do 10 stranica. Pišu se na poziv uredništva Medicinskog pregleda i obrađuju podatke iz prošlosti sa ciljem održavanja kontinuiteta medicinske i zdravstvene kulture, a imaju karakter stručnih radova.

8. Druge vrste publikacija (feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih ustanova, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novine u medicini, pitanja i odgovori, stručne i staleške vesti i *In memoriam*).

Priprema rukopisa

Propratno pismo

– Mora da sadrži svedočanstvo autora da rad predstavlja originalno delo, kao i da nije objavljivan u drugim časopisima, niti se razmatra za objavljivanje u drugim časopisima.

– Potvrditi da svi autori ispunjavaju kriterijume za autorstvo nad radom, da su potpuno saglasni sa tekstom rada, kao i da ne postoji sukob interesa.

– Navesti u koju kategoriju spada rad koji se šalje (originalni naučni rad, pregledni članak, prethodno saopštenje, stručni članak, prikaz slučaja, istorija medicine).

Rukopis

Za pisanje teksta koristiti *Microsoft Word for Windows*. Tekst treba otkucati koristeći font *Times New Roman*, na stranici formata A4, proredom od 1,5 (i u tabelama), sa marginama od 2,5 cm i veličinom slova od 12 pt. Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana. Naslovna strana treba da sadrži kratak i jasan naslov rada, bez skraćenica, zatim kratki naslov (do 40 karaktera), puna imena i prezimena autora (najviše 6 autora) indeksirana brojkama koje odgovaraju onima kojim se u zaglavlju navode uz pun naziv i mesta ustanova u kojima autori rade. Na dnu ove stranice navesti titulu, punu adresu, e-mail i broj telefona ili faksa autora zaduženog za korespondenciju.

2. Sažetak. Sažetak treba da sadrži do 250 reči, bez skraćenica, sa preciznim prikazom problematike, ciljeva, metodologije, glavnih rezultata i zaključaka. Sažetak treba da ima sledeću strukturu:

– originalni naučni radovi: uvod (sa ciljem rada), materijal i metode, rezultati i zaključak;

– prikaz slučaja: uvod, prikaz slučaja i zaključak;

– pregled rada: uvod, odgovarajući podnaslovi koji odgovaraju onima u tekstu rada i zaključak.

U nastavku navesti do deset ključnih reči iz spiska medicinskih predmetnih naziva (*Medical Subjects Headings, MeSH*) Američke nacionalne medicinske biblioteke.

3. Sažetak na engleskom jeziku. Sažetak na engleskom jeziku treba da bude prevod sažetka na srpskom jeziku, da ima istu strukturu i da sadrži do 250 reči, bez upotrebe skraćenica.

4. Tekst rada

– Tekst originalnih članaka mora da sadrži sledeće celine:

Uvod (sa jasno definisanim ciljem rada), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su korišćene u tekstu) i eventualna zahvalnost autora onima koji su pomogli u istraživanju i izradi rada.

– Tekst prikaza slučaja treba da sadrži sledeće celine: Uvod (sa jasno definisanim ciljem rada), Prikaz slučaja, Diskusija i Zaključak.

– Tekst treba da bude napisan u duhu srpskog jezika, oslobođen suvišnih skraćenica, čija prva upotreba zahteva navođenje punog naziva. Skraćenice ne upotrebljavati u naslovu, sažetku i zaključku. Koristiti samo opšte prihvaćene skraćenice (npr. DNA, MRI, NMR, HIV,...). Spisak skraćenice koje se navode u radu, zajedno sa objašnjenjem njihovog značenja, dostaviti na poslednjoj stranici rukopisa.

– Koristiti mere metričkog sistema prema Internacionalnom sistemu mera (*International System Units – SI*). Temperaturu izražavati u Celzijusovim stepenima (°C), a pritisak u milimetrima živinog stuba (mmHg).

– Ne navoditi imena bolesnika, inicijale ili brojeve istorija bolesti.

Uvod sadrži precizno definisan problem kojim se bavi studija (njegova priroda i značaj), uz navođenje relevantne literature i sa jasno definisanim ciljem istraživanja i hipotezom.

Materijal i metode treba da sadrže podatke o načinu dizajniranja studije (prospektivna/retrospektivna, kriterijumi za uključivanje i isključivanje, trajanje, demografski podaci, dužina praćenja). Statističke metode koje se koriste treba da budu jasne i detaljno opisane.

Rezultati predstavljaju detaljan prikaz podataka dobijenih tokom studije. Sve tabele, grafikoni, sheme i slike moraju da budu citirani u tekstu, a njihova

numeracija treba da odgovara redosledu pominjanja u tekstu.

Diskusija treba da bude koncizna i jasna, sa interpretacijom osnovnih nalaza studije u poređenju sa rezultatima relevantnih studija publikovanim u svetskoj i *domaćoj* literaturi. Navesti da li je hipoteza istraživanja potvrđena ili opovrgnuta. Izneti prednosti i ograničenja studije.

Zaključak u kratkim crtama mora da odbaci ili potvrdi pogled na problem koji je naveden u Uvodu. Zaključci treba da proizilaze samo iz vlastitih rezultata i da ih čvrsto podržavaju. Uzdržati se uopštenih i nepotrebnih zaključivanja. Zaključci u tekstu moraju suštinski odgovarati onima u Sažetku.

5. Literatura. Literatura se u tekstu označava arapskim brojevima u uglastim zagradama, prema redosledu pojavljivanja. Izbegavati veliki broj citata u tekstu. Za naslove koristiti skraćenice prema *Index Medicus*-u (http:// www.nlm.nih.gov/tsd/serials/lji.html). U popisu citirane literature koristiti Vankuverska pravila koja precizno određuju redosled podataka i znake interpunkcije kojima se oni odvajaju, kako je u nastavku dato pojedinim primerima. Navode se svi autori, a ukoliko ih je preko šest, navesti prvih šest i dodati et al.

Članci u časopisima:

∗ *Standardni članak*

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

∗ *Organizacija kao autor*

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

∗ *Nisu navedena imena autora*

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

∗ *Volumen sa suplementom*

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

∗ *Sveska sa suplementom*

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

∗ *Sažetak u Časopisu*

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

Knjige i druge monografije:

∗ *Jedan ili više autora*

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

∗ *Urednik(ci) kao autor*

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

∗ *Poglavlje u knjizi*

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

∗ *Rad u zborniku radova*

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

∗ *Disertacije i teze*

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

Elektronski materijal

∗ *Članak u Časopisu u elektronskoj formi*

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

∗ *Monografije u elektronskoj formi*

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

∗ *Kompjuterski dokument (file)*

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

6. Prilozi (tabele, grafikoni, sheme i fotografije).

Dozvoljeno je najviše šest priloga!

– Tabele, grafikoni, sheme i fotografije dostavljaju se na kraju teksta rukopisa, kao posebni dokumenti na posebnim stranicama.

– Tabele i grafikone pripremiti u formatu koji je kompatibilan sa programom *Microsoft Word for Windows.*

– Slike pripremiti u JPG, GIF TIFF, EPS i sl. formatu

– Svaki prilog numerisati arapskim brojevima, prema redosledu njihovog pojavljivanja u tekstu.

– Naslov, tekst u tabelama, grafikonima, shemama i legendama navesti na srpskom i na engleskom jeziku.

– Objasniti sve nestandardne skraćenice u fusnotama koristeći sledeće simbole: *, †, ‡, §, ||, ¶, **, ††, ‡‡.

– U legendama mikrofotografija navesti korišćenu vrstu bojenja i uvećanje na mikroskopu. Mikrofotografije treba da sadrže merne skale.

– Ukoliko se koriste tabele, grafikoni, sheme ili fotografije koji su ranije već objavljeni, u naslovu navesti izvor i poslati potpisanu izjavu autora o saglasnosti za objavljivanje.

– Svi prilozi biće štampani u crno-beloj tehnici. Ukoliko autori žele štampanje u boji potrebno je da snose troškove štampe.

7. Slanje rukopisa

Prijem rukopisa vrši se u elektronskoj formi na stranici: **aseestant.ceon.rs/index.php/medpreg/**. Da biste prijavili rad morate se prethodno registrovati. Ako ste već registrovani korisnik, možete odmah da se prijavite i započnete proces prijave priloga u pet koraka.

8. Dodatne obaveze

Ukoliko autor i svi koautori nisu uplatili članarinu za Medicinski pregled, rad neće biti štampan. Radovi koji nisu napisani u skladu sa pravilima Medicinskog pregleda, neće biti razmatrani. Recenzija će biti obavljena najkasnije u roku od 6 nedelja od prijema rada. Uredništvo zadržava pravo da i pored pozitivne recenzije donese odluku o štampanju rada u skladu sa politikom Medicinskog pregleda. Za sva dodatna obaveštenja obratiti se tehničkom sekretaru:

Društvo lekara Vojvodine
Vase Stajića 9
21000 Novi Sad
Tel. 021/521 096; 063/81 33 875
E-mail: dlv@neobee.net

INFORMATION FOR AUTHORS

Medical review publishes papers from various fields of biomedicine intended for broad circles of doctors. The papers are published in Serbian language with an expanded summary in English language and contributions both in Serbian and English language, and selected papers are published in English language at full length with the summary in Serbian language. Papers coming from non-Serbian speaking regions are published in English language. The authors of the papers have to be Medical Review subscribers.

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

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

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

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

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

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

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

7. History of medicine – up to 10 pages – deals with history in the aim of providing continuity of medical and health care culture. They have the character of professional articles.

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

Preparation of the manuscript

The covering letter:

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

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

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

The manuscript:

Use Microsoft Word for Windows to type the text. The text must be typed in font Times New Roman, page format A4, space 1.5 (for tables as well), borders of 2.5 cm and font size 12pt. The manuscript should contain the following elements:

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

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

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

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

– review papers should have the introduction, subtitles corresponding to those in the paper and conclusion. It is to be followed by up to 10 Key Words from the list of Medical Subject Headings, MeSH of the American National Medical Library.

3. The summary in Serbian language. The summary in Serbian should be the translation of the summary in English, it should be structured in the same way as the English summary, containing up to 250 words, without any abbreviations.

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

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

– The text should be written in the spirit of Serbian language, without unnecessary abbreviations, whose first mentioning must be explained by the full term they stand for. Abbreviations should not be used in the title, summary and conclusion. Only commonly accepted abbreviations (such as DNA, MRI, NMR, HIV…) should be used. The list of abbreviations used in the text, together with the explanation of their meaning, is to be submitted at the last page of the manuscript.

– All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C). and pressure in mmHg.

– No names, initials or case history numbers should be given.

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

Material and methods should contain data on design of the study (prospective/retrospective, eligibili-

ty and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

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

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

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

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

Articles in journals

∗ *A standard article*

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

∗ *An organisation as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

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

∗ *An issue with supplement*

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

∗ *A summary in a journal*

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

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

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

∗ *A chapter in a book*

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

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

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

∗ *Monographs in electronic format*

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

∗ *Acomputer file*

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

6. Attachments (tables, graphs, schemes and photographs). The maximum number of attachments allowed is six!

– Tables, graphs, schemes and photographs are to be submitted at the end of the manuscript, on separate pages.

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

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

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

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

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

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

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

7. Manuscript submission

The manuscripts can be submited on the web-page: **aseestant.ceon.rs/index.php/medpreg/**. The authors have to register with the journal prior to submitting their manuscript, or, if already registered, they can simply log in and begin the 5 step process.

8. Additional requirements

If the author and all co-authors have failed to pay the subscription for Medical Review, their paper will not be published.

Papers which have not met the criteria of Medical Review will not be taken into consideration. The Editorial review of the paper will be announced not later than six weeks after the submission of the paper. The Editorial Board reserves the right to make a decision regarding the publication of the paper according to the policy of Medical Review even if the review is positive. Contact the technical secretary for all additional information:

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