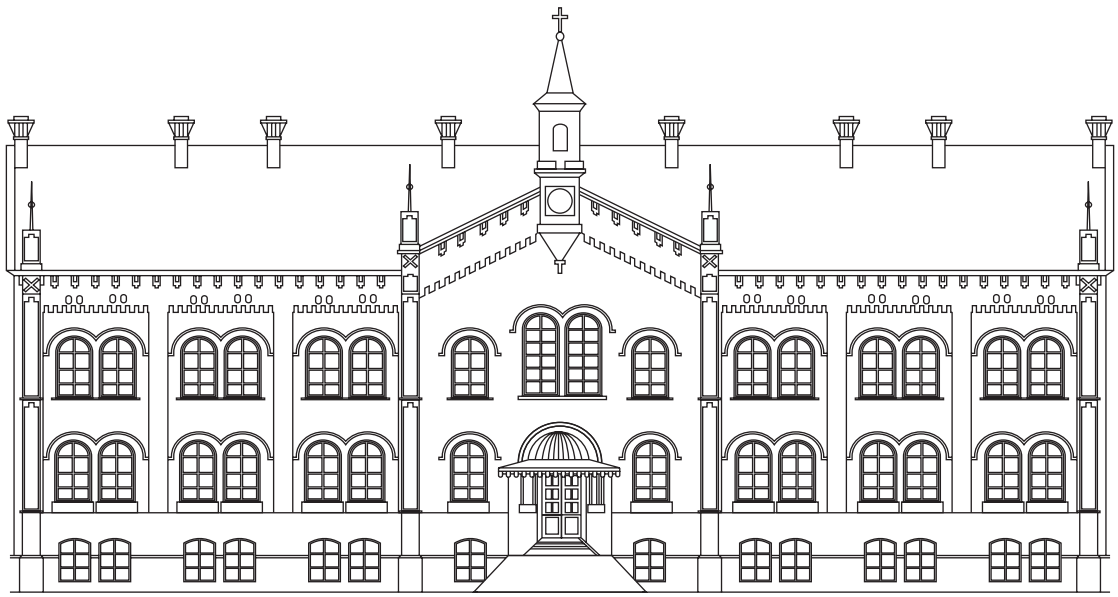
SRP ARH CELOK LEK

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

COBISS.SR-ID 3378434
UDC 61(497.11)

СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА



SERBIAN ARCHIVES
OF MEDICINE

JOURNAL OF THE SERBIAN MEDICAL SOCIETY

VOLUME 148 · JULY–AUGUST 2020 · ISSUE 7–8

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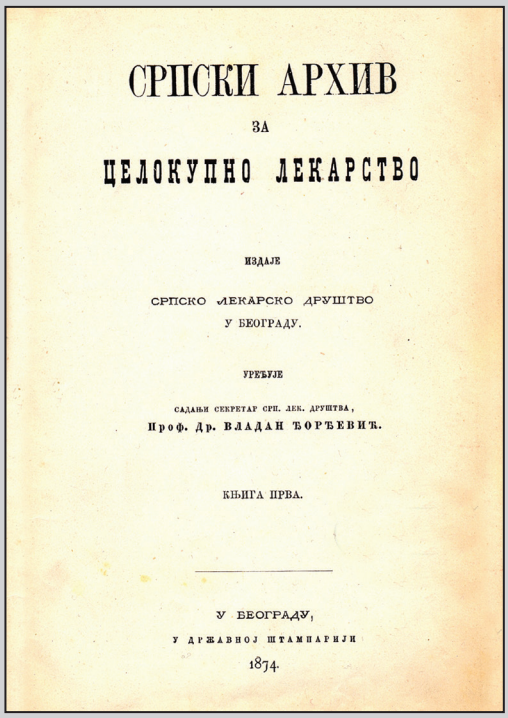

СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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У БЕОГРАДУ.

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У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

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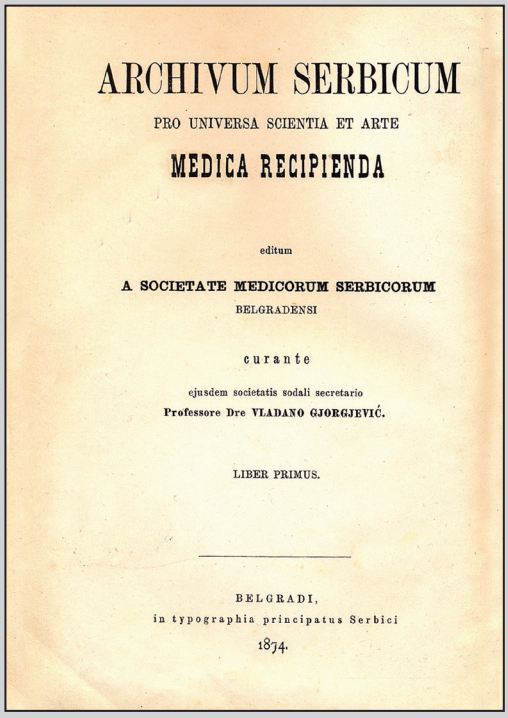

ARCHIVUM SERBICUM

PRO UNIVERSA SCIENTIA ET ARTE

MEDICA RECIPIENDA

editum

A SOCIETATE MEDICORUM SERBICORUM

BELGRADENSI

curante

ejusdem societatis sodali secretario

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LIBER PRIMUS.

BELGRADI,

in typographia principatus Serbici

1874.

The title page of the first journal volume in Latin

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

Српски архив за целокупно лекарство

ГОДИШТЕ 148. ЈУЛ-АВГУСТ 2020. СВЕСКА 7–8

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

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Штампање „Српског архива за целокупно лекарство" током 2020. године помогло је Министарство просвете, науке и технолошког развоја Републике Србије

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Отворен приступ

Штампано у Србији

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

Штампа: ЈП „Службени гласник", Београд

Тираж: 850 примерака

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

VOLUME 148 JULY–AUGUST 2020 ISSUE 7–8

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

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Serbian language editor: Divna Prodanović
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Cover & Logo: MaxNova Creative

Printed by: JP "Službeni glasnik", Belgrade

Circulation: 850 copies

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

The publishing of the Serbian Archives of Medicine during 2020 is supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Open Access

Printed in Serbia

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DOI: https://doi.org/10.2298/SARH190704018J
UDC: 616.314-78

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Analysis of working surface in new manual and rotary endodontic instruments (scanning electron microscopy)

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SUMMARY

Introduction/Objective The objective of this study is to use scanning electron microscopy (SEM) to analyze working surfaces of new manual and rotary endodontic instruments and to check possible existence of manufacture dirt particles or defects on the working surface.

Methods In this study, we used three sets of new manual instruments: K-File, KF (Dentsply Maillefer, Switzerland) and Hedstorm Files, HF (SybronEndo Co, USA) and three sets of mechanical Ni-Ti instruments – type K3 (SybronEndo Co, USA) and BioRaCe (FKG DENTAIRE Swiss Dental Products, Switzerland). The instruments were analyzed using SEM method at 170 × magnification while semi-quantitative energy dispersive x-ray analysis was used to determine chemical composition of dirt particles. Fisher test ($p < 0.05$) was applied in statistical analysis.

Results Results showed that none of the instruments were defect-free. The most common defect type was the presence of metal strips, which were noticed at the surface of all tested instruments. Debris was present on all manual and only one type of mechanical instruments, K3 (39% in the apical and 33% in the middle third). Fretting was noticed in all manual KF and all mechanical instruments of the K3 group. Pitting was common in all manual instruments, KF (33% in the apical and 39% in the middle third) and HF (11% in the apical and 6% in the middle third). Corrosion of the working surface, metal flash, and disruption of the cutting edge were marked only in the KF group.

Conclusion Manufacture defects were noticed in all instruments and the most common type of irregularity were metal strips. Electropolished surface of BioRaCe instruments showed no debris of organic origin.

Keywords: stainless-steel manual instruments; Ni-Ti rotary instruments; defects; SEM; debris

INTRODUCTION

Clinical endodontics implies the so-called "cleaning and shaping" concept, with cleaning the complex endodontic space from vital, necrotic, or infected pulp tissue, bacteria and their products and shaping while preserving the original form of the radix canal [1, 2, 3].

Chemomechanical root canal treatment is usually performed with manual endodontic instruments (made of stainless steel or Ni-Ti alloy) or mechanical Ni-Ti rotary endodontic instruments with adequate and abundant irrigation of the canal system. The use of rotary Ni-Ti files in endodontic practice reduces the possibility of errors during instrumentation, such as obstruction, steps, transportation, and perforation of the canal wall [4].

Even though Ni-Ti rotary instruments are more efficient when compared to manual in almost every aspect (speed, simplicity, and uniformity of instrumentation), their drawback is the possibility of deformation and fracture during instrumentation, most likely due to inadequate use [5].

A fractured instrument is a serious threat to treatment, irrigation, and filling of root canals and it may significantly affect the outcome of endodontic treatment [6]. Numerous studies researched the factors which can influence deformation and fracture of manual and mechanical endodontic instruments: Parashos et al. [7], Di Fiore [8], Shen et al. [9], Kosti et al. [10], Priyanka et al. [11], Gil et al. [12]. In 2018, Boutsioukis and Lambrianidis [13] made an outline of all these factors and grouped them into four categories: operator-related factors, anatomy-related factors, instrument-related factors and technique/use-related factors.

It is confirmed that endodontic instruments, due to their design and different manufacture process, may significantly impact deformation and fracture during root canal instrumentation [10]. Most of new endodontic instruments are non-sterile and can contain various metal debris, dirt particles, and epithelial cells on their surface. The process of production of stainless steel files can lead to the presence of small metal scraps that are more or less retained at the work surfaces of the files [14].

Received • Примљено: July 4, 2019
Revised • Ревизија: February 1, 2020
Accepted • Прихваћено: March 6, 2020
Online first: March 10, 2020

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Stainless steel endodontic instruments are usually made by twisting of various steel profiles by longitudinal axis, thus forming blades from vertical wire edges [15]. Ni-Ti rotary instruments are used in endodontic procedure due to their good mechanical properties, biocompatibility, ductility, corrosion resistance, low elastic modulus, and special characteristics such as super-elasticity and shape memory effect [16]. Production of Ni-Ti mechanical endodontic instruments is more complex when compared to the process of steel instrument manufacture. Due to memory property of the Ni-Ti alloy, the majority of instruments are manufactured by engraving on a milling machine rather than by twisting [15]. Despite the fact that top-notch computer technology is used to manufacture very complicated Ni-Ti instruments (computer-aided design and computer-aided manufacturing – CAD-CAM), surface defects including fretting, cracks, pitting, and dirt are very common [15]. Irregularities at the instrument surface might increase its vulnerability to fracture. Surface defects seem to be points of tension and can cause initiation and spread of cracks, thus potentially highly contributing to possible fractures during instrument activation [13].

The aim of this study is to use a scanning electron microscope (SEM) to analyze working surfaces of new manual and mechanical endodontic instruments and to check possible existence of manufacture impurities or defects on the working surface.

METHODS

This research implied the use of three basic sets (each set consisting of six instruments) of new manual stainless steel instruments: K-File – KF (Dentsply Maillefer, Ballaigues, Switzerland) and Hedstorm Files – HF (SybronEndo Co, Orange, CA, USA) and three basic sets (each set consisting of six instruments) of machine endodontic instruments, type K3 (SybronEndo Co) and BioRaCe (FKG DENTAIRE Swiss Dental Products, La Chaux-de-Fonds, Switzerland). SEM analysis (JEOL JSM-6610LV, Tokyo, Japan) was carried out at the SEM-EDS (energy dispersive X-ray spectroscopy) laboratory of the Faculty of Mining and Geology, University of Belgrade, without any prior preparation.

Microphotographs are realized at 170 × magnification, but in case of noticeable changes on the instruments, for the purpose of more detailed analysis, they are carried out at magnification of up to 800 ×. The apex and the middle third of the instruments were analyzed from two different directions and each side of instrument was analyzed by three images.

Analysis of different irregularities and omissions during manufacture process implied the criteria proposed by Eggert et al. [17]: score 1 – no visible defect; score 2 – pitting; score 3 – fretting; score 4 – micro fractures; score 5 – complete fracture; score 6 – metal flash; score 7 – metal strips; score 8 – blunt cutting edge; score 9 – disruption of cutting edge; score 10 – corrosion; score 11 – debris. Qualitative analysis was performed, though obtained results were not quantified. Semi-quantitative Energy Dispersive X-Ray Analysis (EDXS) determined chemical composition of the found dirt particles.

The study was approved by the Ethics Commission of the School of Dental Medicine, University of Belgrade (36/6).

Statistical analysis of obtained results was performed using the Fisher's test ($p < 0.05$).

RESULTS

Obtained results are presented in Tables 1 and 2 and Figures 1–9.

The results showed that all tested instruments had some kind of defect on their working surface. New manual and mechanical instruments did not show any signs of micro fractures, fractures, or blunt cutting edges (Table1).

Metal strips were the most common defect type noticed on the surface of all tested instruments (Figure 1).

In K3 rotary group of Ni-Ti instruments, the presence of this contamination was 89% in the apical and 78% in the middle third. In all other groups, this defect was present in 100% of the cases (Table 1, Figure 2). Fisher's test statistical analysis did not show any significant differences between the tested instruments and their apical or middle thirds.

Analysis of SEM microphotographs determined the contamination of the working surfaces of the tested instruments, and subsequent EDXS defined the chemical composition of the contamination (Figure 3, Table 2). Thus, we divided instruments into two types – instruments contaminated

Table 1. Presence of defects and dirt on the working surface of the tested instruments

Defects	KF		HF		K3		BioRaCe	
	Apical third	Middle third	Apical third	Middle third	Apical third	Middle third	Apical third	Middle third
Pitting	6	7	2	1	/	/	/	/
Fretting	18	18	/	/	18	18	/	/
Metal-flash	2	1	/	/	/	/	/	/
Metal-strips	18	18	18	18	16	14	18	18
Disruption of cutting edge	1	/	/	/	/	/	/	/
Corrosion	2	3	/	/	1	1	/	/
Debris	18	18	10	10	7	6	/	/

HF – Hedstorm files; KF – K-file

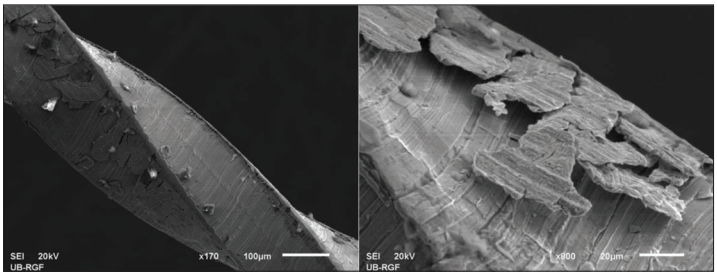

Figure 1. (a) Scanning electron microscopy analysis of a K-File instrument working surface (middle third) with metal strips and fretting (magnification 170 ×); (b) detail from picture (a), metal strips on working surface of the K-File instrument (magnification 800 ×)

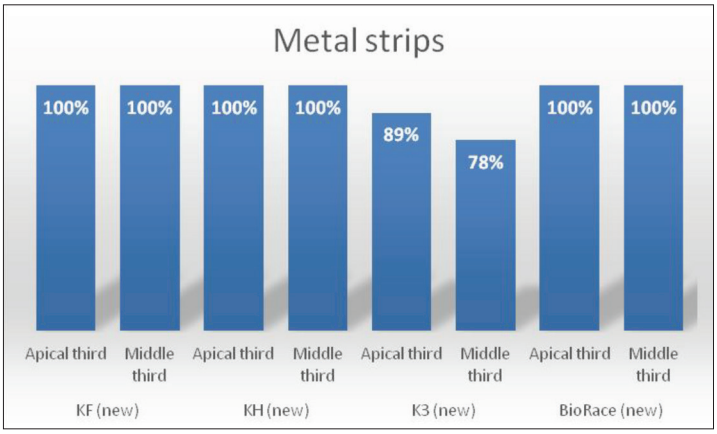

Figure 2. The presence of metal strips on the working surface of the tested instruments

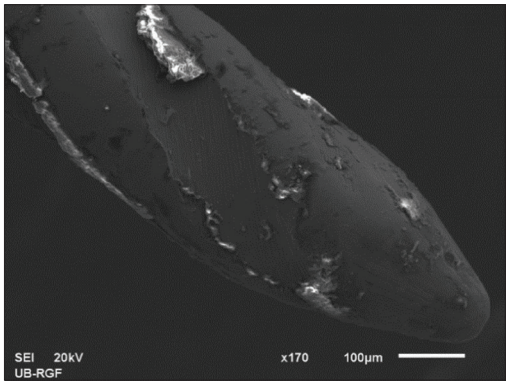

Figure 5. Scanning electron microscopy analysis of the working surface of K3 instruments (apical third) with metal strips, fretting, and debris (magnification 170 ×)

Table 2. Chemical composition of impurities (spectrums 1 and 2) and clean K-3instrument (spectrum 3); chemical analyses are given in wt.% and are normalized to 100 wt.%

Spectrum	C	N	O	Na	Mg	Al	Si	S	Cl	K	Ca	Ti	Fe	Ni	Total
1	47.7	0	37.4	2.3	1	0.2	2.5	0.9	3.6	1.6	1.1	0.6	0	1.1	100
2	49.9	0	34.1	0.7	0.6	0.4	1.8	0.3	0.5	0.4	7.6	2	0	1.7	100
3	0	0	0	0	0	0	0	0	0	0	0	44.3	0	55.7	100

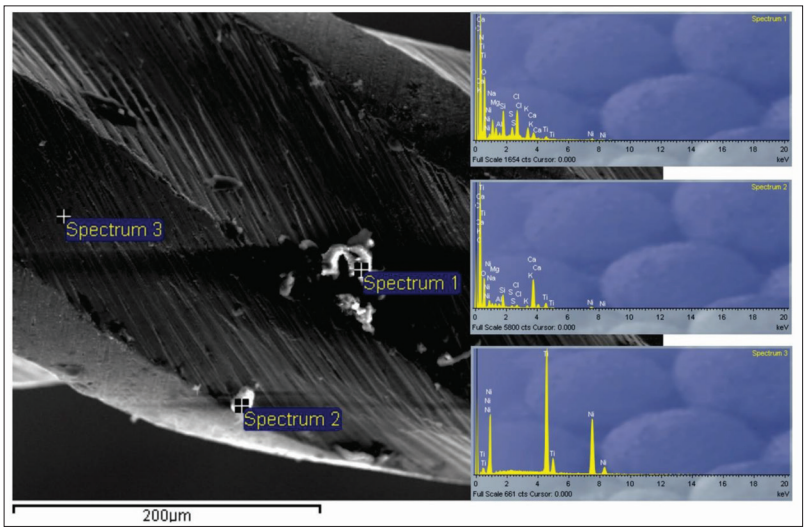

Figure 3. Energy-dispersive X-ray spectroscopy analysis

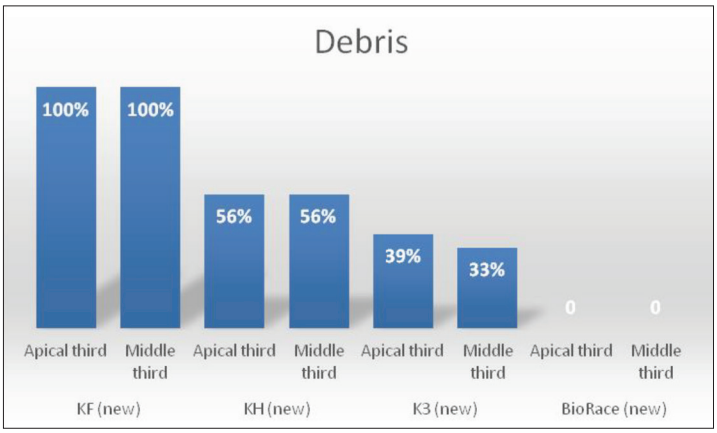

Figure 4. The presence of debris on the working surface of the tested instruments

with metal strips and instruments with debris.

Debris was present in all manual instruments: KF instruments (100% in the apical and middle third) and HF instruments (56% in the apical and middle third). This contamination type was marked in only one type of mechanical Ni-Ti instruments – K3 (39% in the apical and 33% in the middle third), while BioRaCe group did not show any presence of debris. (Table 1, Figure 4). While comparing debris in different manual instruments (KF and HF), a statistically significant difference was noticed ($p = 0.0029$ in the apical and $p = 0.0029$ in the middle third). Also, among different mechanical Ni-Ti instruments (K3 and BioRaCE), there was a statistically significant difference in debris contamination; ($p = 0.076$ in the apical and $p = 0.0191$ in the middle third). Statistically significant difference was also noticed when all manual (KF and KH) instruments were compared to all mechanical rotary Ni-Ti (K3 and BioRaCe) instruments: ($p = 0.0001$in the apical and $p = 0.0001$ in the middle third).

Fretting caused by manufacture was noticed in all manual instruments of the KF group and all mechanical Ni-Ti instruments of the K3 group, while manual HF and mechanical BioRaCe instruments did not show any signs of fretting (Table 1, Figure 5). While comparing fretting on different manual instruments (KF and HF), a statistically significant difference was noticed in the apical and the middle third ($p = 0.0001$ in the apical and $p = 0.0001$ in the middle third). In addition, among mechanical Ni-Ti instruments (K3 and BioRaCE), there was a significant statistical difference in fretting on the working surface ($p = 0.0001$ in apical and $p = 0.0001$ in middle third). A statistically significant difference in

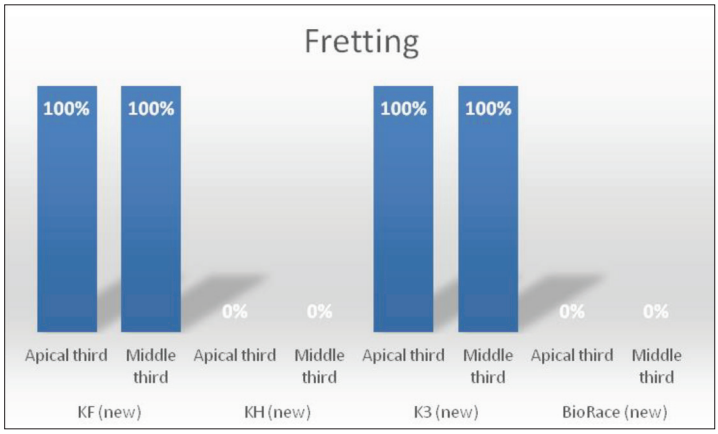

Figure 6. The presence of fretting on the working surface of tested instruments

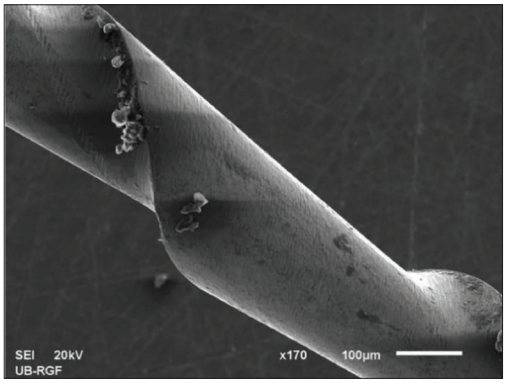

Figure 8. Scanning electron microscopy analysis of the working surface of a Hedstorm file instrument (middle third) with pitting and debris (magnification 170 ×)

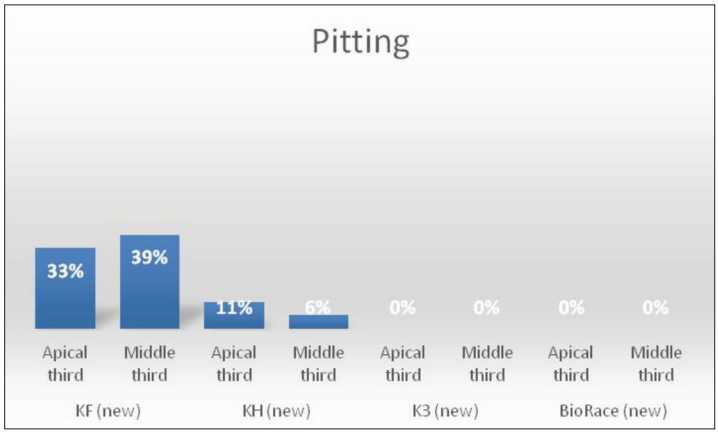

Figure 7. The presence of pitting on the working surface of the tested instruments

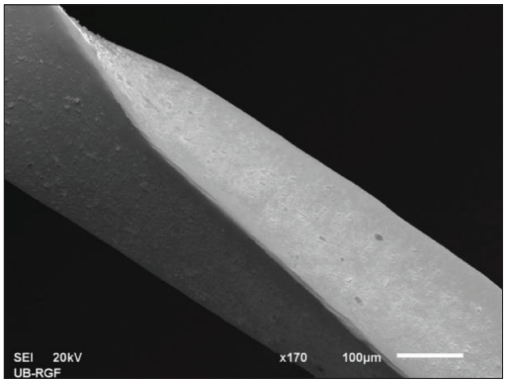

Figure 9. Scanning electron microscopy analysis of theworking surface of a BioRaCe instrument (middle third) with a small number of metal strips on the electropolished surface (magnification 170 ×)

fretting was not marked when all manual instruments (KF and HF) were compared to all mechanical rotary Ni-Ti (K3 and BioRaCe) instruments (Figure 6).

Pitting was marked in the apical and the middle third of the manual instruments, KF (33% in the apical and 39% in the middle third) and HF (11% in the apical and 6% in the middle third), though none of the groups of Ni-Ti instruments (Figure 4) showed any signs of pitting (Table 1, Figures 7 and 8). While comparing pitting in various manual instruments (KF and HF), a statistically significant difference was noticed in the apical third ($p = 0.0051$), which was also marked in the middle third ($p = 0.0045$). Among tested mechanical Ni-Ti instruments, there was no statistically significant difference in pitting (K3 and BioRaCE). Statistically significant difference in pitting was noticed by mutual comparison of all manual (KF and HF) and all mechanical rotary (K3 and BioRaCe) instruments ($p = 0.0051$ in the apical and $p = 0.0051$ in the middle third).

Corrosion of the working surface, metal flash, and disruption of cutting edge were marked only in KF instruments (corrosion – 11% in the apical and 17% in the middle third; metal flash – 11% in the apical and 6% in the middle third; disruption of cutting edge – 2% in the apical third) (Table 1) In the second group of KH manual instruments and in both groups of mechanical NI-Ti instruments (K3 and BioRaCe), corrosion, metal flash, and disruption of the cutting edge were not detected (Figure 9).

DISCUSSION

Above all, success of endodontic therapy depends on proper instrumentation and biomechanical cleaning of the root canal. Design of endodontic instruments, their metallurgical characteristics and surface may complicate endodontic treatment in case the instrument deforms or fractures during use. It is proved that manufacture defects might cause fracture of new instruments even during their first clinical use [18].

Results of this study showed that all analyzed instruments had at least one (or more) different defects prior to any use. Defects found on new instruments only confirm the difficulties in manufacture of specific endodontic instruments, and issues that may arise during their clinical use. New processes of instruments' manufacture that aim at improving used materials, minimizing inherent defects and increasing the resistance of instruments to deformation and fracture very often remain undisclosed, usually due to manufacturers' originality and patents [19].

Fretting caused by manufacture process (due to milling), was marked in almost all tested manual steel instruments. Manufacture process of rotary Ni-Ti endodontic instruments is much more complex than the process of stainless steel instruments manufacture since they have to be mechanically treated instead of just being twisted as steel instruments. As a result, the problem is in this case even more significant.

Attempts to conventionally manufacture Ni-Ti instruments by twisting the wire would probably result in their fracture; therefore, shaping of these instruments is achieved by even pressure from a series of rollers applied to the Ni-Ti wire, thus defining its shape, conicity, form of blade edges, i.e. design characteristics of such instruments. Difficulties during manufacture of rotary endodontic instruments and elimination of surface irregularities such as traces of milling and metal flash (especially on blades) which might compromise efficiency of instrument blade and potentially cause problems related to corrosion or fracture [18].

Presence of metal strips, noticed in all the tested groups with the score of 100% apart from group K3 (78% in the middle and 89% in the apical third), confirms the complexity of endodontic instrument manufacture.

Pitting on the working surface of an instrument was noticed only in case of manual steel instruments (KF, HF), and it could be explained by the specific technological process of manufacture, as is the case with the presence of metal flash and defects on the cutting edge in the KF group.

Manufacturers are constantly in search of metallurgical modifications of the Ni-Ti alloy, trying to find a perfect solution that would increase the performance in terms of super-elasticity and memory properties of the alloy [20]. During the manufacturing process, problems might occur due to the quality of the Ni-Ti alloy since particles of oxide might stay incorporated in the alloy during the manufacturing process. Instrumentation and stress propagation might impact these points and make nucleation spots for the development of micro-fractures and possible instrument defects [21].

Composition of the Ni-Ti alloy used for the construction of endodontic instruments is 56% (weight) of nickel and 44% (weight) of titanium, thus achieving their equiatomic relation. Despite the fact that only one manufacturer (Dentsply Maillefer Instruments) has revealed the complete composition and detailed technological process of rotary instruments manufacture, it is assumed to be the only relation between the elements that gives alloy its super-elastic characteristic. Variation of the Ni-Ti alloy composition enables the manufacture of instruments with different properties: either super-elastic alloy or better memory property. Increasing the percentage of nickel or replacing the elements in traces (e.g. cobalt) results in decreased temperature of transformation. Increase in annealing temperature increases the transformation temperature as well [18].

Results of this study showed the presence of debris in all instruments apart from the BioRaCe group of instruments. This is explained by the existence of electrochemically treated working surface of BioRaCe instruments, thus achieving better cutting edge efficacy and resistance to wear and tear. Electrochemical polishing decreases irregularities at the surface of instruments, thus decreasing the accumulation of organic debris [22, 23].

In order to decrease surface defects and improve resistance of endodontic instruments, various methods are applied: alloy implantation process by argon, boron, or nitrogen ions, thermal nitridation (coating of instruments with a layer of titanium nitride), plasma immersion, deep dry cryogenic treatment and electro polishing [20, 22–25]. Many researchers were focused on increasing efficiency and flexibility and decreasing resistance to cyclic fatigue. As a result, they suggest additional thermo-mechanical treatment of the raw Ni-Ti alloy or even finished instruments [25, 26, 27]. The process of vapor accumulation enables treatment of Ni-Ti instruments with a layer of titanium nitride, thus achieving better cutting-edge efficiency and resistance to corrosion [27]. Memory-shape alloys based on the equiatomic Ni-Ti composition have great importance in the development of modern endodontic rotary instruments [16]. It is necessary and very important to be familiar with metallurgical characteristics of the Ni-Ti alloy in order to use their clinical potential in the best possible way and minimize frustration and fear that many dentists have that such instruments could fracture during root canal treatment [28, 29].

CONCLUSION

Based on the results of this research, it is concluded that all tested instruments showed manufacture defects (one or more), and that the most common defect type was the presence of metal strips on working surfaces of instruments. Due to the presence of debris on working surfaces of instruments, it is necessary to sterilize the instruments before initial use. Electropolished surfaces of BioRaCe instruments showed no presence of organic debris. These facts could be a warning sign to all practitioners – before initial use, the working surface of instruments should be well analyzed in order to avoid possible complications during endodontic treatment.

ACKNOWLEDGEMENT

The research from this article is part of the doctoral dissertation titled "Analysis of deformation and fragment breakage of rotary nickel-titanium instruments after preparation of different root canal systems," by Milica Jovanović-Medojević).

Conflict of interest: None declared.

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Анализа површине радног дела нових ручних и машинских ендодонтских инструмената (скенирајућа електронска микроскопија)

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САЖЕТАК

Увод/Циљ Циљ овог рада је био да се применом скенирајуће електронске микроскопије (СЕМ) анализирају површине нових ручних и машинских ендодонтских инструмената и провери евентуално постојање производних нечистоћа или дефеката на радном делу.

Методе У истраживању су коришћена по три сета нових ручних инструмената: *K-File*, *KF* (*Dentsply Maillefer*, Швајцарска) и *Hedstorm Files*, *HF* (*SybronEndo Co*, САД) и по три сета машинских *Ni-Ti* инструмената, типа К3 (*SybronEndo Co*) и *BioRaCe* (*FKG DENTAIRE Swiss Dental Products*, Швајцарска). Инструменти су подвргнути СЕМ анализи са увећањем 170×, а семиквантитативном, *EDXS* анализом утврђиван је хемијски састав нечистоће. Статистичка анализа је урађена применом Фишеровог теста ($p < 0,05$).

Резултати Резултати су показали да не постоји ниједан инструмент без дефекта. Најучесталији тип дефекта је било присуство металних опиљака, који су уочени на површини свих испитиваних инструмената. Дебри је уочен на свим ручним и само на једном типу машинских инструмената, К3 (39% на апикалној и 33% на средњој трећини). Жлебови су уочени на свим ручним *KF* и свим машинским инструментима групе К3. Присуство удубљења забележено је код ручних инструмената, *KF* (33% апикална и 39% средња трећина) и *HF* (11% апикална и 6% средња трећина). Корозија радне површине, појава углачане површине и прекид сечивне ивице су уочени само у групи *KF*.

Закључак На свим испитиваним инструментима су уочени производни дефекти, а најучесталији тип неправилности су метални опиљци. На електрополираној површини инструмената *BioRaCe* није уочено присуство органског дебрија.

Кључне речи: челични ручни инструменти, *Ni-Ti* ротирајући инструменти, дефекти, СЕМ, дебри

DOI: https://doi.org/10.2298/SARH190305008A
UDC: 616.314-77/-78

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Evaluation of enamel surface after bracket debonding and adhesive removal with six different methods

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SUMMARY

Introduction/Objective After an orthodontic brackets debonding procedure it is necessary to remove any residual adhesive from the tooth surface, as this is a common cause of enamel damage. The aim of this study is to evaluate the enamel surface after the application of six different methods of adhesive removal following brackets debonding, as well as to compare the duration of these procedures.

Methods For the purpose of this study, 245 human premolars were extracted as part of the orthodontic treatment. Metal brackets were bonded to 210 human premolars with the Aspire adhesive system. After the debonding of brackets, the samples were divided into six groups according to the adhesive removal method applied: tapered fissure tungsten carbide bur, round tungsten carbide bur, composite bur, abrasive disc, adhesive removing pliers, and ultrasonic scaler. Out of 245 premolars, 35 served as a control group. The duration of adhesive removal was recorded. Enamel damages were estimated according to the enamel surface index on the scanning electron microscopy images.

Results Maximum preservation of the enamel surface was accomplished by using a composite bur (1.08). The application of abrasive disc was significantly less time-consuming in comparison to the application of a composite bur ($p < 0.01$) and an ultrasonic scaler ($p < 0.01$).

Conclusion The most harmful for the enamel surface was the use of an ultrasonic scaler as well as a round tungsten carbide bur. Adhesive removal done by an abrasive disc thus proved one of the least damaging and the least time-consuming methods.

Keywords: adhesive removal; enamel damage; enamel surface index

INTRODUCTION

The main goal of orthodontic treatment in general is to achieve stability of occlusion and to improve dentofacial aesthetics. The primary concern is to ensure that no permanent damage on the tooth enamel surface has occurred after the completion of multibracket appliance treatment. The optimal method of brackets debonding depends on the type of brackets used in a therapy [1]. Following this procedure, it is necessary to remove any remaining resin from the teeth, which can often cause enamel surface irregularities. The amount of enamel loss may be determined by clinicians' manual abilities and instruments used in clean-up procedures [2, 3]. Resin remnants on the tooth surface could cause enamel discoloration and dental plaque accumulation. Some studies show that the type of adhesive systems and resin removal procedures are responsible even for tooth color changes [4]. Previous studies refer to a variety of instruments that can be used for adhesive removal after brackets debonding. Rotary instruments (diamond, carbide burs, and abrasive discs), hand instruments (pliers and scalers), and ultrasonic scalers are among the most widely used [5–10]. An optimal procedure for adhesive removal that leaves no damage to the enamel surface has not been accepted yet [5]. Recently, in some studies, lasers and sandblasting have been considered as alternative methods for removing the remaining adhesive [11, 12]. Several studies conclude that carbide burs cause less damage to the enamel if compared to fine diamond burs, while still causing greater damage than the composite burs [13, 14]. The visual assessment of the enamel surface is often performed to evaluate and define a type of damage occurred during the adhesive removal procedures [15–18].

Multi-step systems, including fine and superfine tungsten carbide burs or abrasive disks, are commonly applied as part of the adhesive removal procedures followed by different types of polishers for smoothing the enamel surface [19]. These procedures leave no scratches on the enamel surface, even if they have been caused by tungsten carbide burs or abrasive discs. The previous studies focused mostly on different methods for adhesive removal, including the polishers.

Received • Примљено: March 5, 2019
Revised • Ревизија: January 23, 2020
Accepted • Прихваћено: January 28, 2020
Online first: January 31, 2020

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The purpose of the *in vitro* study was to examine the enamel surface, after the application of six different methods for adhesive removal following brackets debonding procedure, as well as to compare their effects on enamel surface topography and the time required for adhesive removal.

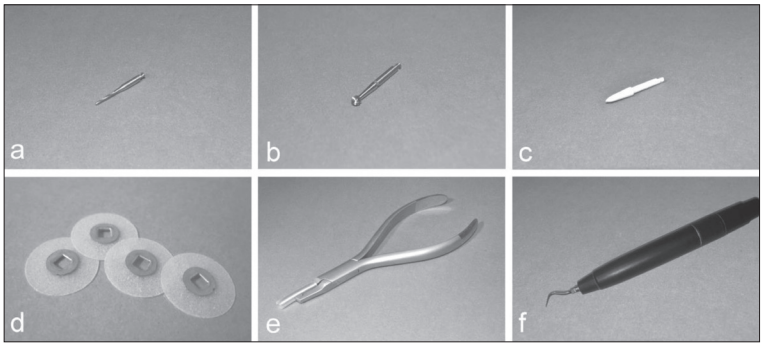

Figure 1. Methods for adhesive removal: a – tapered fissure tungsten carbide bur with a round end; b – round tungsten carbide bur; c – composite bur; d – abrasive discs; e – adhesive removing pliers; f – ultrasonic scaler

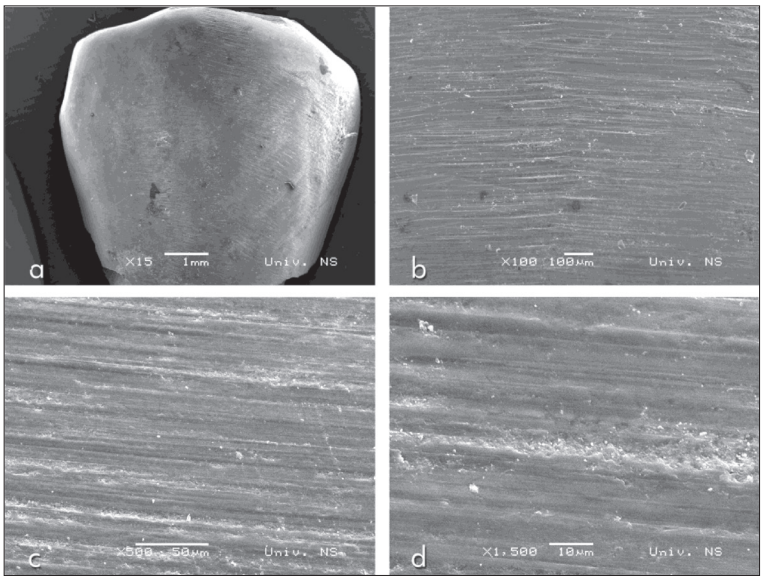

Figure 2. Scaning electron microscope images of enamel surface after residual adhesive removal with a 12-fluted tapered fissure tungsten carbide bur with a round end: a – 15 × magnification; b – 100 × magnification; c – 500 × magnification; d – 1,500 × magnification

METHODS

This study has been approved by the local Institutional Review Board (protocol number 01-2127-10/15). A total of 245 human premolars were extracted for the purpose of orthodontic treatment and consequently appropriately prepared and stored in 0.9% NaCl containing 0.1% thymol according to ISO TS 11405:2015, for no longer than three months [20]. All the teeth specimens were examined with a 10 × magnifying lens (Olympus, SZX 9, Tokyo, Japan) in order to assess whether the collected samples fulfilled the major criteria: an intact oral and buccal surface without visible damages, carious lesions and chemical exposures. Out of the 245 specimens being surveyed, 35 served as an untreated control group [21]. Subsequently, the middle third of the buccal surfaces of 210 premolars was etched for 20 seconds with 38% phosphoric acid (OC Orthodontics, McMinnville, OR, USA). After they had been rinsed with water for 30 seconds and air dried to frosty-white appearance, the buccal surfaces of the teeth were treated with the Aspire primer 7GM (OC Orthodontics) and light-cured for 10 seconds with a LED curing unit (Woodpecker, Guilin, China). Mesh pads of metal brackets Ortho Organizer Elite OptiMIM (Henry Schein® Orthodontics, Carlsbad, CA, USA) were removed by a dull round end tapered multifluted tungsten carbide bur at high speed to determine the mode of bond failure at the bracket base-adhesive interface, allowing the complete amount of resin to be left on the enamel surface of all 210 teeth [22]. A small amount of Aspire resin 5GM (OC Orthodontics) was put on the bases of metal brackets. The brackets were then pressed firmly onto the prepared enamel surface to extrude the excess of composite material around them, which was removed with a tip of the probe. A light curing procedure was performed for 40 seconds according to the manufacturer's instructions [21]. All the samples were left in the artificial saliva for 48 hours, allowing complete polymerization of the adhesive as reported in similar studies [3, 22]. The brackets were debonded using debonding Ixion pliers (DB Orthodontics, Silsden, UK). Furthermore, the teeth samples were divided into six groups (35 teeth in each group), depending on the method used for remaining adhesive removal: Group A – a 12-fluted round end tapered fissure tungsten carbide bur (DB Orthodontics) at 32,000 rpm, Group B – a 12-fluted round tungsten carbide bur (H1SE 204031, Komet Dental, Lemgo, Germany) at 8,000 rpm, Group C – a composite bur (Stainbuster Jumbo, DB Orthodontics) at 40,000 rpm, Group D – an abrasive disc (sand medium abrasive disc, E.C. Moore Co., Dearborn, MI, USA) at 16,000 rpm, Group E – adhesive removing pliers (DB Orthodontics), Group F – an ultrasonic scaler (Sirosonic L scaler, Sirona Dental Systems, Long Island city, NY, USA) (Figure 1). All bonding, debonding and clean-up procedures were carried out by the same operator to eliminate differences among operator's techniques [23]. Adhesive removal from the enamel surface after every third teeth in the study was performed with a new bur for rotary instruments in Groups A, B, C, and D, respectively [22]. The adhesive removal procedure duration was measured in seconds. Residual adhesive removal was fully verified under a dental chair operating light by the operator. The sample was prepared for scanning electron microscopy (JSM 6460 LV, JEOL Ltd., Tokyo, Japan), including a control group. For each specimen, four images were obtained (15 ×, 100 ×, 500 ×, 1,500 × magnification) (Figure 2). The evaluation of

enamel surface was performed by SEM, the enamel surface index (ESI) system being used in the process. ESI was introduced by Zachrison and Arthun, and estimated as in the following [16]:

Score 0 – Regular enamel surface without scratches; Visible intact perikymata;

Score 1 – Satisfactory enamel surface; Minor scratches and some healthy enamel;

Score 2 – Acceptable enamel surface, several deep scratches; Absent perikymata;

Score 3 – Defective enamel surface with several deep and course scratches and no perikymata;

Score 4 – Unacceptable enamel surface with very coarse, deep scratches, healthy enamel absent [16, 17].

It is fundamental to note that ESI evaluation was performed by an examiner who had no previous knowledge of the specific group the specimens belonged to, after one and after two weeks for each specimen. In a case of any discrepancy, the third assessment determined the final score [17].

Statistical analysis

The statistical package IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp. Armonk, NY, USA) and Microsoft Excel 2010 (Windows, Redmond, WA, USA) were used for data analysis. Descriptive results of ESI scores were calculated and expressed as frequencies, percentages, mean values, and standard deviations. The significant differences of the mean values of ESI scores and the duration of all six methods were determined by ANOVA with the F-value and the Fisher's test as well as by Tukey's post hoc test.

RESULTS

The results for ESI scores are shown in Table 1. For Groups A (tapered fissure tungsten carbide bur), C (composite bur) and D (abrasive disc), the ESI score 1 was predominant. The highest incidence of ESI score 2 was observed in Groups E (adhesive removing pliers) and F (ultrasonic scaler). The ESI score 3 was the most frequent in Group B (round tungsten carbide bur) and the ESI score 0 was found only in 35 premolars that served as a control group.

The lowest average value of ESI scores (1.08) was determined in Group C (composite bur), while the highest average value of ESI scores was determined in Group F (ultrasonic scaler, 2.42). The one-way ANOVA test showed statistically significant differences among the ESI scores of all six methods ($F(5.204) = 24.53$, $p < 0.01$) (Table 1). A post-hoc analysis (Tukey's post-hoc test) established different levels of statistically significant differences of ESI scores within the groups (Table 2). The mean values of ESI scores in Groups C (composite bur) and D (abrasive disc) showed a statistically significant difference compared to Groups B (round tungsten carbide bur), E (adhesive removing pliers), and F (ultrasonic scaler).

However, the most time-consuming method for adhesive removal was the application of the composite bur. It is significant to note that using the abrasive disc in the adhesive removal procedure was proved the least time-consuming method (Table 3 and 4).

DISCUSSION

From the results, it is clear that adhesive removal after brackets debonding has a great influence on enamel surface topography [24, 25]. Therefore, clinicians should apply an appropriate adhesive removal procedure, accepting the fact that minor damage to the enamel is inevitable.

Methods used in the process of adhesive removal coincide with the required protocol used in similar studies [26, 27]. The visual assessment of enamel surface

Table 1. Distribution of enamel surface index (ESI) scores for six different adhesive removal methods

Method for adhesive removal	ESI score					Mean ± Standard Deviation	ANOVA		
	0	1	2	3	4		df**	F test	p
Fissure TCB*	0	22	13	0	0	1.37 ± 0.49	5	24.53	0.001
Round TCB*	0	0	10	24	1	1.94 ± 0.93			
Composite bur	0	32	3	0	0	1.08 ± 0.28			
Abrasive disc	0	29	6	0	0	1.17 ± 0.38			
Pliers	0	7	26	1	1	1.88 ± 0.58			
Ultrasonic scaler	0	4	15	13	3	2.42 ± 0.81			
Control group	35	0	0	0	0				

*Tungsten carbide bur; **degrees of freedom

Table 2. Post-hoc analysis of significant differences in mean values of enamel surface index (ESI) scores for all six methods

Method for adhesive removal (J)	Fissure tungsten carbide bur		Round tungsten carbide bur		Composite bur		Abrasive disc		Adhesive removing pliers		Ultrasonic scaler	
Method for adhesive removal (I)	M (I–J)	p	M (I–J)	p	M (I–J)	p	M (I–J)	p	M (I–J)	p	M (I–J)	p
Fissure tungsten carbide bur	.	.	-0.57*	0.002	0.28	0.399	0.2	0.764	-0.51*	0.009	-1.05*	0.001
Round tungsten carbide bur	0.57*	0.002	.	.	0.85*	0.001	0.77*	0.001	0.05	0.999	-0.48**	0.017
Composite bur	-0.28	0.399	-0.85*	0.001	.	.	-0.08	0.993	-0.80*	0.001	-1.34*	0.001
Abrasive disc	-0.2	0.764	-0.77*	0.001	0.08	0.993	.	.	-0.71*	0.001	-1.24*	0.001
Adhesive removing pliers	0.51*	0.009	-0.1	0.999	0.80*	0.001	0.71*	0.001	.	.	-0.54*	0.005
Ultrasonic scaler	1.05*	0.001	0.48**	0.017	1.34*	0.001	1.25*	0.001	0.54*	0.005	.	.

*significant at $p < 0.01$;
**significant at $p < 0.05$

Table 3. Descriptive statistics for the duration of adhesive removal procedures in seconds with the results of ANOVA with F value and Fisher test

Adhesive removal method	n	Mean (sec) ± Standard Deviation	df*	F test	p
Fissure tungsten carbide bur	35	29.17 ± 6.78	5	4.13	0.001
Round tungsten carbide bur	35	25.51 ± 6.2			
Composite bur	35	30.93 ± 6.33			
Abrasive disc	35	17 ± 6.20			
Adhesive removing pliers	35	24.31 ± 10.49			
Ultrasonic scaler	35	29.94 ± 10.99			

*degrees of freedom

Table 4. Post hoc analysis of significant differences in mean values of adhesive removal times for all six methods

Time for adhesive removal (J)	Fissure tungsten carbide bur		Round tungsten carbide bur		Composite bur		Abrasive disc		Adhesive removing pliers		Ultrasonic scaler	
Time for adhesive removal (I)	M (I–J)	p	M (I–J)	p	M (I–J)	p	M (I–J)	p	M (I–J)	p	M (I–J)	p
Fissure tungsten carbide bur	.	.	3.65	0.912	-1.76	0.997	12.17*	0.011	4.85	0.757	-0.77	1
Round tungsten carbide bur	-3.65	0.91	.	.	-5.41	0.662	8.51	0.174	1.2	0.999	-4.42	0.822
Composite bur	1.76	1	5.41	0.662	.	.	13.93**	0.002	6.61	0.444	0.98	1
Abrasive disc	-12.17*	0.01	-8.51	0.174	-13.93**	0.002	.	.	-7.31	0.328	-12.94**	0.005
Adhesive removing pliers	-4.85	0.76	-1.2	0.999	-6.61	0.444	7.31	0.328	.	.	-5.62	0.624
Ultrasonic scaler	0.77	1	4.42	0.822	-0.98	1	12.94**	0.005	5.62	0.624	.	.

*significant at $p < 0.01$;
**significant at $p < 0.05$

was performed by using ESI on SEM images, under four different magnifications for each specimen. Significant differences were found among different tested methods. The tapered fissure tungsten carbide bur, abrasive disc and composite bur caused less damage to the enamel in comparison to other three methods applied during the course of the study.

The operator's control and proficiency in the use of the instruments for adhesive removal is another important factor to be considered in enamel surface evaluation [6, 8, 27, 28]. In the present study, two types of tungsten carbide burs have been applied: a 12-fluted round end tapered fissure tungsten carbide bur and a 12-fluted round tungsten carbide bur with reduced vibrations. As it had been assumed based on the study by Palmer et al. [22], the visual assessment confirmed more enamel damage caused by a round bur. However, using the SEM image evaluation in their study, Pignatta et al. [9] concluded that a tungsten carbide bur caused several scratches on the enamel surface, which were not observable after polishing.

Nevertheless, the results demonstrated only small irregularities on the enamel surface after removing adhesive remnants with a composite bur. This result is in line with those obtained by Karan et al. [13] and Erdur et al. [29] who reported that a composite bur provided a smoother enamel surface in comparison to a tungsten carbide bur,. They emphasized that a composite bur decreased enamel surface roughness. Similarly, Cardoso et al. [27] reported that a composite bur and a Sof-Lex disc restored the enamel closely to its pre-treatment condition. The results obtained by the present study were based on the visual assessment allowing a comparison of all six methods. While some of the methods caused visible enamel damage (ultrasound scaler and round tungsten carbide bur), the other methods caused only minimal surface irregularities (composite bur, abrasive disc). An abrasive disc was less damaging to the enamel in comparison to a tungsten carbide bur, which is in accordance with the results obtained by Khatria et al. [30].

One of the concerns in orthodontic practice is also enamel loss during pumice prophylaxis, etching, debonding, and adhesive removal procedures. Even though this study is based only on the visual evaluation of SEM images, our results partly agree with the results reported by Hosein et al. [10] who used a quantitative method for enamel loss assessment. They concluded that significant enamel loss was caused by the use of a high-speed tungsten carbide bur and an ultrasonic scaler, while the use of a low-speed tungsten carbide bur and adhesive removing pliers caused only minor enamel loss.

Operating time for each method was measured in seconds. The duration of adhesive removal procedures can be influenced by different factors, including a method used for adhesive removal, a type and amount of residual adhesive and individual manual abilities of orthodontists [24]. The time required for residual adhesive removal with the composite bur, ultrasonic scaler, and adhesive-removing pliers was longer than time required for the application of other three methods (Table 3). Similarly, Karan et al. [13] and Erdur et al. [29] reported that the application of composite bur for adhesive removal required more time than the application of tungsten carbide bur. However, Eminkahyagil et al. [28] concluded that a high-speed tungsten carbide bur was the quickest method for adhesive removal in comparison to a low-speed tungsten carbide bur, a microetcher, and a Sof-Lex disc.

Although some methods were the most preserving to the enamel surface, they were also the most time-consuming. In clinical conditions, the use of polishing systems creates an aesthetically pleasant enamel surface after different adhesive removal methods. These systems also extend the duration of adhesive removal. Polishing systems were not applied in this study in order to achieve a clear and precise visual assessment of enamel surface after the use of all six methods. In addition, the efficacy of methods and their

influence on temperature changes of the pulp area and enamel loss should be considered in further studies in order to determine an optimal protocol for adhesive removal.

CONCLUSIONS

Significant enamel damage is found after the application of all six methods examined for adhesive removal following bracket debonding. Enamel surface examination confirms that minor enamel damage occurs after the use of a composite bur, followed by an abrasive disc and a tapered fissure tungsten carbide bur with a round end. The greatest damage to the enamel is determined after the application of an ultrasonic scaler followed by a round tungsten carbide bur and adhesive removing pliers.

Application of a composite bur, an ultrasonic scaler, and a tapered fissure tungsten carbide bur with a round end was more time-consuming than the application of adhesive removing pliers, a round tungsten carbide bur, or an abrasive disc.

ACKNOWLEDGEMENT

This paper is part of a research thesis on "The Evaluation of Enamel Surface After Removing Fixed Orthodontic Appliances" by Adriana Arbutina. The authors would like to thank Ivana Kitonjić and Jovana Milutinović for their assistance in translating this paper into English.

Conflict of interest: None declared.

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Испитивање површине глеђи после уклањања бравица и адхезива помоћу шест различитих метода

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САЖЕТАК

Увод/Циљ После уклањања ортодонтских бравица неопходно је уклонити остатак адхезива са површине зуба, што често узрокује оштећење глеђи.

Циљ овог рада је био испитати површину глеђи после примене шест различитих метода за уклањање адхезива после уклањања бравица те упоредити трајање ових процедура.

Метод У овом истраживању прикупљено је 245 људских премолара, екстрахованих у ортодонтске сврхе. Металне бравице су постављене на 210 људских премолара применом адхезивног система *Aspire*. После одлепљивања бравица узорак је подељен на шест група према методи која се примењивала за уклањање адхезива: фисурно тунгстен-карбидно сврдло, округло тунгстен-карбидно сврдло, композитно сврдло, абразивни диск, клешта за уклањање адхезива и ултразвучни инструмент. Од укупно 245 премолара, 35 премолара је чинило контролну групу. Време уклањања адхезива је мерено за сваку од метода. Оштећење глеђи је процењено према индексу површине глеђи на микрографијама добијеним скенирајућом електронском микроскопијом.

Резултати Композитно сврдло је довело до најмањег оштећења глеђи (1,08). Примена абразивног диска је у краћем периоду довела до потпуног уклањања адхезива у односу на композитно сврдло ($p < 0,01$) и ултразвучни инструмент ($p < 0,01$).

Закључак Највеће оштећење површине глеђи је уочено после примене ултразвучног инструмента и округлог тунгстен-карбидног сврдла. Уклањање адхезива помоћу абразивног диска се показало као метода која најбрже уклања преостали адхезив са зуба, а да при томе најмање оштећује глеђ.

Кључне речи: уклањање адхезива; оштећења глеђи; индекс површине глеђи

DOI: https://doi.org/10.2298/SARH190923025M
UDC: 615.461:616.314-77

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Retention force of overdenture retained with telescopic crowns – a comparison of polyether ether ketone and zirconia ceramic telescopic crowns

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SUMMARY
Introduction/Objective Recently, new materials for double crowns have been introduced, such as zirconia and polyether ether ketone (PEEK). However, some characteristics of these materials, such as retentive force and duration of "settling in phase," have not been investigated sufficiently. During the "settling in phase," telescopic overdenture has not yet achieved its definitive retention force, and it can be harmful for periodontal tissue if the value is above optimal for a long period of time.
The objective was to measure the *in vitro* overall pull-off force of telescopic crowns where primary crowns were made from zirconia ceramics and a survey of the "settling in phase" duration.
Methods Forty zirconia primary telescopic crowns were produced on prepared canine teeth. Twenty secondary crowns were of PEEK and other 20 of zirconia with electroplated gold copings. The pull-off force measurements were conducted utilizing a dynamometer until a constant value was obtained.
Results The specimens of the PEEK group showed higher initial retentive force values. Settling in phase was finished between 800 and 900 cycles of separation for both groups. Comparing the value of the pull-off force between individual different cycles, a statistically significant reduction was recorded up to the 800th cycle, while between the 800th and the 900th cycle there was no difference.
Conclusions The settling in phase was finished between 800 and 900 cycles of separation in both groups. Final retentive force values for both tested telescopic groups were in the optimal range which is 5–9 N per one telescopic crown.
Keywords: telescopic crowns; PEEK; zirconia ceramics; retentive force; CAD-CAM

INTRODUCTION

Although dental implants' placement has become a standard procedure in prosthetic rehabilitation, there are still some situations where conventional overdentures retained with double crowns are the best solutions especially in elderly patients, having in mind some diseases such as osteoporosis, their economic situation and number, and the position of leftover teeth [1, 2]. They are indicated in cases where there are few leftover teeth (2–4) with good biological value, preferably distributed on both sides of the dental arch [3]. Double crowns consist of two main parts: a primary or male part permanently fixed to an abutment tooth or implant, and a congruent secondary or female part, rigidly connected to a removable partial denture. A cylindrical structure known as a telescopic crown is often used for double crowns and is characterized by equivalent gingival and occlusal circumference; therefore, no taper is employed [4]. Double crown systems offer more advantages than other types of attachments such as cross-arch stabilization of the abutment teeth, axial loading of the teeth, good retention, longevity, and are therefore suitable for elderly people, giving them oral comfort and self-confidence [5, 6]. Commonly, double crowns are made of metal alloys, precious and non-precious, making a homogenous or heterogeneous friction pair. During decades of use, gold alloys have proved to be the best solution in terms of creating clinically acceptable values of retention force, longevity, and biocompatibility [2, 4]. However, despite these many advantages of double crowns, they have been repressed from use mainly due to high prices of the gold alloy. Consequently, dental technicians have less experience in double crown production and avoid doing them.

Double crowns have undergone changes recently, in terms of the material selection, manufacturing technique, and design concepts, mainly in order to increase the level of precision through digitalization and consequently their performance. Modern systems of double crowns are based on zirconia ceramics (ZrO_2) and polyether ether ketone (PEEK). Ceramic materials combined with electroplated gold provide numerous advantages such as small plaque susceptibility, absence of marginal

Received • Примљено: September 23, 2019
Revised • Ревизија: April 29, 2020
Accepted • Прихваћено: April 30, 2020
Online first: May 6, 2020

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gingiva discoloration and important esthetic qualities [7]. Another material utilizing computer-aided design and computer-aided manufacturing (CAD/CAM) technique for manufacturing double crowns, PEEK, provides many advantages. It is a low-priced material, compared to gold alloys, it is light weight and easy to work with compared to non-precious metal alloys, titanium, and ceramics. Its insolubility distinguishes it as an excellent material for patients with allergies [8].

Precision made telescopic crowns achieve reliable and long-lasting retention, usually by friction of touching surfaces. However, during the telescopic retained overdenture initial period of use, the retentive force value is variable. The retentive force is at its highest immediately after the denture construction and progressively decreases until the end of the "settling in phase," i.e. until the retention force value becomes well established [3]. Throughout the settling-in phase, wear of the material occurs, thus only after a certain period of wear do telescopic crowns achieve their final geometric form.

The aim of the study was to measure the in-vitro overall retention force of telescopic crowns where primary crowns were fabricated from zirconia ceramics with PEEK secondary crowns, and those where primary crowns were fabricated from zirconia ceramics and gold electroplated secondary crowns were made with zirconia ceramics. Also, the intention was to evaluate the number of cycles after which the retentive force becomes steady for all mentioned telescopic crowns under simulated clinical conditions. We hypothesized that different materials of secondary crowns have an impact on: (i) the initial retentive force value and (ii) the duration of initial retentive force value reduction.

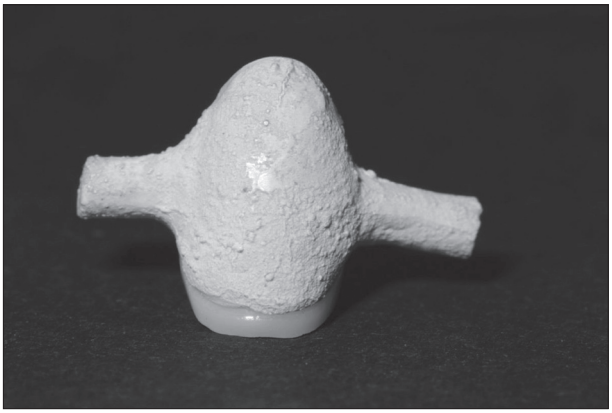

Figure 1. Polyether ether ketone (PEEK) secondary crown

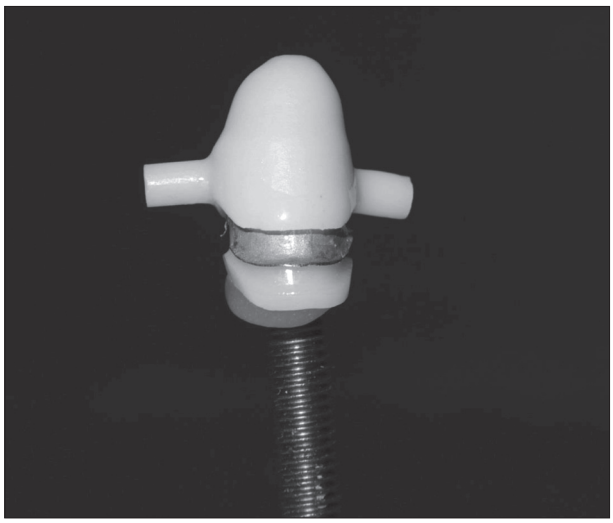

Figure 2. ZrO_2 secondary crown with electroplated gold coping

METHODS

Specimen preparation

Maxillary canine typodont resin model (KaVo Dental GmbH, Biberach an der Riss, Germany) was prepared for conventional telescopic crowns. Height of the prepared canine was 5 mm with 2 mm occlusal reduction, with a 1-mm-thick 360°-rounded shoulder margin. Afterwards, impressions of the resin model including the prepared tooth were obtained utilizing standard metal trays and additional silicone material (Zhermack SpA, Badia Polesine, Italy). According to 40 silicone impressions, 40 master casts were fabricated in dental stone type IV (Fuji Rock, GC, Leuven, Belgium) and were subsequently used for fabricating ZrO_2 primary crowns.

Primary and secondary crowns fabrication

All 40 primary crowns (40 master casts with prepared canine teeth) were fabricated from zirconia blocks (ZENOSTAR, 98 mm, Wieland Dental, Pforzheim, Germany). The stone models were scanned using an extraoral scanner (3 Shape D 800 scanner, 3Shape A/S, Copenhagen, Denmark), designed (Dental System Premium 2014, 3Shape A/S, Copenhagen Denmark) and milled in a Wieland Dental CNC milling unit. The primary crowns were polished with a special bur kit for zirconia (sets 4430 and 4431, Komet Dental Gebr. Brasseler GmbH & Co. KG, Lemgo, Germany) with water cooling using a hand piece [9].

The prepared primary crowns were afterwards divided into two groups – 20 primary crowns were randomly selected for PEEK secondary crowns (Figure 1); the rest of the 20 crowns were left for ZrO_2 secondary crowns with electroplated gold copings (Figure 2). The parameters used for PEEK secondary crowns were adjusted for breCam BioHPP blanks (Bredent, Senden, Germany, LOT: 394172), with proximal extension to enable precise separation of the crowns. Twenty PEEK secondary crowns were milled utilizing Wieland Dental CNC. The polishing procedures of the outer surfaces of peek secondary crowns were conducted under standardized condition, which implies silicone polishers (Ceragum Wheel, Bredent Medical GmbH & Co.KG, Senden, Germany) and polishing brushes (Komet Dental) with polishing paste (Abraso-Starglanz asg, Bredent, Germany); inner surfaces were not polished, in accordance with manufacturer recommendations [8].

Another 20 secondary crowns were fabricated combining electroplated gold copings and ZrO_2. The gold

copings were produced in the electroforming machine (Gammat Optimo 2, Dental Gramm Technik GmbH, Ditzingen, Germany). The primary crowns were covered with thin layer of electroconductive lacquer (Conductive Silver Lacquer art. No. 910.00.049) using a special brush. Special attention was paid to producing a thin homogeneous layer. The properties of the gold solution (Ecolyt SG 200), activator (Activator SG 200), and time required were automatically calculated by the system to create a 0.2 mm thin layer of gold. Afterwards, the copings were submersed in a 40% nitric acid solution for 15 minutes to remove metallic lacquer. On the master cast with primary and secondary telescopic crowns in place, another digital scan was performed and a tertiary structure was designed (Dental System Premium) and milled (Wieland Dental CNC, Wieland Dental) from zirconia blocks (Zenostar, Wieland Dental). Afterwards, the gold copings were introduced into the ZrO_2 secondary crowns and luted using Multilink Automix adhesive (Ivoclar Vivadent AG, Liechtenstein) according to the manufacturer's directions.

Pull-off force measurement

Measurements were performed on 40 sets of telescopic crowns. The study adopted the "pull off force" as a force needed for pulling off the secondary from the primary crown. The measurements were preformed manually as complete separation of the telescopic crowns with artificial saliva substitute interposed (Biotene; GSK, Brentford, UK in physiological sodium chloride solution, ratio 1:2). The pull-off force measurements were conducted by a Bredent dynamometer (Friktionsmesgerat fmg 20) [10]. This dynamometer measures forces ranging 0–20 N. The existence of proximal extensions on the secondary telescope crowns was required for precise separation of the crowns. Measurements of the overall pull-off force were done in several steps. First, the interiors of the primary crowns were filled with autopolymerizing acrylic resin, and using the movable arm of the surveyor the dynamometer pins were immersed into the acrylic (Figure 3). Following the polymerization of the acrylic resin, adequate secondary crowns were seated over the primary crowns with finger pressure. The telescopic crown and pin assemblies were mounted onto the perforated plate of the dynamometer and fixed with an appropriate screw. The vertical post was then secured using a proper screw. The described method was performed for each of the 40 telescopic crown specimen sets. In summary, 40 specimens for each telescopic system were fabricated consisting of 20 for each material group combination.

Manual complete separation of the secondary crowns from the primary telescopic crowns in an axial direction was performed respectively at the baseline and presented the initial pull-off force. Readings of the pull-off force values were evaluated on the dynamometer scale. Insertion and separation of the telescopic crowns and adequate measurements were repeated until a constant value of the pull-off force was obtained. The final measurement refers to the pull-off force values that repeat in at least 10 consecutive readings, while the number of cycles until steady force value is achieved, represents the settling-in phase.

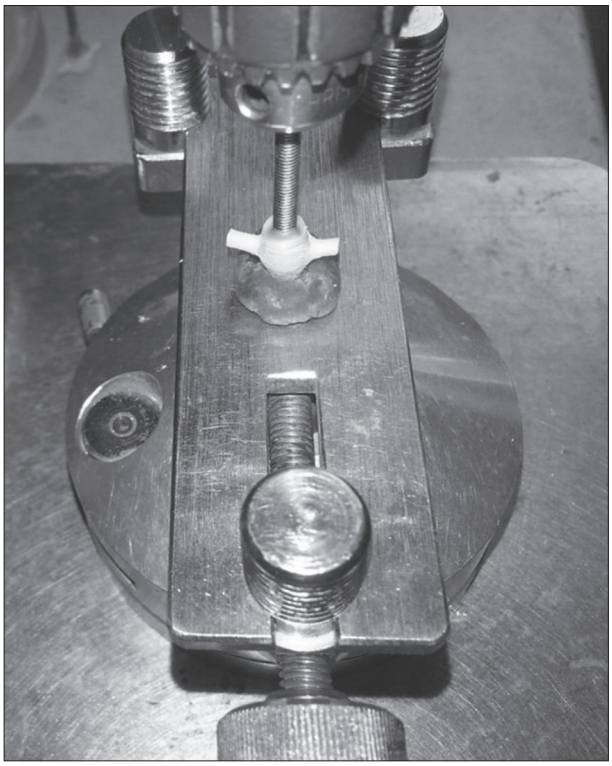

Figure 3. The dynamometer pin was immersed into the acrylic using the movable arm of the surveyor

Statistical analyses

For statistical analysis, the values of the pull-of force obtained after the first measurement (baseline) were used, as well as after each hundred measurements to the end of the settling in phase (the end of the test). Statistical analyses were performed using IBM SPSS Statistics, Version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive data for all groups and variables were expressed as mean ± standard deviation, median, and interquartile range. Obtained data were tested for normal distribution by the Kolmogorov–Smirnov test. All our data was non-parametric. Quantitative non-parametric variables, between two groups, were compared by the Mann–Whitney U-test. For the comparison within a group (between different observed times), Friedman and Wilcoxon tests were performed. Logistic regression model was used to determine predictors of different groups: the PEEK group and the electroplated-gold-ZrO_2 group. All reported p-values were two-sided; the differences were considered significant when p-value was < 0.05.

RESULTS

The initial settling-in phase was finished between 800 and 900 cycles of separation, due to the fact that the 900th

cycle of separation was presented as the end of the test for both groups. On average, the initial settling-in phase was finished after 892 cycles of separation in the PEEK group and 858 in the electroplated-gold-ZrO_2 group. The initial values showed the range of the pull-off force: 7.5–10.2 N for the PEEK group and 2.4–10 N for the electroplated gold-ZrO_2-group. The respective final pull-off forces were 4.1 N and 3 N. The descriptive statistics, such as mean with standard deviation, median, and interquartile range together with the result from Mann–Whitney and Friedman tests are summarized in Table 1. By comparing the values of the pull-off forces between the groups analyzed, a statistically significant difference was found at all observed times, commencing from the baseline to the 900th separation cycle. The p-values in question are also shown in Table 1.

When comparing inside the groups, a statistically significant reduction in the pull-off force value was observed in both groups. By comparing the value of this parameter between individual different cycles, a statistically significant reduction was recorded up to the 800th cycle, while between the 800th and 900th cycle there was no difference (Table 2). The percentage change in the finish value (900th separation cycle) compared to the baseline (start) did not statistically significantly differ from the observed groups (Figure 4).

Multiple regression analysis was used for identification of parameters that may predict changes in the initial retention force of different telescopic crowns: the PEEK group and the electroplated-gold-ZrO_2 group. For the assessment of univariate predictors, all values for the pull-off force and the percentage change from baseline to finish values were analyzed. When the univariate predictors were obtained, all values of the pull of force during different cycles of separation were introduced in a multivariate model. In the multivariate model, none of these factors showed statistically significant differences between the observed telescopic crowns.

Table 1. Descriptive statistics values; all values for pull-off force are presented in newtons (N)

Number of test cycles $\bar{x} \pm SD$ (Med, IQR)	PEEK group	Electroplated Au-ZrO_2 group	p[a]
Baseline	9.3 ± 1.2 (9.7; 2.4)	7 ± 2.6 (7.3; 2.4)	p = 0.001*
100	7.9 ± 1.6 (7.2; 3)	6.1 ± 2.1 (64; 1.4)	p = 0.006*
200	7.1 ± 1.3 (6.4; 2.2)	5.5 ± 1.9 (5.8; 1.6)	p = 0.017*
300	6.1 ± 0.8 (6.1; 1.8)	4.6 ± 1.5 (4.8; 1)	p = 0.001*
400	5.4 ± 0.6 (5.38; 1)	4.2 ± 1.3 (4.4; 0.8)	p = 0.000*
500	4.8 ± 0.6 (4.65; 0.8)	3.7 ± 1.2 (4; 0.6)	p = 0.000*
600	4.5 ± 0.6 (4.4; 0.3)	3.5 ± 1.2 (3.6; 0.3)	p = 0.000*
700	4.3 ± 0.4 (4.4; 0.8)	3.4 ± 1.1 (3.6; 0.8)	p = 0.000*
800	4.2 ± 0.5 (4.3; 0.8)	3.1 ± 1.1 (3.2; 0.6)	p = 0.000*
900	4.1 ± 0.5 (4.3; 0.8)	3 ± 0.9 (3.2; 0.6)	p = 0.000*
p[b]	p = 0.000*	p = 0.000*	

IQR – interquartile range;
*statistically significant;
[a]Mann–Whitney U-test;
[b]Friedman test

Table 2. Statistically significance of reduction of pull-off force over time in two groups

Test cycles	PEEK group	Electroplated Au-ZrO_2 group
baseline–100	p = 0.000*	p = 0.000*
100–200	p = 0.000*	p = 0.000*
200–300	p = 0.000*	p = 0.000*
300–400	p = 0.000*	p = 0.000*
400–500	p = 0.000*	p = 0.000*
500–600	p = 0.000*	p = 0.001*
600–700	p = 0.004*	p = 0.045*
700–800	p = 0.002*	p = 0.004*
800–900	p = 0.157	p = 0.063

*Statistically significant; Wilcoxon test

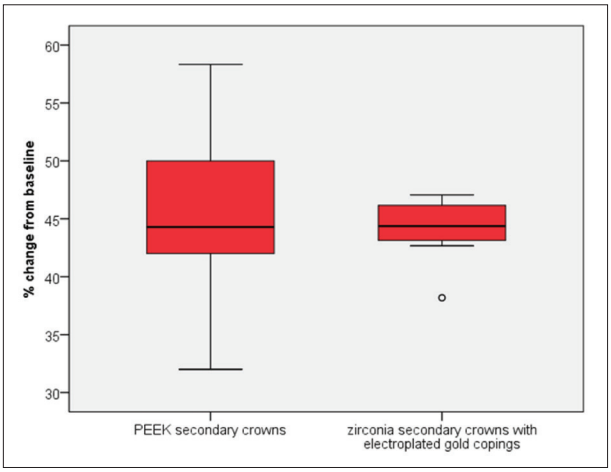

Figure 4. The percentage change from baseline to finish values

DISCUSSION

Upon evaluating the obtained results regarding the first hypothesis, it could be said that both groups of investigated telescopic sets had achieved sufficient retention forces. The PEEK telescopic crown group in our study showed higher initial retentive force values (mean value of 9.3) compared to the ZrO_2 crowns (median value of 7). Also, the PEEK group showed a larger range of retention force before the end of the settling-in phase and slightly longer duration of settling-in phase compared to the ZrO_2 group. The possible explanation may be that known recommendation not to polish inner surfaces of PEEK crowns contributes to an initial high abrasiveness and consequently robust initial retentive force values. In addition to that, PEEK as a flexible material undergoes the process of better adaptation to the primary coping [9, 10, 11]. The results concerning the second hypothesis showed that final pull-off forces were 4.1 N and 3 N, respectively for each group. Phenomenon that occurs during the settling-in phase represents plastic deformation of materials with an increase of actual contact surface area resulting in tension reduction between surfaces [3, 11]. The existing tension will decrease as long as the limits of elasticity are exceeded anywhere in the contact area, whereas elasticity is specific for any given material. The results correspond to the statement that the retention mechanism of electroformed secondary crowns is based on adhesion, not on the wedge effect [5].

The retention of telescopic crowns in which the secondary parts are electroplated is based on the combination of capillary gap and saliva [12, 13]. Capillary gap occurs as a result of gold ion deposits on a thin layer of silver lacquer which is applied during the fabrication of the coping. Furthermore, by implementing the artificial saliva, design of the tooth preparation and chamfer design and dimensions may have an impact on adhesion between the smooth surfaces of telescopic crowns, as well as having a hydraulic effect, thus increasing the initial retentive force [10]. Also, as stated by Weigl et al. [14], double crown assemblies with electroformed secondary crowns have more stable retention forces than double-crown assemblies with cast secondary crowns [14].

The main limitation of this study is that the dynamometer pin was positioned manually, and that some errors may have occurred when reading the measured values. However, to avoid significant errors, the dynamometer pin was positioned using the surveyor arm, thus providing the vertical direction for the separation/insertion process. Under *in vivo* conditions, the insertion path of the denture in most cases is slightly different from the path used during the measurements. Also, the lubricant was interposed during the "pull-off force" measurement, although the presence of artificial saliva is a controversial subject concerning the validity of the results ranging from those that indicate the presence of saliva substitute does not alter the withdrawal force in individual withdrawal force tests to those that assert the absence of such intermediary leads to significant changes in frictional wear [15].

Double crowns have been exposed to numerous criticisms over decades of use. However, research has shown that properly planned and precisely manufactured overdenture retained with double crowns does not show a higher incidence of complications than other types of attachments. Ishida et al. [16] investigated survival and complication probabilities of the prosthesis retained with clasps and double crowns. Decementation was the most frequent cause of failure in double crowns (which is neither expensive nor complicated to solve), but other complications such as fracture of crown restoration, fracture of tooth, caries, and periodontal disease were more frequent in abutment teeth with clasps [16]. Similar conclusion was made by Hofmman et al. [17], who reported the loss of cementation for double crowns and fractures of the clasps. Schwindling et al. [18] concluded that the most frequent complications of double crown retained overdentures were decementation of primary crowns, need for denture relining, and fracture of the veneer of secondary crowns. All these complications are considered minor and low-cost, and overall survival rate was 90% after seven years. According to the most recent research, the cumulative survival rate of double crowns was higher in implants compared to tooth-supported overdentures, but still above 80% in both teeth- and implant-supported overdentures over 10 years [19]. Based on these results, it can be said that the main drawbacks of the telescopic overdenture are in the complex design and production, as well as the price of gold alloys. For this reason, the idea of introducing new materials for double crowns means a potential reduction of the production cost, but the main advantage is digitalization, which reduces the errors caused by the human factor. For example, due to CAD/CAM fabricating, casting beads, inevitable during conventional casting, were avoided [20, 21]. In addition, a recent study has shown that fully digital protocol for RPD production with clasps is possible, meaning digital impression, design with CAD software, fabrication with CAM machine, and 3D printer and assembly with adhesive material [22]. This means that soon it will be possible to produce telescopic overdenture with fully digital protocol as well.

Non-precious metal alloys are convenient because of the much lower price compared to gold alloys, but also to PEEK and ZrO_2. However, literature data and also experience in practice point out that these alloys often cannot reach sufficient retention force and therefore need additional retention elements which complicate the production process. Also, because of the existence of carbides, oxide layer creation, and high elasticity module, double crowns made of non-precious alloys are much more difficult to handle and process [23, 24, 25].

The optimal retention force value per one telescopic crown amounts to 5–9 N [3, 8, 23], which correlates with our own results. The results from Stančić and Jelenković [4] demonstrate that when a larger number of matrix–patrix components are present, as in most cases, there is an initial force stronger than optimal and the settling-in phase will last longer, thus providing the possibility of potentially harmful outcome for the periodontium over a longer interval [4]. Considering the retention force values, contrary to our results, initial retentive force in the 3.6–3.7 N range or less were reported by Özyemişci-Cebeci and Yavuzyilmaz [12] prior to applying different friction varnishes that improved retention to satisfactory 4.6 and 6 N. Güngör et al. [25], similar to our results, reported that only after the initial 800 cyclic procedures were performed, a decrease in the retentive force could be found, with no further changes afterwards. Contrary to our findings, the results of Stock et al. [8] showed a decrease of retention force in PEEK secondary crowns as soon as the first 20 cycles.

Bearing in mind the obtained results as well as the difference in the crown production cost which is approximately 2:1 in favor of PEEK, authors give mild advantage to the electroplated gold ZrO_2. However, further prospective clinical studies are needed to determine which material is more durable and has better clinical characteristics after some period of use. Nowadays, more implant-supported overdentures are retained with double crowns with good survival rate [2, 26], and researches about different computer-aided technologies for those double crowns should give precious information [19, 22].

CONCLUSION

The first hypothesis that different materials of the secondary crown have an impact on initial retentive force value has been shown as correct. The specimens of the PEEK

telescopic group showed higher initial retentive force values than electroplated-gold-ZrO_2 group. The settling-in phase was finished between 800 and 900 cycles of separation in both groups; thus, material combination did not have an impact on the duration of the initial retentive force reduction. Both tested telescopic groups showed retentive force values in the optimal range.

ACKNOWLEDGEMENT

The authors are very grateful to master dental technician Nemanja Grkinić and Dental Design Studio, Belgrade, Serbia for the help in preparation of samples used in the present study, and to dental technician Gustav Bačlija (G-dent, Subotica, Serbia) for providing the galvanic device.

Conflict of interest: None declared.

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Ретенциона сила протезе ретиниране телескопским крунама – поређење телескопских круна од полиетеркетона и цирконијумске керамике

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САЖЕТАК

Увод/Циљ Последњих година уведени су у праксу нови материјали за двоструке круне, као што су цирконија и полиетеретеркетон (ПЕЕК). Међутим, неке карактеристике ових материјала нису довољно испитане, као што су ретенциона сила и трајање „фазе уходавања". „Фаза уходавања" је иницијални период употребе телескопске протезе када финална ретенциона сила још увек није постигнута, и може имати штетни утицај на пародонтално ткиво ако су у том периоду силе превисоке и предуго трају.

Циљ је био да се измери ин витро укупна сила раздвајања телескопских круна, где су примарне круне израђене од цирконијумске керамике, и испитати трајање фазе уходавања.

Методе Четрдесет примарних телескопских круна од цирконијумске керамике је израђено на препарисаним очњацима. Двадесет секундарних круна је израђено од ПЕЕК-а, и још 20 круна од цирконије са галванизованим златом. За мерење силе раздвајања коришћен је динамометар. Спајање и раздвајање телескопских круна и мерење силе раздвајања је вршено док није добијена константна вредност.

Резултати Узорци из групе ПЕЕК показали су вишу иницијалну вредност ретенционе силе. Фаза уходавања је завршена између 800 и 900 циклуса раздвајања код обе групе. Када се упореде индивидуалне вредности силе раздвајања између различитих циклуса, статистички значајно смањење је забележено до 800. циклуса, док између 800. и 900. циклуса није било разлике.

Закључак Фаза уходавања је завршена између 800 и 900 циклуса раздвајања у обе групе. Финална ретенциона сила код обе тестиране групе показала је оптималне вредности, које износе 5–9 N по телескопској круни.

Кључне речи: телескопске круне; ПЕЕК; цирконијумска керамика; ретенциона сила; *CAD-CAM*

DOI: https://doi.org/10.2298/SARH200322046P
UDC: 616.716.4-001.5-053.9

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical characteristics of mandibular fractures in patients over 50 years of age

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SUMMARY

Introduction/Objective The most commonly used methods of treatment of mandibular fracture are not always successful in older patients. This is due to decreased regenerative ability, impaired vascularization, osteoporosis, and atrophic changes. The corresponding changes are often found in patients over 50 years of age, especially accompanied with teeth loss.
The objective was to review the clinical characteristics of mandibular fractures in older patients based on a retrospective analysis of medical records.

Methods A group of patients over 50 years of age was selected and analyzed among patients with mandibular fractures who had been treated for 10 years.

Results A total of 642 patients over 50 years with 1,003 fracture lines were identified. This represents 8.53% of the total number of patients with mandibular fractures. Comorbidities were diagnosed in 67% of cases. Significant differences in the distribution of the frequency of fracture lines by localization were identified, depending on the presence or absence of occlusal contact. A high incidence rate of open fractures and bone fragment dislocation was observed both in individuals with or without occlusive contact.

Conclusion Patients over 50 years of age are a statistically important group in the general population of patients with mandibular fractures with a number of clinical features. To the author's knowledge, this study comprises the largest number of patients over the age of 50 with mandibular fractures, including those with edentulous mandible, which ensures the required level of representation, allowing reliable clinical characterization of this contingent of patients.

Keywords: mandibular atrophy; occlusion; edentulous; older patients

INTRODUCTION

At old age, any injury is a serious threat. This is due to the reduced regenerative ability caused by the depletion of the pool of mesenchymal stem cells, impaired vascularization as a result of systemic atherosclerosis, and osteoporosis resulting from changes in mineral metabolism. The course of a traumatic disease is significantly influenced by comorbidities, which are common in this age group.

Maxillofacial injuries are not an exception, as they frequently lead to disability, including from the social perspective. It is known that mandibular fractures are one of the most frequent types of facial bone injuries, which also holds true for the individuals of older age groups [1, 2]. However, as a result of the loss of teeth, atrophic changes of the alveolar area and body of the mandible, standard treatment methods are not always effective in these patients [3]. According to several authors, the rate of complications associated only with impaired consolidation reaches 25% [4, 5]. In the age population over 50 years old, people with the loss of a large number of teeth and the lack of occlusal relationships are often found. As a result, they develop atrophic changes in the mandible of varying degrees of severity. Accordingly, its damage, in this case, will have a number of clinical features.

The objective of this paper is to review the clinical characteristics of mandibular fractures in older patients based on a retrospective analysis of medical records.

METHODS

Medical records of 7,532 patients with mandibular fractures undergoing treatment in the Maxillofacial Surgery Clinic of the N. I. The First Pirogov Municipal Clinical Hospital (the clinical base of the university department) within a period of 10 years was analyzed. We selected a group of patients over 50 years of age. As noted above, this age criterion was chosen based on the fact that mandibular atrophic changes related to the loss of teeth are common enough at this age thus inevitably influencing the clinical course of a traumatic disease.

At admission, all patients provided a written informed consent for the statistical processing of their data.

All procedures performed in this study were in accordance with the ethical standards of the

Received • Примљено: March 22, 2020
Revised • Ревизија: June 7, 2020
Accepted • Прихваћено: June 28, 2020
Online first: July 2, 2020

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institutional research and with the 1964 Helsinki declaration. Permission from the local Committee on Ethics has been obtained to conduct this research (protocol from May 30, 2019).

The distribution of patients by sex and age, as well as the presence or absence of comorbidities, was analyzed.

To characterize mandibular fractures, the Association for Osteosynthesis/Association for the Study of Internal Fixation (AO/ASIF) classification was applied [6]. This is the most convenient classification for the statistical processing of data in large groups in research studies and it also allows the highest possible number of clinical features of practical surgical significance to be taken into consideration. According to the requirements of this classification, the following categories were evaluated: F (fracture), L (localization), S (soft tissue), O (occlusion) (Table 1).

Table 1. The Association for Osteosynthesis/Association for the Study of Internal Fixation (AO/ASIF) classification of fractures of the mandible

Category		Fracture
F	F_1	simple fracture
	F_{1s}	oblique split fracture
	F_2	double or multiple unilateral fractures
	F_3	splintered fracture
	F_4	fracture associated with the formation of a bone defect
L	L_1	fracture located in the incisor region
	L_2	fracture located in the canine region
	L_3	fracture located in the lateral portions of the mandibular body, in the area from the first premolar to the second molar
	L_4	fracture located in the mandibular angle region.
	L_5	fracture located in the mandibular ramus region
	L_6	fracture located in the condylar process region
	L_7	fracture located in the coronoid process region
	L_8	fracture of the alveolar portion of the mandible
S	S_0	closed fracture
	S_1	open fracture communicating with the oral cavity
	S_2	open fracture accompanied by skin injuries
	S_3	fracture which is open both intra- and extraorally
	S_4	fracture associated with the formation of a soft tissue defect
O	O_0	no malocclusions
	O_1	disocclusion
	O_2	no occlusal contact

RESULTS

In the retrospective study of the archival documents, medical records of 642 patients aged over 50 years were identified, which represents 8.53% of the total number of patients with mandibular fractures. The relative share of older patients in different years ranged 7–11.3%, i.e. this parameter remained rather stable. Cumulatively, 1,003 fracture lines were diagnosed in these patients.

A total of 90 patients were female, representing 14% of the total number of the studied group, while 552 patients, who constitute 86%, respectively, were male.

Comorbidities were identified in a total of 67% of patients. Among these, cardiovascular disorders were predominant (Table 2). They were also detected in patients with other types of diseases, as a concomitant condition.

Table 2. Comorbidity structure in patients over 50 years of age with mandibular fractions

Parameter	Male		Female		Total	
	n	%	n	%	n	%
Total number of patients	552	86	90	14	642	100
Patients with comorbidities	359	55.9	71	11	430	67
Cardiovascular disorders	290	45.1	51	7.9	341	53.1
Respiratory disorders	39	6	9	1.4	48	7.5
Gastrointestinal disorders	20	3.11	4	0.6	24	3.7
Urinary tract disorders	4	0.6	4	0.6	8	1.2
Diabetes mellitus	3	0.4	2	0.3	5	0.7
Other	3	0.4	1	0.2	4	0.6

Occlusal contact was present in 305 patients, while 337 had no occlusal contact (O_2 category). The number of fracture lines diagnosed was 477 in the first group and 525 in the second group, respectively. Table 3 shows the distribution of unilateral and bilateral fractures in these groups.

Table 3. Number of unilateral and bilateral mandibular fractures in patients over 50 years of age by the presence or absence of tooth rows

Fractures	Dentulous		Edentulous		Total
	n	%	n	%	
Bilateral fractures	158	51.8	201	59.6	359
Unilateral fractures	147	48.2	136	40.4	283
Total	305	100	337	100	642

In O category (occlusion), the distribution of fracture frequency in various regions of the mandible was completely different in patients with preserved dentition and patients with loss of occlusal contact. The corresponding data relative to the total number of fractures are presented in Table 4. The incidence rate of fracture lines in various regions of the mandible relative to the total number of patients with present and absent occlusal contacts is presented in Figure 1.

The distribution of bilateral mandibular fracture lines in patients over 50 years of age by their localization in both present and absent occlusal contacts are shown in Table 5.

Dislocated bone fragments were observed in 79.1% of patients without occlusal contacts and in 66.3% of patients with occlusal contacts. The frequency distribution of bone fragment displacement by localization of the fracture line is shown in Figure 2.

DISCUSSION

The incidence rate of mandibular fractures in individuals over 50 is significantly lower than in other age groups (the maximum rate is reported in individuals aged 20–29 years: 37.53%), however they still represent a statistically significant population with specific clinical manifestations. Specifically, they include an increasing number of patients

Table 4. The distribution of mandibular fracture lines by localization in patients over 50 years of age

Dentulous* (n = 477, 100%)						
Injury region	S_0		S_1		S_3	
	n	%	n	%	n	%
L_1	5	1	46	9.7		
L_2	4	0.8	20	4.2		
L_3	26	5.5	75	15.8	2	0.4
L_4	74	15.5	110	23.1	2	0.4
L_5	11	2.3				
L_6	102	21.4				
Total	222	46.5	251	52.6	4	0.8
Edentulous (n = 525, 100%)						
Injury region	S_0		S_1		S_3	
	n	%	n	%	n	%
L_1	12	2.3	14	2.7		
L_2	14	2.7	15	2.9	1	0.2
L_3	89	16.9	101	19.2	2	0.4
L_4	84	16	97	18.4	2	0.4
L_5	14	2.7				
L_6	80	15.2				
Total	293	55.8	227	43.2	5	1

*Category L8 cases (three cases) are not included in this table

Table 5. The distribution of bilateral mandibular fracture lines in older patients by their localization

Fracture line localization pattern	Dentulous		Edentulous	
	n	%	n	%
L_1/L_3	-	-	2	1
L_1/L_4	14	8.9	5	2.4
L_1/L_5	2	1.2	-	-
L_1/L_6	14	8.9	18	9
L_2/L_4	7	4.4	10	5
L_2/L_5	2	1.3	-	-
L_2/L_6	5	3.2	10	5
L_3/L_3	1	0.6	18	9
L_3/L_4	48	30.4	60	29.9
L_3/L_5	7	4.4	5	2.4
L_3/L_6	23	14.6	32	16
L_4/L_4	21	13.2	21	10.4
L_4/L_6	12	7.7	16	8
L_5/L_5	-	-	2	1
L_6/L_6	2	1.3	2	1
Total	158	100	201	100

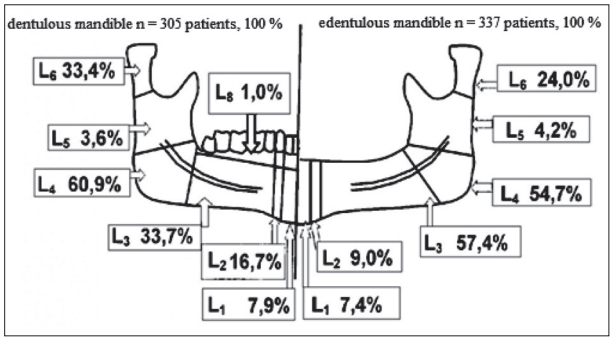

Figure 1. The frequency of mandibular fractures among the patients over 50 years of age (number of fracture lines to number of patients ratio)

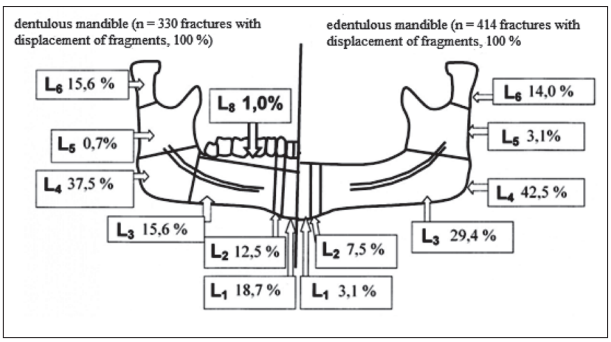

Figure 2. The frequency of dislocation of bone fragments in fractures of the mandible among the patients over 50 years of age

with comorbidities, predominantly cardiovascular disorders. This implies the long-term use of various drugs influencing the function of different body systems (for example, anticoagulants), which should be taken into consideration when planning surgery.

The characteristics of the actual fractures fundamentally depend on the presence or absence of occlusal contacts; their loss leads to severe atrophic changes in the mandible. This affects the distribution of fracture lines by localization. In patients with occlusal contacts, the higher incidence rate of fracture lines is observed in the mandibular angle region, similarly to patients of other age groups. In patients with teeth loss, fracture lines are most prevalent in the lateral portions of the mandibular body, where the most pronounced atrophic changes occur. According to Newman [7], the incidence rate of fracture lines in this region is 57%, which is fully consistent with our results.

We noted that in a rather high proportion of cases (9%) in the O_2 category according to the AO/ASIF classification, bilateral symmetrical fracture lines located in the lateral portions of the mandibular body are diagnosed. In the corresponding age group with occlusal contacts, a single such case was reported; moreover, this patient had bilateral free-end edentulous spaces from the first molars, while fracture lines were immediately behind them.

Luhr et al. [8] proposed a classification of atrophic jaw changes in patients with fractures, based on the vertical size of the bone. The mandibular height in the area of injury of 16 to 20 mm corresponds to class I atrophy, a height of 11 to 15 corresponds to class II, and a height below 10 mm corresponds to class III. Mugino et al. [9] also distinguished extremely severe atrophy with a mandibular height lower than 5 mm. Consequently, the recommendations on performing osteosynthesis of the atrophied mandible based on experimental data and clinical observations depend specifically on the assessment of the vertical size of the mandibular body [9–13].

However, atrophy of the edentulous mandible body progresses unevenly. The increase in the incidence rate of fracture lines in the L_3 region that we observed in

association with the loss of occlusal contacts suggests that atrophic changes in the bone tissue develops predominantly in the lateral portions of the mandibular body, while being less pronounced in the angle and frontal regions. These changes are related precisely with the atrophy of the mandibular body in cross-section, rather than with the loss of its height [14]. These fractures should be characterized as extremely unfavorable because of the abovementioned processes, contact surface between bone splinters is reduced, which negatively influences bone wound healing and can lead to impaired consolidation. According to Bruce and Ellis [5], in 20% of cases healing in this region occurs by syndesmosis, without callus formation. Consequently, it seems reasonable to perform computed tomography scanning when planning treatment if the fracture line is located in the lateral portions of the atrophied mandibular body.

Another factor considerably complicating bone wound healing in cases of severely atrophied mandibular body is luminal narrowing of the inferior alveolar artery; thus, bone tissue blood supply is provided predominantly by periosteal vessels [15], which are severely damaged following injury or surgery.

Spiessl [16] described a non-union type of fracture typical for atrophied edentulous mandible, which is referred to as "elephant's-foot-like" in literature, due to hypertrophy of the bone fragment ends. In this study, in the patients admitted to the clinic we observed non-union atrophic fractures accompanied by necrosis in the area of bone wound margins leading to the formation of secondary sequestra and, respectively, marginal bone defects after their removal (Figure 3).

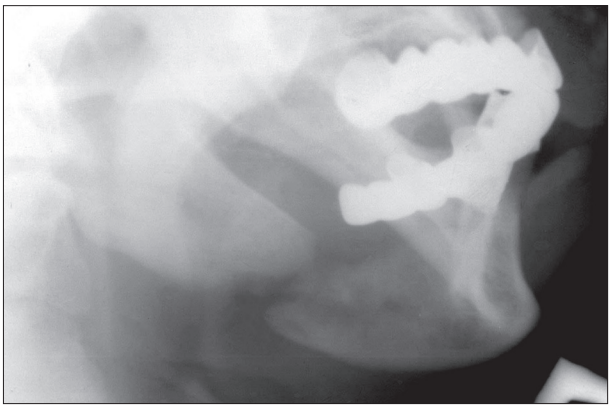

Figure 3. Pseudarthrosis of the atrophic type in the angle of the mandible

According to de Amaratugna [14], fractures in the angle of an edentulous mandible are rare. The author observed only three types of distribution of bilateral fractures by their localization with injury in the condylar process region in all cases. However, in our study, fractures in the mandibular angle area had the second highest prevalence in the O_2 category. We observed 13 different variants of fracture line localization in bilateral fractures. These differences could be related to the higher number of observations included in this study (337 versus 67).

Moreover, fractures in the condylar process region were slightly less frequent then in patients with occlusal contacts. Obviously, changes in the anthropometric parameters in the area of condylar processes in cases of mandibular atrophy do not essentially influence their resistance to injury.

In the current study, we determined that the incidence rate of fractures in the frontal portion of the edentulous mandible is 1.5 × lower than in dentulous subjects.

The structure of etiological factors of mandibular fractures differs by country and region; however, the fact that in the absence of occlusal contacts fractures commonly occurred following an insignificant impact confirms the view of Barber [17] of decreased resistance of atrophied mandibles to damaging impact. Nevertheless, the frequency of bilateral fractures was only slightly higher compared to the group of patients with occlusal contacts. No significant differences were found between the two groups by the F category.

There is a widespread opinion expressed long ago by Rowe and Killey [18] that in older patients the risk of mandibular fracture infections is low, since in edentulous mandibles the injury leads to the detachment of mucosa and periosteum, whereas the fractures remain closed. On the contrary, our data showed that open fractures were diagnosed rather frequently not only in patients with occlusal contacts, but in edentulous patients as well (Table 2). This could be related to the decreased thickness of the mucosa covering the alveolar region of the mandible, which is observed in older patients [19]. Thus, the fracture area communicates with the oral cavity, which can lead to its infection.

The high frequency of bone fragment dislocation observed in the patients included in this study correlates with data reported by other authors [5, 7]. Obviously, the loss of teeth is a significant risk factor contributing to the displacement of splinters.

No unified clear algorithm for managing older patients with mandibular fractures has been developed yet. In practice, considering the presence of comorbidities and atrophic changes in the injured area, there is a tendency to extend the indications for conservative treatment. However, the results of this study show that such an approach is not justified, considering the high incidence rate of open fractures and bone fragment dislocation, which will negatively influence the probability of complications and the subsequent quality of life of older subjects. By contrast, stable fixation of bone fragments contributes to the immediate recovery of the normal mandibular function [20]. Nonetheless, the application of bone plates and screws causes an additional and rather significant injury, which is associated with the risk of subsequent impairment of blood supply to the mandible, including in the area of injury itself [21]. In older patients, a shorter duration of surgery should be attempted; however, the correct plate placement requires a considerable amount of time due to atrophic changes in the mandible [20]. In this regard, preoperative computer planning technologies are currently being developed [22].

To solve this issue, opposite surgical concepts are sometimes proposed. Some authors postulate the principle that "The smaller the bone, the larger the plate" [13, 23], while others insist on a minimally invasive approach [9, 24]. It was experimentally shown that although the bone mass is decreased, the minimal acceptable thickness of the bone plate for an atrophied mandible should be at least 2 mm [25], since without occlusal contacts the distribution of load and the force generated by the multidirectional action of the masticatory muscles are transmitted directly to the injured area [13, 21]. Whether the use of bone transplants or tricalcium phosphate with rhBMP-2, fixed by an encircling suture or a locking plate [7, 13, 22, 26, 27], is appropriate or whether the plate should be placed over the periosteum, over the mucosa or directly on the bone remains controversial [13, 21, 23, 28]. Overall, as shown by the results of the most complete Cochrane Review by Nasser et al. [29], there is no consensus on this issue, which could be explained by the fact that most studies included comparatively small numbers of observations due to the relatively low incidence of such cases in clinical practice.

To date, there are no reliable randomized clinical trials based on sufficient statistically significant material that allows substantial advantages of a particular method of treatment of older patients with mandibular fractures at the evidence level, which requires the continuation of the relevant multicenter clinical studies [30].

CONCLUSION

Patients over 50 years of age represent a rather consistent and statistically important subset of the general population of individuals with mandibular fractures. At the same time, a number of clinical features determined by a background of comorbidities and atrophic mandibular changes distinguish them from other age groups.

This study is the largest in literature by the included number of people over 50 years of age with mandibular fractures, including those with edentulous mandible, which ensures the required level of representation, allowing reliable clinical characterization of this contingent of patients. The presented material could be used for the development of a complex treatment algorithm for elderly patients with mandibular fractures, which would take into consideration both general and local status. This task can be accomplished with a wide approach to the problem overall rather than by separating different clinical aspects.

Conflict of interest: None declared.

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Клиничке карактеристике прелома доње вилице код болесника старијих од 50 година

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САЖЕТАК

Увод/Циљ Најчешће коришћене методе лечења прелома доње вилице нису увек успешне код старијих болесника, због смањења регенеративне способности, поремећаја васкуларизације, остеопорозе, атрофичних промена. Одговарајуће промене су честе код болесника старијих од 50 година, нарочито у позадини губитка великог броја зуба. Циљ студије је преглед клиничких карактеристика прелома доње вилице код старијих болесника на основу ретроспективне анализе медицинске документације.

Методе Међу болесницима са преломима доње вилице који су били на лечењу 10 година изабрана је и анализирана група болесника старијих од 50 година.

Резултати Студија је открила 642 болесника старија од 50 година са 1003 линије прелома, што представља 8,53% укупног броја болесника са преломима доње вилице. Коморбидитет је дијагностикован у 67% случајева. Идентификоване су значајне разлике у расподели учесталости линија прелома локализацијом у зависности од присуства или одсуства оклузивног контакта. Висока учесталост отворених прелома и дислокација костних фрагмената примећена је и код особа са оклузивним контактом и без њега.

Закључак Болесници старији од 50 година су статистички значајна група у општој популацији болесника са преломима доње вилице са низом клиничких карактеристика. Колико нам је познато, ова студија је највећа по укљученом броју старијих особа са преломима доње вилице, укључујући и безубу доњу вилицу, која обезбеђује потребан ниво репрезентативности, омогућавајући поуздану клиничку карактеризацију овог контингента болесника.

Кључне речи: атрофија доње вилице; оклузија; адентија; старији болесници

DOI: https://doi.org/10.2298/SARH181120006K
UDC: 616.36:577.1; 616.1

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Are liver function biomarkers independently associated with Framingham risk score in women?

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SUMMARY

Introduction/Objective Given the contradictory results regarding the association of liver function biomarkers [e.g., alanine-aminotransferase (ALT), gamma-glutamyl transferase (GGT) and total bilirubin)] and the risk of cardiovascular disease (CVD), we aimed to explore the relationship between these biomarkers and Framingham risk score (FRS), an established tool used in the prediction of 10-year CVD risk in the cohort of women.

Methods A total of 278 women participated in this cross-sectional study. Anthropometric, biochemical parameters, and blood pressure were obtained.

Results There was a significant increase in ALT and GGT activity, as well as a decrease in total bilirubin level in the high-risk FRS group compared to moderate-, and low-risk FRS (p for trend = 0.025, $p < 0.001$, $p < 0.001$, respectively). Multivariate logistic regression analysis showed that body mass index, triglycerides, creatinine, and high sensitivity C-reactive protein levels were the independent predictors of FRS in women [odds ratio (OR) = 1.234, p = 0.001; OR = 2.856, p = 0.001; OR = 1.090, p = 0.002, and OR = 1.295, p = 0.045, respectively]. In contrast, total bilirubin, ALT and GGT lost their independent predictions for high CVD risk.

Conclusion Liver function biomarkers (i.e. ALT, GGT, and total bilirubin) are not independently associated with FRS. It seems that some other cardiometabolic disturbances might modulate this relationship.

Keywords: cardiovascular risk; inflammation; obesity; liver function

INTRODUCTION

Cardiovascular disease (CVD) in women is still the leading cause of death in most developed and developing countries. In addition, the manifestation of heart disease differs between sexes, often leading to worse consequences in women than in men [1]. Women at menopause experience increased visceral obesity, insulin resistance, and unfavorable hormonal milieu compared with women in premenopausal period, which leads to increased CVD risk [2]. On the other hand, women of reproductive age with hypertensive disorders of pregnancy are among the populations with the highest risk for premature CVD [1].

So far, a larger number of researches dealing with this pathology has been conducted in men, but implies the need for the optimal screening of women at high CVD risk [1].

Considering a complex phenotype of CVD, a search for a variety of biomarkers that act via different biological pathways, thus preceding overt CVD, has been increased [2, 3]. Among them, liver function biomarkers have shown to be independently associated with CVD risk in many studies so far [4, 5]. In addition, the association between severity of ultrasonographic nonalcoholic fatty liver disease (NAFLD), as the commonest manifestation of hepatic disorder, and cardiometabolic risk has been reported [6].

However, research papers lack consistency, showing contradictory results on the utility of liver function biomarkers when predicting CVD risk [7–11]. There are also inconsistencies when sex influence on this relationship is concerned, as well as assumptions that association of liver function biomarkers with CVD risk was dependent on some other potential predictors' influence [12]. In line with this, although concordant results show that aspartate aminotransferase (AST) was not associated with an increased risk for CVD [13], it is still a matter of debate whether other liver function biomarkers [i.e. alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), and total bilirubin] have a causal role in the pathogenesis of CVD or they are just simple markers of coexisting CVD risk factors [7–11].

Although the relationship between NAFLD and cardiometabolic risk has been shown by some previous reports, the underlying pathophysiological mechanism of this association has not yet been clarified [6]. We speculate that obesity-related inflammation and dyslipidemia might modulate the relationship between liver enzymes and CVD risk, having in mind that the highest prevalence of NAFLD is observed in individuals with obesity or type 2 diabetes mellitus (DM2), who have a two-fold risk increase for the development and progression of CVD [14, 15].

Received • Примљено: November 20, 2018
Revised • Ревизија: October 14, 2019
Accepted • Прихваћено: January 22, 2020
Online first: January 28, 2020

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Given the contradictory results regarding the relationship of liver function biomarkers (i.e. ALT, GGT, and total bilirubin) and risk for CVD, we aimed to explore the relationship between these biomarkers and Framingham risk score (FRS), an established tool used in the prediction of 10-year CVD risk, in the cohort of women population [12].

METHODS

Study population

The examined cohort included 278 women who volunteered to participate in this cross-sectional study. All participants were consecutively recruited into the study when visiting the Primary Health Care Center in Podgorica, Montenegro, for their regular check-up, between October 2012 and May 2016. Women were regarded to be postmenopausal if they self-reported the absence of menstrual bleeding for more than one year. Examined women were considered to have DM2 based on previously described criteria [14, 16].

Exclusion criteria for all the women were the following: previously known CVD, type 1 diabetes mellitus, pregnancy, kidney diseases other than nephropathy, liver diseases other than hepatic steatosis, ethanol consumption > 20 g/day, gout, high sensitivity C-reactive protein (hsCRP) > 10 mg/L, malignant diseases, as well as unwillingness to participate in the research.

A total of 70.1% women were overweight/obese, whereas 32.4% were with DM2. Also, the majority of women (82%) were postmenopausal. A total of 14% of women used hypolipidemic drugs, whereas 26.3% were treated for hypertension. A total of 29.1% of the patients used oral hypoglycemic drugs, and 3.2% of them were on insulin therapy.

Written informed consent was obtained from all the patients. The research was carried out in compliance with the Declaration of Helsinki, while the study protocol was approved by the Ethical Committee of the Primary Health Care Center in Podgorica, Montenegro.

Anthropometric measurements

All the participants' anthropometric measurements' proceedings have been described previously [15].

Biochemical analyses

Biochemical parameters [i.e. hsCRP, creatinine, glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), uric acid, bilirubin, AST, ALT, and GGT], were measured as described previously [14, 16].

Blood pressure was measured and glomerular filtration rate was estimated (eGFR), as was shown previously [15, 16].

The FRS calculation included information on age, sex, TC, HDL-c, smoking status, presence of diabetes, and systolic blood pressure (SBP). Thereafter, the cohort of studied women was divided into low-risk (FRS < 10%), moderate-risk (10% ≤ FRS < 20%), and high-risk FRS status (FRS ≥ 20%) [17].

Statistical analyses

Distribution of data was tested with Kolmogorov–Smirnov test. Comparisons of continuous normal and log-normal variables were performed by ANOVA with the Tukey–Kramer *post hoc* test for subgroup differences. Skewed distributed data were compared by Kruskal–Wallis *post hoc* test. The data are shown as mean ± standard deviation (SD) for normally distributed data, geometrical mean [95% confidence interval (CI)] for log-normal distributed data [18], median (25th–75th percentile) for skewed distributed data, and as relative frequencies for categorical variables. Analysis of categorical variables was performed by using the χ^2 test for contingency tables. Categorical variables were coded as follows: smoking status (0 – non-smoker, 1 – smoker); diabetes mellitus (0 – without diabetes mellitus, 1 – patients with diagnosed diabetes mellitus), menopausal status (0 – premenopausal, 1 – postmenopausal) and therapy (0 – no therapy, 1 – therapy). To estimate the correlation between the examined cardiometabolic parameters with FRS, Spearman's correlation analysis was performed. The data were given as correlation coefficient (ρ). Independent associations between high FRS and cardiometabolic parameters were tested by univariate and multivariate binary logistic regression analyses. The low FRS category was coded as 0, while the medium and high FRS categories were coded as 1. To examine independent predictions of continuous variables, multivariate adjustment was made for all continuous variables which did not enter the FRS calculation, and which significantly correlated with FRS ($p < 0.05$), as well as categorical variables which were not included in the FRS calculation, and which showed unequal distribution between low-, moderate-, and high-risk FRS groups. Odds ratio (OR) and the 95 CI were estimated. The explained variation in FRS was given by Nagelkerke R^2 value. The Hosmer–Lemeshow test was used to examine if there was a linear relationship between the predictor variables and the log odds of the dependent variable. Receiver operating characteristic (ROC) curve analysis was used to examine diagnostic performance of each cardiometabolic parameter and the model, as well as to discriminate women with moderate and high FRS from those with low FRS. The area under the ROC curve (AUC) of 0.5–0.7 suggested that diagnostic test had low accuracy; 0.7–0.8 satisfactory accuracy, 0.8–0.9 good accuracy, while AUC higher than 0.9 suggested excellent accuracy of the diagnostic test [19]. A p-value less than 0.05 was considered statistically significant. All statistical calculations were performed in the PASW® Statistics, Version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 summarizes general characteristics of the study groups according to their calculated FRS. Women in the

Table 1. General characteristics of the studied patients

Characteristics	Low risk (FRS < 10%)	Moderate risk (10% ≤ FRS < 20%)	High risk (FRS ≥ 20%)	p
n	144	65	69	
Age, years	53 (48–57)	61 (55–64)[a*]	66 (61–70)[a*, b*]	< 0.001
BMI, kg/m^2	25.5 (22.7–28.3)	28.3 (26.2–33.3)[a*]	31.2 (28.7–33.9)[a*, b*]	< 0.001
SBP, mmHg	125 (110–135)	150 (130–158)[a*]	140 (130–155)[a*]	< 0.001
DBP, mmHg	76 (68–86)	90 (80–97)[a*]	80 (75–90)[a*]	< 0.001
Smokers, %	8.33	3.08	17.40	0.015
Diabetes mellitus, %	4.86	35.38	87	< 0.001
Menopausal status, %	69.44	95.38	95.65	< 0.001
Hypolipidemics, %	0.69	13.85	42.03	< 0.001
Antihypertensives, %	2.78	26.15	75.36	< 0.001
Oral antidiabetics, %	4.17	29.23	81.16	< 0.001
Insulin therapy, %	0.69	4.62	7.25	0.032

Data are presented as median (interquartile range) and compared by Kruskal–Wallis test; categorical variables are presented as relative frequencies and compared by χ^2 test;
BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FRS – Framingham risk score;
[a]significantly different from the first group; *post-hoc* Kruskal–Wallis test;
[b]significantly different from the second group; *post-hoc* Kruskal–Wallis test;
*p < 0.05

Table 2. Clinical parameters of women in different Framingham risk score groups

Parameters	Low risk (FRS < 10%)	Moderate risk (10% ≤ FRS < 20%)	High risk (FRS ≥ 20%)	p
TC, mmol/L	5.97 ± 1.16	6.34 ± 1.11	5.93 ± 1.26	0.125
HDL-c, mmol/L	1.71 ± 0.43	1.46 ± 0.33[a*]	1.25 ± 0.29[a*, b*]	< 0.001
LDL-c, mmol/L	3.77 ± 1.09	4.19 ± 1.12	3.72 ± 1.21	0.052
TG, mmol/L[+]	1.18 (1.11–1.27)	1.76 (1.59–1.95)[a*]	2 (1.78–2.23)[a*]	< 0.001
Glucose, mmol/L[++]	5.2 (4.9–5.6)	6.0 (5.2–7.2)[c*]	7.0(6.2–8.1)[c*, d*]	< 0.001
Creatinine, µmol/L[++]	57 (51–62)	59 (54–65)[c*]	64 (57–74)[c*]	< 0.001
Uric acid, µmol/L[+]	235 (226–245)	277 (254–302)[a*]	300 (282–320)[a*]	< 0.001
Total bilirubin, µmol/L[++]	7.20 (5.80–9.32)	7.10 (5.20–9.85)	5.70 (4.17–7.12)[c*, d]	< 0.001
HsCRP, mg/L[+]	0.87 (0.74–1.02)	1.62 (1.23–2.14)[a*]	2.33 (1.88–2.89)[a*]	< 0.001
AST, U/L[++]	18 (15–21)	18 (16–22)	18 (16–22)	0.352
ALT, U/L[++]	17 (13–22)	21 (14–27)[c*]	19 (15–27)	0.025
GGT, U/L[++]	11 (9–16)	14 (10–16)	17 (14–25)[c*, d*]	< 0.001

Data are presented as arithmetic mean ± SD and compared with Student's t-test;
TC – total cholesterol; HDL-c – high density lipoprotein cholesterol; LDL-c – low density lipoprotein cholesterol; TG – triglycerides; hsCRP – high-sensitivity C-reactive protein; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; FRS – Framingham risk score;
[+]log-normal distributed data are presented as geometric mean (95% CI) and compared with Student's t-test after logarithmic transformation;
[++]skewed distributed data are presented as median (interquartile range) and compared with Mann–Whitney U-test;
[a]significantly different from the low risk group; *post-hoc* Tuckey–Kramer test;
[b]significantly different from the medium risk group; *post-hoc* Tuckey–Kramer test;
[c]significantly different from the low risk group; *post-hoc* Kruskal–Wallis test;
[d]significantly different from the medium risk group; *post-hoc* Kruskal–Wallis test;
*p < 0.05

high-risk FRS group were older and had higher body mass index (BMI) than those in low-and moderate-risk FRS groups. Also, women in the moderate-risk FRS group were older and had higher BMI than women in the low-risk group. SBP and DBP were significantly lower in the low-risk FRS group than in the moderate- and high-risk group. As expected, the high-risk FRS group had significantly higher percentage of smokers, women with DM2, women on hypolipidemic, antihypertensive, oral hypoglycemic and insulin therapies, compared to low- and moderate-risk FRS groups. Higher percentage of postmenopausal women were in the moderate- and high- FRS group than in the low-risk one.

Although TC was entered into the FRS calculation algorithm, its concentration was not significantly different between low-, moderate-, and high-risk FRS group of women (Table 2). The HDL-c concentration was higher in the first than in the second and third risk group. Also, its concentration was higher in the moderate- than in the high-risk FRS group. The opposite was found for glucose concentration in women. Moreover, TG, creatinine, uric acid, and hsCRP concentrations were higher in the moderate- and high-risk FRS groups than in the first one. The lowest bilirubin concentrations were determined in the high-risk FRS group. ALT activities were higher in the moderate- than in the low-risk FRS group, whereas GGT activities were the highest in the high-risk FRS group.

Beside parameters used in its algorithm, FRS significantly positively correlated with BMI, DBP, TG, glucose, creatinine, uric acid, hsCRP, ALT, and GGT. Significant negative correlations were established between FRS and HDL-c, which was used for its calculation, and between FRS and total bilirubin (Table 3).

Table 3. Bivariate Spearman's correlation analysis between Framingham risk score and other general and clinical parameters

Parameters	FRS	
	P	p
Age, years	0.703	< 0.001
BMI, kg/m^2	0.578	< 0.001
SBP, mmHg	0.606	< 0.001
DBP, mmHg	0.447	< 0.001
TC, mmol/L	0.172	0.004
HDL-c, mmol/L	-0.510	< 0.001
LDL-c, mmol/L	0.201	0.001
TG, mmol/L$^+$	0.559	< 0.001
Glucose, mmol/L^{++}	0.639	< 0.001
Creatinine, μmol/L^{++}	0.279	< 0.001
Uric acid, μmol/L$^+$	0.459	< 0.001
Total bilirubin, μmol/L^{++}	-0.241	< 0.001
HsCRP, mg/L$^+$	0.435	< 0.001
AST, U/L^{++}	0.035	0.564
ALT, U/L^{++}	0.120	< 0.001
GGT, U/L^{++}	0.407	< 0.001

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol; HDL-c – high density lipoprotein cholesterol; LDL-c – low density lipoprotein cholesterol; TG – triglycerides; hsCRP – high-sensitivity C-reactive protein; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; FRS – Framingham risk score
$^+$log-normal distributed data are presented as geometric mean (95% CI) and compared with Student's t-test after logarithmic transformation;
$^{++}$skewed distributed data are presented as median (interquartile range) and compared with Mann–Whitney U-test

Table 4. Odds ratios (OR) after univariate and multivariate logistic regression analysis for parameters predicting Framingham risk score risk

Predictors	Unadjusted OR (95% CI)	p	Nagelkerke R^2
BMI, kg/m^2	1.300 (1.210–1.396)	0.015	0.328
TG, mmol/L	4.358 (2.817–6.743)	< 0.001	0.273
Creatinine, μmol/L	1.060 (1.033–1.088)	< 0.001	0.120
Total bilirubin, μmol/L	0.915 (0.854–0.980)	0.011	0.036
HsCRP, mg/L	1.375 (1.204–1.571)	< 0.001	0.132
ALT, U/L	1.028 (1.003–1.054)	0.021	0.025
GGT, U/L	1.026 (1.004–1.049)	0.021	0.032
Model	Adjusted OR (95% CI)	p	Nagelkerke R^2
BMI, kg/m^2	1.234 (1.088–1.399)	0.001	0.725 (for the model)
TG, mmol/L	2.856 (1.545–5.277)	0.001	
Creatinine, μmol/L	1.090 (1.033–1.150)	0.002	
Total bilirubin, μmol/L	0.930 (0.823–1.052)	0.249	
HsCRP, mg/L	1.295 (1.085–1.490)	0.045	
ALT, U/L	1.008 (0.955–1.063)	0.782	
GGT, U/L	1.003 (0.963–1.004)	0.893	

Model: BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT, and GGT (all continuous variables); menopausal status and hypolipidemic therapy (categorical variable);
BMI – body mass index; TG – triglycerides; HsCRP – high-sensitivity C-reactive protein; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase

Logistic regression analysis was used to test if any of cardiometabolic parameters which were not used in FRS algorithm and showed significant correlations ($p < 0.05$) with FRS, had potential to predict high CVD risk (Table 4). Those predictors were continuous variables such as BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT, and GGT, as well as categorical variables such as menopausal status and hypolipidemic therapy. Predictors were unadjusted and adjusted for other parameters and tested by univariate and multivariate analysis, respectively (Table 4). Significant OR for tested predictors from univariate analysis were shown in Table 4. It was shown that BMI, TG, creatinine, total bilirubin, hsCRP, ALT, and GGT were significant predictors for higher FRS. As BMI rose for 1 kg/m^2, TG for 1 mmol/L, creatinine for 1 μmol/L, hsCRP for 1 mg/L, ALT for 1 U/L, and GGT for 1 U/L, probability for higher CVD risk rose by 30%, 4.358 times, 6%, 37.5%, 2.8%, and 2.6%, respectively. As total bilirubin concentration rose by 1 μmol/L, probability for higher CVD risk decreased by 8.5%. Nagelkerke R^2 showed that each predictor in univariate analysis, BMI, TG, creatinine, total bilirubin, hsCRP, ALT, and GGT could explain the variation in higher risk for CVD occurrence by 32.8%, 27.3%, 12%, 3.6%, 13.2 %, 2.5%, and 3.2%, respectively. All predictors tested in univariate analysis (BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT, GGT, menopausal status, and hypolipidemic therapy) were further tested in multivariate logistic regression analysis in order to determine their independent association with high FRS. Namely, four parameters having significant odds in univariate analysis (BMI, TG, creatinine, and hsCRP) kept independent predictive power for high CVD risk in the model. In contrast, total bilirubin, ALT, and GGT lost their independent predictions for high CVD risk. In multivariate analysis, as BMI rose by 1 kg/m^2, TG by 1 mmol/L, creatinine by 1 μmol/L, and hsCRP by 1mg/L, probability for higher CVD risk rose by 23.4%, 2.856 times, 9%, and 29.5%, respectively. Nagelkerke R^2 of 0.725 showed that the model could explain 72.5% of variation in the FRS.

Thereafter, a ROC analysis was used to discriminate women with low risk from those with moderate and high risk of developing CVD (Table 5). The calculated AUC for BMI, TG, and hsCRP indicated satisfactory accuracy, whereas ROC analysis showed low accuracy for creatinine, total bilirubin, ALT, and GGT as diagnostic tools. The calculated AUC for the model (which included BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT, GGT, menopausal status, and hypolipidemic therapy) was 0.944, which suggested excellent clinical accuracy. Also, the model had higher sensitivity than single predictors (Table 5, Figure 1).

DISCUSSION

The findings of the current study reveal that liver function biomarkers (i.e. ALT, GGT, and total bilirubin) are not independently associated with FRS, even though there was a significant increase in ALT and GGT activity, as well as a decrease in total bilirubin level in the high-risk FRS group compared to the moderate- and low-risk FRS group (Table 2). In addition, although all these biomarkers correlated with FRS in Spearman's non-parametric correlation analysis (Table 3), in multivariate logistic regression analysis these biomarkers lost their independent predictions for high CVD risk (Table 4). This may give rise to the

Table 5. Receiver operating characteristic analysis for single parameters and the model discriminatory abilities regarding Framingham risk score in the studied patients

Predictors	AUC (95% CI)	SE	Sensitivity (%)	Specificity (%)	p
BMI, kg/m^2	0.800 (0.748–0.845)	0.026	81	66	< 0.001
TG, mmol/L	0.781 (0.728–0.828)	0.027	83	64	< 0.001
Creatinine, μmol/L	0.649 (0.590–0.705)	0.033	31	94	< 0.001
Total bilirubin, μmol/L	0.588 (0.521–0.654)	0.034	40	76	0.012
HsCRP, mg/L	0.739 (0.684–0.790)	0.029	79	58	< 0.001
ALT, U/L	0.594 (0.528–0.661)	0.034	79	37	0.006
GGT, U/L	0.693 (0.631–0.755)	0.031	63	70	< 0.001
Model	0.944 (0.910–0.968)	0.012	90	83	< 0.001

Model: BMI, DBP, LDL-c, TG, creatinine, uric acid, total bilirubin, hsCRP, ALT and GGT (all continuous variables); menopausal status and hypolipidemic therapy (categorical variable);
AUC – area under the ROC curve; BMI – body mass index; TG – triglycerides; hsCRP – high-sensitivity C-reactive protein; ALT – alanine aminotransferase; GGT-gamma-glutamyl transferase

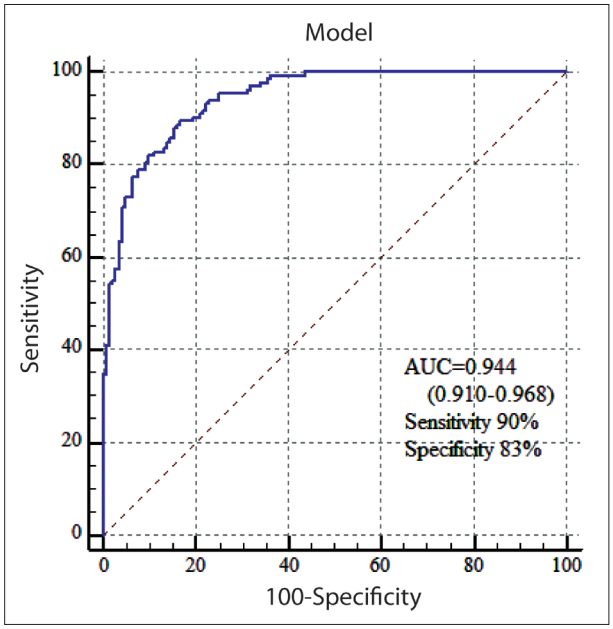

Figure 1. Discriminatory ability of the model regarding cardiovascular disease risk

assumption that these biomarkers might only be bystanders in CVD prediction, instead of direct contributors to CVD onset and progression.

Indeed, previous findings have shown that the association of GGT with FRS is dependent on the other potential predictors [12]. Furthermore, the addition of GGT to traditional risk factors does not improve CVD risk prediction [8, 20].

Concerning the ALT activity in relation to CVD risk, several large sample studies reported that ALT is positively associated with CVD events and long-term mortality in middle-aged adults, independently of other cardiometabolic factors [21, 22, 23]. However, some others suggest that ALT level is not a reliable marker for screening for the CVD occurrence in the general population [7], whereas some of them found an inverse relationship between ALT levels in the normal range and adverse cardiovascular and non-cardiovascular outcomes [24].

Similar discordant results were also found for bilirubin. While some studies report its independent relationship with CVD risk [5, 9], others claim the opposite [11]. Moreover, the addition of total bilirubin to traditional risk factors showed no significant improvement in prediction of CVD risk [9].

There is also sex difference concerning the relationship between liver enzymes and CVD risk, showing that GGT was positively associated only with higher levels of FRS in women, but not in men [12]. On the other hand, ALT showed a significant inverse relationship with FRS in men, while this relationship remained significant in women only for lower and intermediate FRS status [12].

We speculate that some other cardiometabolic disturbances (e.g. obesity-related dyslipidemia and inflammation) might modulate the relationship between liver function biomarkers and CVD risk. In line with this, unlike liver function biomarkers (i.e. ALT, GGT, and total bilirubin), BMI, TG, hsCRP, and creatinine were the independent predictors of FRS in women in our study (Table 4), showing that as BMI rose by 1 kg/m^2, TG by 1 mmol/L, creatinine by 1 μmol/L, and hsCRP by 1mg/L, probability for higher CVD risk rose by 23.4%, 2.856 times, 9%, and 29.5%, respectively, suggesting that the mentioned model could explain as much as 72.5% of variation in the FRS. Moreover, a ROC analysis used to discriminate women without low risk from those at moderate and high risk for developing CVD, revealed that calculated AUC for BMI, TG, and hsCRP indicated satisfactory accuracy, whereas ROC analysis showed low accuracy for creatinine, total bilirubin, ALT, and GGT as diagnostic tools (Table 5).

One of the potential explanations for such findings may lie in the obesity status and its relationship with CVD [25]. In our study, a total of 70.1% of examined women were overweight/obese. Moreover, the majority of individuals with NAFLD are obese [15], which was found to be the independent risk factor for progression of this hepatic disorder [6]. Namely, in the obese state, an increase in free radicals' production, a decrease in antioxidant defense [14, 26], as well as low-grade inflammation with consequent insulin resistance [15, 27], lead to an increased free fatty acids hepatic influx. These pathophysiological processes further aggravate increased lipogenesis and triglyceride storage, thus promoting dysfunction of hepatocytes [28]. All of these metabolic disturbances may lead to increased ALT and GGT activity, and to a decreased bilirubin level [6, 25]. Moreover, not only do high levels of free fatty acids in addition to insulin resistance lead to hepatocytes dysfunction, but they also promote endothelial dysfunction, reduce production of nitric oxide, vasoconstriction, and inflammation with consequent initiation and progression of atherosclerosis [29, 30], thus further supporting the link between obesity, high triglycerides, and inflammation level and CVD.

The limitations of this study need to be reported. Namely, the cross-sectional design of our study does not allow us to establish the causal link between liver function biomarkers and CVD risk. Also, we have included only women population in our study. Thus, longitudinal studies comprising both sexes are needed to explore the mechanism of this relationship in order to elucidate if liver function biomarkers have a causal role in the pathogenesis of CVD.

CONCLUSION

Liver function biomarkers (i.e. ALT, GGT, and total bilirubin) are not independently associated with FRS. It seems that some other cardiometabolic disturbances (e.g. obesity-related dyslipidemia and inflammation) might modulate this relationship. New large sample-size studies with longitudinal design and with both sexes included are needed to clarify the potential mechanism of the relationship between liver function biomarkers and CVD risk.

ACKNOWLEDGEMENT

This work was in part financially supported by a grant from the Ministry of Education, Science and Technological Development of the Republic of Serbia (project number 175035).

Conflict of interest: None declared.

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Да ли су биомаркери функције јетре независно повезани са Фрамингхамским скором за ризик у женској популацији?

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САЖЕТАК

Увод/Циљ С обзиром на контрадикторне резултате који се односе на повезаност биомаркера функције јетре [аланин-аминотрансферазе (АЛТ), гама-глутамил трансферазе (ГГТ) и укупног билирубина)] и ризика за појаву кардиоваскуларних болести, циљ студије је био да се испита повезаност између ових биомаркера и Фрамингхамског скора за ризик (ФСР), алгоритма за процену 10-годишњег ризика за појаву кардиоваскуларних болести у кохорти женске популације.

Методе У овој студији пресека учествовало је укупно 278 жена. Мерени су антропометријски, биохемијски параметри и крвни притисак.

Резултати Уочен је статистички значајан пораст активности АЛТ и ГГТ, као и пад вредности укупног билирубина у групи са високим статусом ФСР, у поређењу са средњим и ниским ФСР ($p = 0,025$, $p < 0,001$, $p < 0,001$, редом). Мултиваријантна логистичка регресиона анализа показала је да су индекс телесне масе, вредности триглицерида, креатинина и високоосетљивог *c*-реактивног протеина независни предиктори ФСР код жена ($OR = 1,234$, $p = 0,001$; $OR = 2,856$, $p = 0,001$; $OR = 1,090$, $p = 0,002$ и $OR = 1,295$, $p = 0,045$, редом). С друге стране, укупни билирубин, АЛТ и ГГТ су изгубили независну предикцију за високи ризик за појаву кардиоваскуларних болести.

Закључак Биомаркери функције јетре (тј. АЛТ, ГГТ и укупни билирубин) нису независно повезани са ФСР. Претпоставља се да неки други кардиометаболички поремећаји могу утицати на ову повезаност.

Кључне речи: ризик за појаву кардиоваскуларних болести; инфламација; гојазност; функција јетре

DOI: https://doi.org/10.2298/SARH200125032S
UDC: 616.12-073(497.11)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Current echocardiography practice in Serbia – a national survey by the Echocardiographic Society of Serbia

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SUMMARY

Introduction/Objective The purpose of the Echocardiographic Society of Serbia (ECHOS) national survey was to assess current echocardiography practice in Serbia, the availability of different echocardiographic techniques and self-perceived need for improvement at personal and institutional level.

Methods A survey comprising 20 questions about demographics, numbers and distribution of echocardiographic equipment and techniques, image acquisition and reporting standards as well as future educational preferences was sent to all ECHOS members via email.

Results A total of 106 members (42%) answered the survey. Echocardiographic examinations are most frequently performed by cardiologists and internal medicine specialists. Transesophageal echocardiography (TOE), stress echocardiography (SECHO) and speckle tracking echocardiography (SpTE) are available in approximately 20% of centers, three-dimensional echocardiography in 11%, while contrast echocardiography is practiced in only two centers. Less than a third of respondents always attach electrocardiographic electrodes and archive examinations. Almost all respondents (96%), always evaluate both systolic and diastolic function of the left ventricle (LV), although systolic LV function is frequently assessed (55%) using non-standard methods. The newer echocardiographic machines are more often available at university than non-university centers (87 *versus* 44%, $p < 0.01$). SECHO was perceived as the most needed technique at the institutional level, while SpTE and TOE were most often reported personal aspirations of the respondents.

Conclusion Advanced techniques, SECHO and TOE are needed but rarely performed outside the university hospitals in Serbia. In order to achieve a better adherence to standards of practice in echocardiography, the development of national guidelines and personal and laboratory accreditation seem warranted.

Keywords: echocardiography; survey; Serbia

INTRODUCTION

Echocardiography is a cornerstone clinical tool used for the diagnosis, treatment, and follow up of patients with cardiovascular diseases [1]. It is the most frequently used imaging modality in a clinical cardiology [2]. Furthermore, the need for using echocardiography not only by cardiologists, but also by non-cardiologists, is rising [3, 4, 5]. In Serbia, echocardiography was implemented shortly after its introduction at the world stage and it has been used extensively ever since. Notwithstanding the long history of availability and widespread use of echocardiography, at the moment, there are no national guidelines for practice and implementation of echocardiography in Serbia. In addition, there is neither individual nor laboratory accreditation at the national level and the current echocardiography standards in Serbia are largely unknown.

The mission of the Echocardiographic society of Serbia (ECHOS) is to foster development of echocardiography by promoting and advocating personal and institutional high standards of practice, education and research in the field of echocardiography in Serbia. Setting up the national standards and guidelines for clinical practice, education, and training is an important step towards optimal use, quality improvement, and modern practice of echocardiography. However, a complete lack of data on the usage, international guideline implementation, and educational needs in echocardiography in Serbia is a serious challenge.

In order to adequately address the educational needs in echocardiography, and to develop the national recommendations and standards, ECHOS conducted a survey to demonstrate the current state of echocardiography practice in Serbia.

Received • Примљено: January 25, 2020
Revised • Ревизија: May 24, 2020
Accepted • Прихваћено: May 26, 2020
Online first: June 1, 2020

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METHODS

The survey was conducted by the ECHOS Scientific Initiatives, Membership, and affiliations Committees from June 6 to August 16, 2019. A questionnaire comprising 20 questions about demographics, numbers and distribution of echocardiographic equipment and techniques, image acquisition and reporting standards as well as educational preferences was sent to all ECHOS members (a total of 254 members at the time of conducting the survey) via email. The data were gathered and analyzed using commercially available software PASW Statistics, version 18, (SPSS Inc., Chicago, IL, USA). Categorical data were summarized by proportions and compared using a Fisher's exact test. All statistical tests were two-tailed, and a p-value < 0.05 was considered significant.

We confirm that we have read the Journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All ECHOS members received the survey and accompanying cover letter stating the intention of academic publication of the obtained data.

RESULTS

Overall, 106 ECHOS members (42%) from all regions of Serbia, including Kosovo and Metohija, answered the survey. The majority of respondents (42%) were affiliated with university hospitals, 29% were employed in general hospitals, 20% in private cardiology practices, and 9% in community health centers. Respondents' general characteristics are summarized in Table 1. Most respondents were female, older than 35 years, with more than 10 years of experience in echocardiography. In Serbia, echocardiography is performed almost exclusively by physicians while echo sonographers are currently employed in only one echocardiography laboratory. Physicians performing echocardiography have different educational backgrounds and are at different levels of training. In the vast majority of centers, echocardiography was performed by cardiologists (92%), followed by residents or fellows (24%; only at university centers) and internal medicine specialists (22%). Only 4% of respondents reported that radiologists (2%), anesthesiologists (1%) and emergency medicine specialists (1%) also perform echocardiographic examinations at their centers. Expectedly, transthoracic echocardiography (TTE) was available in all centers, but almost 65% of responders refer their patients for further evaluation to expert centers. Other echocardiographic techniques, both standard and advanced, were significantly less distributed among cardiology centers in Serbia (Table 1). The introduction of stress echocardiography (SECHO) and transesophageal echocardiography (TOE) to the existing echocardiographic armamentarium was considered the most needed improvement of the respondents' centers. Respondents' personal educational preferences were strain echocardiography, SECHO, and TOE. Contrast echocardiography was the least available but also the least desired technique, both at personal and institutional level (Table 1).

Table 1. Characteristics of respondents and summary of available and most needed echocardiographic techniques at personal and institutional level

Characteristic	%	
Age (years)		
< 35	7	
35–50	57	
> 50	36	
Sex (male/female)	35/65	
Experience in echocardiography (years)		
< 5	35	
5–10	17	
> 10	48	
Echocardiographic techniques available at the center		
Transthoracic echocardiography	100	
Transesophageal echocardiography	20	
Dobutamine stress echocardiography	22	
Exercise stress echocardiography	22	
Speckle tracking strain echocardiography	19	
Three-dimensional echocardiography	11	
Coronary flow reserve testing	8	
Agitated saline contrast study	32	
Contrast echocardiography	8	
Most desired/needed new techniques	Personal	Institutional
None	12	23
Transesophageal echocardiography	41	27
Dobutamine stress echocardiography	45	34
Exercise stress echocardiography	31	21
Speckle tracking strain echocardiography	48	26
Three-dimensional echocardiography	37	13
Coronary flow reserve testing	25	20
Agitated saline contrast study	12	7
Contrast echocardiography	16	13

Equipment, standard practice, and indications for echocardiography

Most common indications for echocardiography are cardiomyopathies (79%), coronary artery disease (76%), valvular heart diseases (70%), hypertension (63%), arrhythmias (58%), and pulmonary embolism (47%). There are significant variations among echocardiography laboratories in Serbia with regard to the equipment and standard echocardiography practice (Table 2). A daily workload ranges from up to five examinations (35% of respondents), 5–10 (34%) to more than 10 examinations (31%).

Most responders (59%) have 15–30 minutes to complete an echocardiographic study, 24% have less than 15 minutes, while 16% have approximately 30–45 minutes. Only one respondent (0.9%) usually has more than 45 minutes for examination.

Electrocardiographic (ECG) electrodes are attached to the patient during each echocardiographic examination by

Table 2. Characteristics of echocardiographic examinations and equipment

Characteristic	%
Number of examinations	
< 5 per week	9
< 5 per day	26
5–10 per day	34
> 10 per day	31
Average duration of examination	
< 15 minutes	24
15–30 minutes	59
30–45 minutes	16
> 45 minutes	1
The need for additional expertise/supervision	
Never	36
Sometimes	50
Often	14
ECG electrodes during examination	
Always	27
Sometimes	37
Never	36
Recording and archiving of examinations	
Always	39
Sometimes	41
Never	20
The age of the newest echocardiographic machine	
< 5 years	61
5–10 years	19
> 10 years	20

ECG – electrocardiography

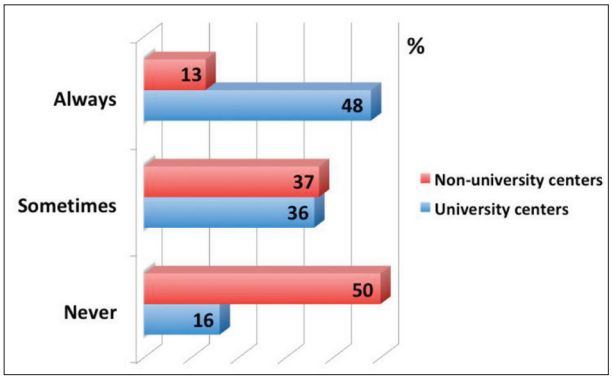

Figure 1. The practice of electrocardiographic electrodes attachment during echocardiographic examination in university *versus* non-university centers

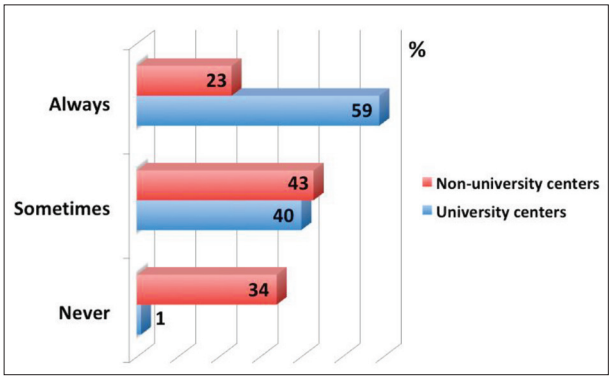

Figure 2. The practice of recording and archiving of echocardiographic examinations in university *versus* non-university centers

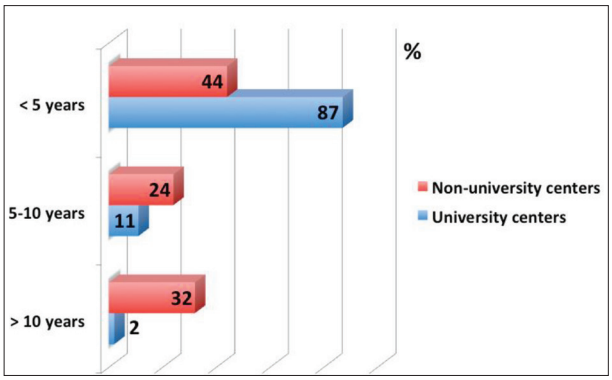

Figure 3. The age of the newest echocardiographic machine in university *versus* non-university centers

27% of respondents, occasionally by 37%, while 36% never obtain ECG signal during echocardiographic examination. All echocardiographic studies are being recorded and archived by 39% of respondents, 41% do this occasionally and 20% never record or store their examinations. The practice of attaching ECG electrodes and archiving exams is significantly more employed by physicians from university hospitals than by their colleagues from non-university centers ($p < 0.01$, for both) (Figures 1 and 2).

Almost all respondents (96%), always evaluate systolic and diastolic function of the left ventricle (LV), although systolic LV function is frequently assessed (55%) using non-standard methods (M-mode based Teichholz formula was reported by 24% and visual assessment by 31% of respondents). The newer echocardiographic machines (purchased over the last five years) are more often available at university than non-university centers (87% *versus* 44%, $p < 0.01$, Figure 3). Approximately 20% of respondents reported that the last echocardiographic machine at their center was purchased more than 10 years ago.

DISCUSSION

This is the first survey carried out by the ECHOS about the current echocardiography practice in Serbia. The scope of the survey and the response rate are in agreement with similar surveys conducted by the European and British cardiac imaging societies [6, 7]. The majority of echocardiographers (48%) who answered the survey had more than ten years of echocardiographic practice, which is in line with a trend of rapid aging of the healthcare workforce in the EU and Serbia [8]. The majority of respondents were from university hospitals whose echocardiography standards are, on average, at the higher level compared to non-university centers in terms of equipment and technical aspects of examination (ECG electrodes attachment and exams archiving). These three components of echocardiography practice are also measures of quality and, for the time being, are not at the satisfactory level in Serbia.

While equipment renewal depends on financial solvency of the center and society, regular ECG electrodes attachment and exams archiving policy are inexpensive, purely technical issues entirely dependent on the human factor, i.e. attitude of the echocardiography laboratory director. It is important to note that many advanced echocardiographic techniques (e.g. strain and 3D echocardiography) are technically impossible without a stable ECG signal. On the other hand, advantages of recording and archiving exams are numerous, including medico-legal issues, the possibility of off-line analysis for clinical purposes, research, and education, as well as comparison of patient examinations recorded at different time points. Although routine ECG electrodes attachment and exam archiving are significantly more frequently performed in the university setting, it is surprising that these basic technical aspects of echocardiographic examination are not regularly implemented in a large proportion of patients examined in university hospitals. The activities to raise awareness of these quality issues regarding image acquisition will be among the ECHOS priorities. In Serbia, echocardiography is performed mostly by cardiologists and internal medicine specialists. It should be noted, in a significant number of university centers, exams are being performed by residents or fellows whose reports should be supervised and signed by fully trained senior physicians.

In the past, some of the best echocardiographers in Serbia were technicians/nurses, while the current survey revealed that only one center has echo sonographers performing examinations. There are many potential reasons for the lack of motivation of technicians/nurses to pursue a career of echo sonographer and the ECHOS will acknowledge their value by establishing the committee for echo sonographers within the association. Finally, with miniaturization of ultrasound devices and rising availabilities for training, echocardiography became attractive to non-cardiologists [3, 4]. There is a trend of increasing use of echocardiography in emergency settings by non-cardiologists, i.e. emergency physicians, intensive care specialists, anesthesiologists, cardiac surgeons, and cardiac physiologists [9]. Our survey revealed that only a small percentage of non-cardiologists (radiologists, anesthesiologists, and intensive medicine specialists) are currently using echocardiography in their practice. The ECHOS supports this trend but insists on high-quality training and will work towards establishing education and accreditation in focus cardiac ultrasound on European and national level.

A daily caseload varied to a great extent, with two thirds of respondents performing more than five examinations, and approximately one third more than 10 examinations. In addition, the majority of respondents have less than 30 minutes to complete the examination. The ECHOS supports quality over quantity and with that also supports international standards (45 minutes per examination – for image acquisition and reporting) as good practice to maintain quality and prevent musculoskeletal injuries of echocardiographers [10, 11].

The deviations from the proposed guidelines of chamber quantification seem to be another weakness of echocardiography practice in Serbia. Although the majority of respondents evaluate both systolic and diastolic LV function, systolic LV function is not routinely quantified using guideline-proposed criteria. Instead, visual estimation or obsolete, M-mode based methods are still frequently being used which is a serious downfall, since many guideline-directed pharmacological and device therapies depend on accurate measurement of LV ejection fraction. All these technical, logistical, and fundamental inefficiencies are possible barriers to further development of echocardiographic centers outside university hospitals. TOE and SECHO, as well as advanced echocardiographic techniques seem to be the exception rather than a rule in non-university hospitals. It is, therefore, not surprising that the majority of respondents need expert supervision.

Only 12% of respondents are satisfied with the current personal educational level in echocardiography, while the vast majority is willing to master new techniques and to have new modalities implemented in their centers. While some of these advances (e.g. strain and 3D echocardiography) require substantial investments in new equipment and software, those regarded as direly required at institutional level (TOE and SECHO) can be established without significant costs. The ECHOS will address the needs expressed in this survey by organizing dedicated teaching courses and workshops in order to accelerate the development of advanced echocardiography in non-university centers.

It is important to underline that the current survey was voluntary; thus, it is possible that our members who chose to participate had particularly strong opinions towards the survey questions resulting in a positive or negative response bias. In line with this, the actual echocardiography practice in Serbia may be somewhat different from what the survey results revealed. However, in the absence of the central register or the national network of echocardiography laboratories, it is impossible to obtain more credible data. Similar to other imaging societies, the ECHOS will use data from the current survey to create an action plan in order to provide guidance to its members and foster development of echocardiography in Serbia. In parallel with the publication of the textbook on clinical echocardiography, ECHOS will produce and propose a series of expert consensus documents and position statements on training, education, competence and accreditation in echocardiography in Serbia. Ultimately, the production of national guidelines for the practice and implementation of echocardiography in clinical practice should be the final step towards a bright future of echocardiography in Serbia.

Less than 50% of ECHOS members participated in the present survey and a great care must be taken when extrapolating our results to the entire population of echocardiographers in Serbia. On the other hand, response rate to this survey is comparable to similar surveys run by international organizations [7, 12]. In addition, it would be of interest to assess the views expressed in this survey with regard to the level and type of education of the respondents. Unfortunately, data on education in echocardiography are not available and will be addressed in an upcoming ECHOS survey.

CONCLUSION

There is room for improvement in all aspects of echocardiography practice in Serbia. Advanced echocardiographic techniques, SECHO and TOE are needed but rarely performed outside the university hospitals in Serbia. In order to achieve a better adherence to standards of practice in echocardiography, the development of national guidelines and personal and laboratory accreditation are necessary.

ACKNOWLEDGMENT

We would like to thank all ECHOS member who answered the survey.

Conflict of interest: None declared.

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Актуелно стање ехокардиографије у Србији – национална анкета Ехокардиографског удружења Србије

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САЖЕТАК

Увод/Циљ Сврха националне анкете Ехокардиографског удружења Србије је процена актуелног стања ехокардиографије у Србији, доступности различитих ехокардиографских техника и потреба за напредовањем на личном и институционалном нивоу.

Методе Анкета састављена од 20 питања о демографским подацима, броју и распрострањености ехокардиографске опреме и техника, стандардима извођења прегледа и писања извештаја, као и приоритетима за едукацију, послата је електронском поштом свим члановима Ехокардиографског удружења Србије.

Резултати Анкету је попунило укупно 106 чланова (42%). Ехокардиографске прегледе најчешће обављају кардиолози и специјалисти интерне медицине. Трансезофагеална ехокардиографија, стрес ехокардиографија и *speckle tracking* ехокардиографија су доступне у око 20% центара, тродимензионална ехокардиографија у 11%, док се контрастна ехокардиографија обавља само у два центра. Мање од трећине анкетираних чланова редовно користи електрокардиографске електроде и снима прегледе. Скоро сви анкетирани чланови (96%) увек процењују систолну и дијастолну функцију леве коморе, иако се систолна функција леве коморе често процењује (55%) употребом нестандардних метода. Новији ехокардиографски апарати чешће су доступни у универзитетским него у неуниверзитетским центрима (87 наспрам 44%, $p < 0,01$). Стрес ехокардиографија се сматра најпотребнијом техником на нивоу центра, док су *speckle tracking* ехокардиографија и трансезофагеална ехокардиографија најчешће навођене личне аспирације анкетираних чланова.

Закључак Напредне технике, стрес ехокардиографија и трансезофагеална ехокардиографија су неопходне, али ретко доступне ехокардиографске технике ван универзитетских центара. У циљу бољег поштовања стандарда ехокардиографске праксе, доношење националних препорука као и лична и лабораторијска акредитација делују као неизбежан потез.

Кључне речи: ехокардиографија; анкета; Србија

DOI: https://doi.org/10.2298/SARH190509131D
UDC: 616.24-036.1-036.88:613.1

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effects of meteorological conditions on mortality from chronic obstructive pulmonary disease

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SUMMARY

Introduction/Objective Previous studies have confirmed the effect of different meteorological parameters on patients suffering from lung diseases.
The objective of the study is to investigate the impact of meteorological phases on the death rate from chronic obstructive pulmonary disease (COPD).

Methods The data on the number of deaths caused by COPD and meteorological phases during a five-year period (2011–2015) in Šumadija District (Central Serbia) were obtained from the Republic Hydrometeorological Service and the Center for Biostatistics and Informatics of the Kragujevac Institute of Public Health.

Results A statistically significant correlation was determined between certain meteorological phases and COPD death rate. The highest death rate was determined during colder months, February and March. The lowest death rate was detected during the warm months (June–September). Although men died more often from COPD than women, the death rate of women showed a considerable increase during the five-year period.

Conclusion COPD death rate is highly dependent on the season of the year and might be associated with certain meteorological phases. There is a need for further research of the impact of meteorological phases on the morbidity and mortality from COPD.

Keywords: chronic obstructive pulmonary disease; meteorology; humidity; temperature

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most important health problems [1, 2]. According to the data from the World Health Organization, almost three million people that suffer from COPD die yearly, and by year 2020 this disease might become the world's fourth most frequent cause of death [3]. Morbidity and mortality rates of COPD are increasing steadily, most likely due to exposure to cigarette smoke, air pollution, but also because of ageing of the population. Morbidity and mortality rate vary from country to country and from region to region [2, 4, 5].

Basic risk factors for COPD are the following: smoking, outdoor air pollution, poor quality of indoor air, genetic predisposition, age, sex, pneumonia, nutritional status, socioeconomic status, etc. [3, 6, 7]. Patients suffering from COPD have an increased risk of developing other pulmonary diseases – respiratory infections and primary lung cancer, cardiovascular disorders, osteoporosis, diabetes, and mental disorders such as neurosis and depression [3, 7, 8, 9].

Prevention of COPD includes healthy lifestyle, healthy nutrition and nutritional status, daily physical activity, and preserving a high quality of ambient air. COPD is characterized by a frequent changing of the phases of remission and the exacerbation of symptoms. Exacerbation of chronic respiratory and cardiovascular diseases can appear as a consequence of exposure to infectious agents, or noninfectious factors – an increase in concentration of sulfur dioxide and nitrogen oxides in the ambient air, and the impact of certain meteorological parameters such as wind speed and direction, air temperature, air pressure, humidity, and precipitation [10, 11, 12].

Meteoropathy is a group of symptoms and reactions related to a change in one or multiple meteorological factors. By the combination of meteorological and climate elements, 10 meteorological phases have been determined. Meteorological phases are a combination of the following factors: cyclone-anticyclone, air temperature, air humidity, the advance of the cold/warm front, dry/wet weather. Meteorological phases are as follows [13]:

1. Cyclone, warm, dry – CWD: an influx of warm or very warm air (warm sector). Sunny weather prevails, but the weather develops towards cloudiness and an increase in windiness from the southern quadrant (warm wind).
2. Cyclone, warm, wet – CWW: precipitation from compact, layered clouds.

Received • Примљено: May 9, 2019
Revised • Ревизија: December 3, 2019
Accepted • Прихваћено: December 5, 2019
Online first: December 23, 2019

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Relatively warm, wind blows from the southern quadrant, (southern tip), pressure drops, temperature rises or stagnates because of the precipitation, relative humidity increases.

3. Cyclone, warm front – CWF: several hours before and after the warm front passes, the weather is cloudy with precipitation, and during the actual transit of the front a sudden change in wind direction can be observed, temperature keeps rising, especially when precipitation in the back of the front weakens or stops. Relative humidity rises. In addition to precipitation, very low cloudiness occurs.
4. Cyclone, cold front – CCF: cloudiness develops followed by downpours, thunder and strong wind. Temperature drops rapidly, pressure rises significantly, relative humidity rises because of precipitation, but observed globally stagnates, and after the precipitation stops, it falls quickly. The wind keeps changing its direction and intensity suddenly.
5. Cyclone, cold, wet – CCW: layered cloudiness (Ns) prevails paired with long-lasting precipitation, pressure rises, temperature drops or stagnates, humidity does not change much, but drops as precipitation stops. The wind is more intense and blows from the northern quadrant.
6. Cyclone, cold, dry – CCD: after precipitation ends, cold and windy weather persists. Precipitation can occur, but only for a short while and in a small quantity. The weather is cloudy, with a lack of precipitation, cold and with a tendency to change towards clear weather.
7. Anticyclone, cold, dry – ACD: clear weather prevails. The wind comes from the northern quadrant, and its intensity is mostly weak. During the summer it is chilly, and during the winter half of the year it is cold. Pressure, temperature, and humidity do not change much.
8. Anticyclone, cold, wet – ACW: foggy, gloomy, and cold weather in the area of the anticyclone.
9. Anticyclone, warm, dry – AWD: clear and calm weather. The anticyclone is still dominant. Air temperature either does not change at all, or it has a slight increase on a daily basis. Transport of slightly warmer air from lower latitudes starts, weak winds from the southern quadrant start blowing.
10. Anticyclone, warm, wet – AWW: cloudiness develops followed by precipitation and thunder. It manifests during the warm part of the year.

The impact of various meteorological phases on lung diseases has been intensively studied, but it still needs clarification.

The objective of this paper was to investigate the correlation between particular meteorological phases and the mortality rate from COPD.

METHODS

This study is a retrospective, descriptive study conducted during a five–year period, 2011–2015, in the Šumadija District, Central Serbia. The Šumadija District is located at 185–220 m above sea level, between latitudes 43° and 44° N and longitudes of 20° and 21° E. The climate is temperate continental, with relatively cold winters, hot summers, and the average annual temperature of 11.5°C.

Data on current meteorological phases used in this study was obtained from the Republic Hydrometeorological Service (RHMS). Information on the mortality of COPD was obtained from the database of the Center for Biostatistics and Informatics of the Kragujevac Institute of Public Health.

This research was approved by the Ethics Committee of the Kragujevac Institute of Public Health, Serbia (No. 01-2092). Spearman correlation analysis was conducted to investigate the relationship between meteorological phases and the mortality from COPD. IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY. USA) was used.

RESULTS

COPD death rate in the Šumadija District grew from 20.99 per 100,000 inhabitants in 2011 to 24.14 in 2015. Table 1 presents the incidences of 10 meteorological phases (in percentages to total number of phases) and number of deaths by months, during the 2011–2015 period. Phases 4 and 9 were dominant during the entire period. The incidence of phase 9 was higher during the warm months (April–November) than in winter months (December–March). On the other hand, phase 10 occurred only in spring and summer, while phase 8 was observed in autumn and winter.

Total number of deaths caused by COPD was 955 (617 men and 338 women). The highest number of deaths (114) was recorded in February and March, while the risk of dying from COPD was significantly lower during the "warm"

Table 1. The incidence of meteorological phases and number of deaths from chronic obstructive pulmonary disease (COPD) by months during the 2011–2015 period

Month	Meteorological phase [%]										Number of deaths from COPD
	1	2	3	4	5	6	7	8	9	10	
January	5.8	1.9	11	21.3	15.5	6.5	18.1	8.4	11.6	0	89
February	8.5	2.1	9.2	22.5	14.1	11.3	14.1	1.4	16.9	0	114
March	9	2.6	11	25.2	14.2	9	12.3	0	16.8	0	114
April	8.7	4.7	4	26	13.3	9.3	6.7	0	26	1.3	99
May	9.7	5.2	1.3	29	12.9	4.5	7.7	0	27.1	2.6	88
June	8	3.3	2	22.7	17.3	6	5.3	0.7	32.7	2	56
July	9	4.5	1.3	22.6	14.8	8.4	7.1	0	30.3	1.9	67
August	11.6	3.2	1.9	22.6	9	7.7	6.5	0	36.1	1.3	50
September	10	2	1.3	18.7	14	10	14.7	0	28.7	0.7	52
October	9.7	2.6	3.9	18.1	9.7	9	12.9	0.6	33.5	0	68
November	9.3	2	6	23.3	12.7	8	10	2	26.7	0	70
December	7.7	4.5	9.7	20.6	14.8	7.7	11.6	15.5	7.7	0	88

Meteorological phases: 1 – cyclone, warm, dry; 2 – cyclone, warm, wet; 3 – cyclone, warm front; 4 – cyclone, cold front; 5 – cyclone, cold, wet; 6 – cyclone, cold, dry; 7 – anticyclone, cold, dry; 8 – anticyclone, cold, wet; 9 – anticyclone, warm, dry; 10 – anticyclone, warm, wet

months (June–September). COPD death rate was two to three times higher for males than for females. However, an increase in the death rate was more prominent for women (from 13.4 to 16.2 per 100,000) while for men a slight decrease was observed (from 39.74 to 34.75 per 100,000).

The correlation of the death rate with the incidence of each meteorological phase (by months) was investigated using the Spearman correlation analysis. The results are presented in Table 2.

Table 2. Spearman correlation coefficients (Spearman's ρ) between meteorological phases and death rate of chronic obstructive pulmonary disease (COPD)

Meteorological phases	COPD death rate	p
Phase 1 (cyclone, warm, dry)	rho = -0.564	0.056
Phase 2 (cyclone, warm, wet)	rho = -0.016	0.961
Phase 3 (cyclone, warm front)	rho = 0.744	0.006
Phase 4 (cyclone, cold front)	rho = 0.274	0.389
Phase 5 (cyclone, cold, wet)	rho = 0.235	0.462
Phase 6 (cyclone, cold, dry)	rho = 0.265	0.404
Phase 7 (anticyclone, cold, dry)	rho = 0.371	0.235
Phase 8 (anticyclone, cold, wet)	rho = 0.260	0.415
Phase 9 (anticyclone, warm, dry)	rho = -0.816	0.001
Phase 10 (anticyclone, warm, wet)	rho = -0.480	0.115

DISCUSSION

Mortality rate detected in our study was higher than the values previously reported in Serbia [14]. The death rate from COPD grew by 15% during the five-year period. A particularly high increases of COPD prevalence and death rate observed in women were also reported by some other authors [1, 15].

The mortality rate from COPD is increased during the cold period of the year. This observation is in agreement with the results of some previous studies. For example, a large study in Taiwan reported a 0.8% increase in COPD exacerbations with 1°C decrease of the mean air temperature [16]. Cold weather usually contributes to lung diseases through bronchoconstriction, inflammation, mucous hypersecretion, as well as through modifying susceptibility to air pollution [10]. Although extremely hot temperatures and heatwaves have also been identified as a significant risk factor for patients suffering from lung diseases, cold temperatures and temperature changes have more pronounced effect [17–20].

COPD mortality rate was negatively related to the incidence of meteorological phases 1, 9, and 10 (Spearman's ρ = -0.564, -0.816, and -0.480, respectively). All these three phases occur more often during the warm period of year. A strong negative correlation with meteorological phase 9 indicates that clear and calm weather, which is typical for this phase, has particularly positive effects on patients with COPD. This result is rather understandable, considering the fact that sudden changes of certain meteorological parameters might aggravate symptoms of respiratory diseases. For example, some previous studies have suggested that sudden changes of inhaled air temperature could cause the release of inflammatory mediators produced by mast cells and more nasal inflammatory responses [21–25].

A positive correlation was found between meteorological phase 3 and the mortality rate from COPD (ρ = 0.744). This phase is more typical for autumn and winter seasons. It is characterized by cloudy weather with precipitation, sudden change in wind direction, temperature rise, and an increase in relative humidity. Our results are consistent with the studies reporting that COPD and cardiovascular mortality are higher during the cold season [26, 27].

Investigations have confirmed that a high content of water molecules in the air can cause dyspnea. High air humidity is related to the presence of allergens, pathogens, and noxious chemicals in the environment, consequently increasing the incidence of respiratory infections, allergies and exacerbation of COPD [21, 28, 29]. Research conducted in Novi Sad also points to the fact that an increase in relative air humidity leads to exacerbation of COPD [30].

CONCLUSION

An increasing trend of COPD death rate was observed in a five-year period. Of particular concern is a marked increase in mortality from COPD among women compared to men. There is a significant statistical correlation between certain meteorological phases and the mortality rate from COPD. There is a need for further research of the impact of meteorological phases on the morbidity and mortality from COPD. Special attention should be paid to warm and cold fronts, cyclones, and anticyclones.

ACKNOWLEDGEMENT

We would like to express our gratitude to the Kragujevac Institute of Public Health for permission to use the database of the Center for Biostatistics and Informatics.

Conflict of interest: None declared.

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Утицај метеоролошких услова на смртност од хроничне опструктивне болести плућа

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САЖЕТАК

Увод/Циљ Велики број студија је потврдио утицај различитих метеоролошких параметара на болеснике са плућним болестима.

Циљ ове студије био је да се истражи утицај метеоролошких фаза на стопу смртности од хроничне опструктивне болести плућа (ХОБП).

Методе Подаци о учесталости метеоролошких фаза и броју умрлих од ХОБП-а током петогодишњег периода (2011–2015) у Шумадијском округу (Централна Србија) добијени су од Републичког хидрометеоролошког завода и Центра за биостатистику и информатику Института за јавно здравље у Крагујевцу.

Резултати Нађена је статистички значајна корелација између одређених метеоролошких фаза и стопе смртности од ХОБП-а. Највиша стопа смртности забележена је током хладних месеци (фебруар и март). Најнижа стопа смртности је уочена током топлих месеци (јун–септембар). Иако су мушкарци умирали чешће од ХОБП-а него жене, стопа смртности је код жена имала значајан пораст током овог петогодишњег периода.

Закључак Стопа смртности од ХОБП-а зависи од годишњих доба и може се повезати са одређеним метеоролошким фазама. Неопходно је даље истраживање утицаја метеоролошких фаза на морбидитет и морталитет од ХОБП-а.

Кључне речи: хронична опструктивна болест плућа; метеорологија; влажност; температура

DOI: https://doi.org/10.2298/SARH191118037O
UDC: 612.2

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Changes in power of surface electromyogram during breath-holding

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SUMMARY

Introduction/Objective Numerous studies on surface electromyographic (sEMG) signals in response to different respiratory parameters, particularly on sternocleidomastoid (SCM) muscles and diaphragm (DIA), indicated the promising advantages of their simultaneous monitoring with possible applications in the analysis of their correlation. This motivated a detailed statistical analysis of the average power (P_{AV}) on sEMG signals during prolonged breath-holding, simultaneously measured in the SCM and DIA areas.

Methods The physiological breath-holding method was applied to 30 healthy volunteers, with sEMG of SCM and DIA regions measured before, during, and after the breath-holding exercise. All the subjects were sitting in an upward position, with nostrils closed by the right index finger and thumb during breath-hold. To synchronize the records, the user would press a special switch using the other hand at the beginning and at the end of breath-holding experiment. The average power of sEMG (P_{AV}) was measured for each 500 ms signal window.

Results The P_{AV} remains constant before and 3 seconds after the exercise. During the ending of breath-holding, at least one region had the P_{AV} afflux of a minimum of 91%. Student's t-test between SCM signals shows a significant difference of $p < 0.001$, while the DIA lacks it. Although the results showed that SCM is the dominant region in 76.67% of cases, the exclusive P_{AV} afflux in the DIA region was detected in precisely five cases (16.67% of the total namber of participants).

Conclusions Our research concludes that there is the necessity of simultaneous measurement of SCM and DIA to observe dominant changes in sEMG during breath-holding. The physiological response of the respiratory center can be observed by approximately doubling P_{AV} in one of SCM or DIA regions.

Keywords: surface electromyogram; breath-holding; muscle sternocleidomastoideus

INTRODUCTION

In the last decade of the previous millennium, the appearance of the first studies on the topic of surface electromyography (sEMG) started in the correlation with the miscellaneous respirational effects [1]. Given its exponential increase, several reviews of these papers have been published [1]. There are at least 10,000 studies, while about 1% have been classified positive in the light of precise settings and repeatability of the experiments [2]. The strict postulates are not firmly grounded, but a consensus has been established on the placement of surface electrodes, the method of application, as well as on the expected recorded signals [3].

There are three distinct measurement regions "regarding electromyographic (EMG) activation of the sternocleidomastoid muscle (SCM), parasternal muscles (PARA), and the diaphragm (DIA)" [4]. However, a more detailed analysis of recordings ensigns PARA and DIA as the same regions, which could be taken as synonyms.

The sEMG researches have already found their application in at least three areas: "a) advances in surface EMG detection and processing techniques, b) recent progress in surface EMG clinical research applications, and c) myoelectric control in neuro-rehabilitation" [2].

These studies include both sick and healthy volunteers. Thus, in the case of chronic diseases, the most common are patients with chronic obstructive pulmonary disease (COPD) and asthma, with the emphasis on the experiment repeatability [5, 6]. There are also numerous studies conducted on healthy volunteers that measure the different effects of breathing exercises versus changes in the exhaled air [7, 8]. Numerous published papers on sEMG include volunteers with acute cases [9].

The authors have recently demonstrated the possibility of acquiring the sEMG signals in healthy volunteers in the two most often recorded regions, as the answer to the most passive breathing activity, the prolonged breath-holding [10]. The organism's response to breath-holding comes from the main respiratory center in the medulla through a series of electrical impulses in order to activate the respiratory muscles. This response should be especially augmented at the end of

Received • Примљено: November 18, 2019
Revised • Ревизија: June 9, 2020
Accepted • Прихваћено: June 11, 2020
Online first: June 18, 2020

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Figure 1. Electrode setup with Neurofax equipment

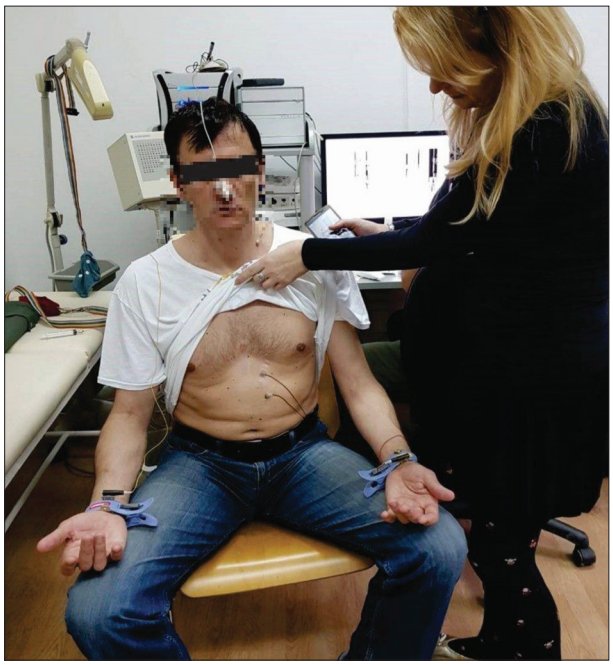

Figure 2. The electrode setup

breath-holding, due to a permanent increase in activation impulses from the respiratory center. The change in the average sEMG power was the first measurable psychological phenomenon characterized by a push or swallow feeling at the end of breath-holding. In this regard, the main goal of this paper is to detect this involuntary muscle activity in the SCM and DIA region at the end of breath-holding. Statistical analysis of the entire population should provide an answer as to whether this phenomenon is an individual peculiarity or occurs simultaneously in both zones.

A series of initial signal analyses had been proposed, but with a lack of clear answer which method should give the most reliable statistical significance.

During the recording of biosignals, noise artifacts from different sources are common and quite noticeable [11]. Having this in mind, we concentrated mainly on the changes in the mean power (P_{AV}), since a large amount of constant noises is permanently present. At least in the first approximation, its influence could be considered constant in all phases of the recordings [12]. This further facilitates a complete statistical analysis.

METHODS

Research sample

Thirty healthy young volunteers, 19–25 years old, students of a sports faculty, were beforehand instructed in the procedure of breath-holding after spontaneous exhalation, as well as in recognizing the response of physiological muscle activity (the "bump") upon prolonged breath-holding [13, 14]. The procedure has the following steps:

- Phase 1 – sitting and resting for 5–7 minutes. Complete relaxation of all muscles, including the breathing muscles. This relaxation produces a natural spontaneous exhalation (breathing out).
- Phase 2 – pinching the nose with the right thumb and index finger at the end of the exhalation with simultaneous pressing of the switch with the left hand (the first switch press) to mark the end of the exhalation and keeping the nose pinched.
- Phase 3 – the appearance of the first urge to breathe (practice shows that this first desire emerges together with an involuntary push of the diaphragm or swallowing movement in the throat) that we will refer to as the "bump."
- Phase 4 – pressing of the switch the second time (the second switch press) to mark the "bump," releasing the nose and again complete relaxation of all muscles.

Instruments

The typical electrode setup for the SCM and DIA regions followed the suggestions given by Merletti and Muceli [3] and Afsharipour et al. [15]. The method is completely non-invasive and only surface electrodes were applied, as shown in Figures 1 and 2.

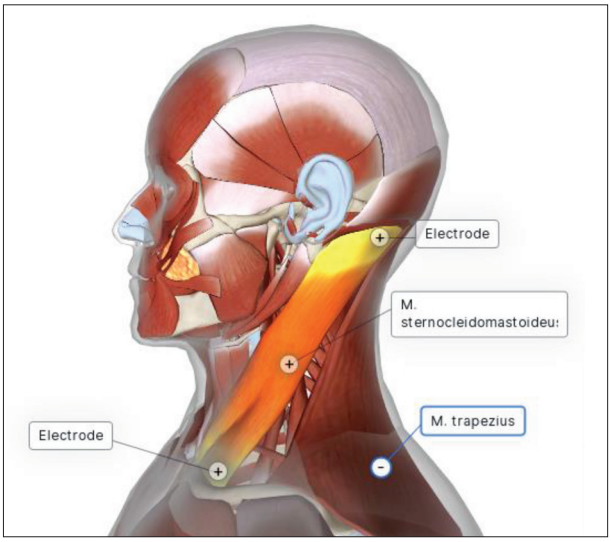

Figure 3: Sternocleidomastoid – the figure shows this biggest neck muscle and the positions of the applied surface electrodes

The measurement was performed using the 1200K Neurofax apparatus (Nihon Kohden Corporation, Tokyo, Japan) with surface ring Au electrodes filled with electroconductive gel and electrocap with 19 Ag/AgCl electrodes for electroencephalography (EEG) measurement (10/20 international electrode placement system). The experimental procedure is corroborated by the ethical standards of the Serbian Medical Society and is labeled by protocol CE 01342. The procedure has been performed in accordance with the Declaration of Helsinki. The participants gave their written informed consent prior to the experimental procedure.

Although we practically used only two sEMG recorded signals by Au-surface electrodes for this study, the system also contained the following recordings [16]:

- 16 EEG signals,
- electrocardiography (ECG) according to Einthoven,
- respiratory air-flow signal,
- HD camera built into this system,
- light hand built-in switch for the event labeling.

The sEMG on the neck was measured at the ends of the *sternocleidomastoideus* muscle (SCM), also illustrated by Figure 3 [17].

The method of placing the DIA electrodes was according to the internationally agreed topographic lines of the thorax, which also include the actual lines for this study: *linea mediana anterior* (extends from the *incisura jugularis* to *siphysis pubica*) and *linea sternalis* (extends parallel along the lateral edge of the sternum) [3]. First, a small extension at the end of the sternum (*prosessus xyphoideus*) located in the direction of the *linea mediana anterior* was defined by palpation, in order to mark the initial position (upper point). The direction of the *linea sternalis* was then determined. The last step was to draw a line from point A to the direction of the *linea sternalis* perpendicularly in order to obtain the marking location (lower point) where the upper electrode was placed on the abdomen. The lower electrode was placed in the marked position located in the direction of the *linea sternalis*, and below the upper electrode, at a distance of 10 cm [18].

The signal values are expressed in μV per unit resistance, allowing simple squaring to obtain power in μW.

The entire recording procedure is non-invasive, lasts less than five minutes and allows the export of signals for the specific analysis on different platforms [19]. In order to perform the original signal analysis, we initially used the signal processing toolbox of MATLAB, and custom C-programs [20, 21].

RESULTS

After the performed measurement of all 30 participants, the quality continuous ECG, RESP, SCM and diaphragmatic EMG signals were obtained. A sample of recorded signals during normal breathing and the "bump" phase are shown in Figures 4A and 4B, respectively.

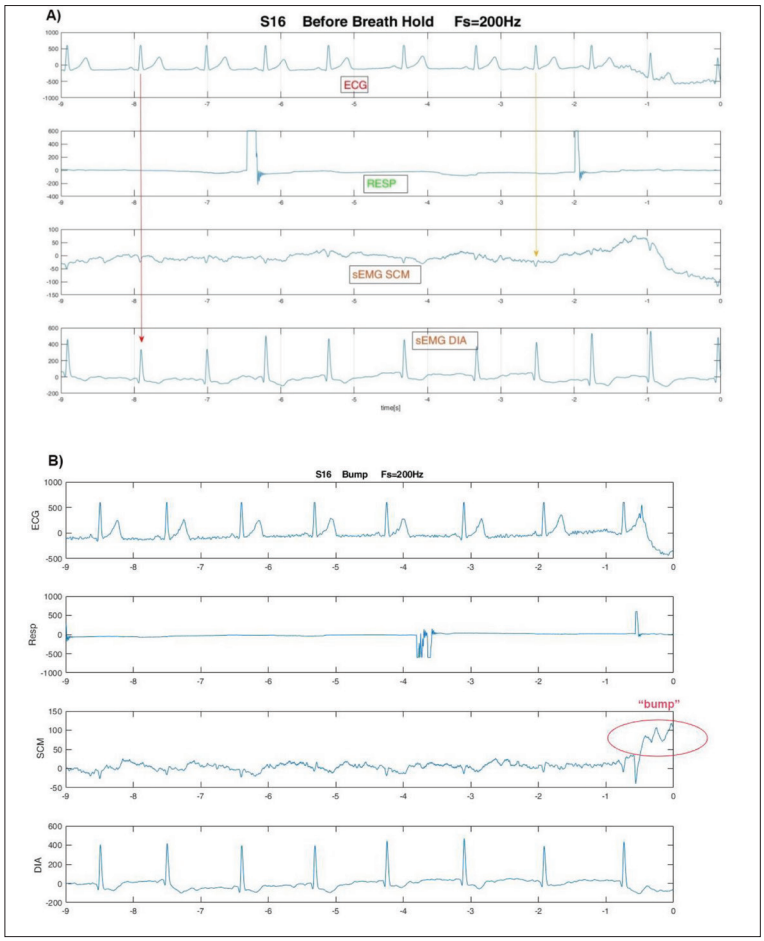

Figure 4. Signals recorded during A) normal breathing (Phase 1 in Methods) and B) the end of breath-holding – the "bump" phase (Phase 3); electrocardiography (ECG), respiration, surface electromyography (sEMG) sternocleidomastoid (SCM), sEMG diaphragm (DIA), signal amplitude is in [μV]; the influence of R peak on sEMG signals is visible, particularly on sEMG DIA, due to the vicinity of the heart

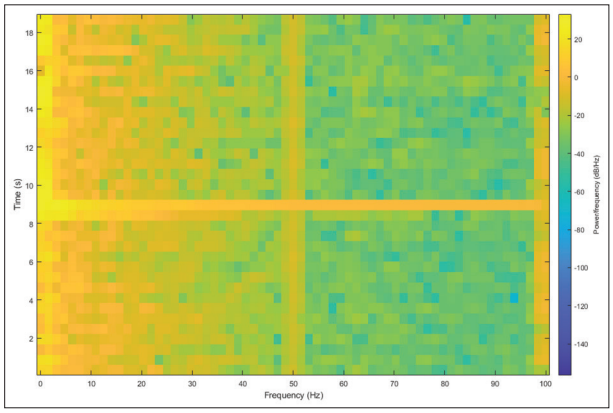

Figure 5. Power spectral density of sternocleidomastoid during breath-holding; "bump" recorded at t = 9 seconds; sampling frequency Fs = 200 Hz, Hanning window; nonequispaced fast Fourier transform (NFFT) = 128; noverlap = 108 samples

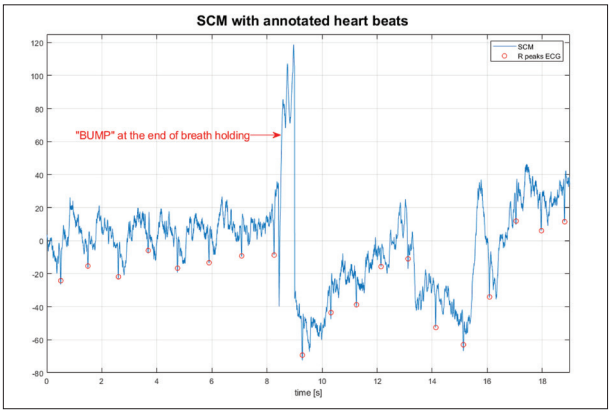

Figure 6. Changes of sternocleidomastoid at the end of breath-holding; "bump" recorded at t = 9 seconds; exact moments of heart beats marked with red circles

Figure 5 shows the power spectral density (PSD) of SCM signal during and after the breath-hold phase. The spectrum belongs principally to the same area as the standard EEG signal and practically does not exceed 40 Hz. Power line interference is clearly visible at 50 Hz.

Figure 6 demonstrates the change of pattern of SCM during the "bump" at the end of the breath-holding period. Exact periods of individual heart beats are extracted from the ECG signals and marked in Figure 6 as red circles to demonstrate the effect of ECG in SCM.

The common method with overlapping processing windows has been used to calculate the average power of sEMG in SCM and DIA regions [22]. Since DIA is heavily contaminated with ECG, we used a 1 second window to minimize the influence of ECG on signals. For example, the average RR interval of the signal represented in Figure 5 is 1.02 seconds. The typical method with overlapping processing windows has been used to calculate the average power of sEMG in SCM and DIA regions [22]. Since DIA is heavily contaminated with ECG, we used a 1-second window to minimize the influence of ECG on signals since the average RR interval of the signal represented in Figure 5 is 1.02 seconds. In the case of a sampling frequency of 200 Hz, the overlapping size between two consecutive windows is equal to 100 samples.

The visible influx of power was observed immediately before the "bump" in all cases, mainly in the SCM region [23].

The volunteers S08, S14, S18, S24, and S25 showed the "bump" in the DIA region.

It is noticeable that the return to the initial values in the DIA region is no longer than 3 seconds. The different artifacts by breathing musculature should be kept in mind here. The properly performed exercise was supposed to be done in such a way that volunteers should keep holding the breath for at least 2 seconds after the switch is pressed before resuming normal breathing [24].

Table 1 shows the overall results for the whole group of 30 volunteers.

The increase for ΔP^{SCM} and ΔP^{DIA} is positive in most cases where a simple averaging gave a surplus of 425.16% and 133.19% for the SCM and DIA regions, respectively. However, for each case, at least one of ΔP^{SCM} and ΔP^{DIA} values showed a significant increase. Such instances are bolded in their respective columns. This is more frequent for the ΔP^{SCM}, although the exclusive P_{AV} enlargement in the DIA region can be observed in exactly five cases (16.67% of the total number). The overall view of the completed results imposes the conclusion that both muscle regions must be recorded in order to spot the P_{AV} enlargement for every volunteer. For all the participants, the P_{AV} relaxation period is below 3 seconds.

The t-test for the SCM region data only, P^{SCM}_{rest} and P^{SCM}_{bump}, shows significant statistical difference ($t = 1.69913$, $p < 0.001$), contrary to the DIA region, since P^{D}_{rest} and P^{D}_{bump} show no significant statistical difference. However, the newly formed group ΔP^{MAX} (defined as the maximum increase of the SCM and DIA regions) shows as much as one order higher significant statistical difference, e.g. $t = -6.09$, $df = 32.12$, $p < 0.0001$.

DISCUSSION

We recorded sEMG during breath-holding exercise on 30 healthy participants. The analysis of P_{AV} changes during breath-holding was a simple method that provides effective assessment of sEMG changes in real time. An increase of P_{AV} was observed in the pilot study with five participants. In this paper, we present a complete statistical analysis for all 30 subjects, and P_{AV} return time to the initial rest values.

P_{AV} changes of the EMG signals practically showed at least a doubling of its value related to the rest state and very quickly returned to its initial state, within 2.2 seconds as the maximum value. In Table 1, we can see that the changes can be observed literally in every case, with the particular necessity of observing both EMG signals.

The visible influx of power was observed immediately before the "bump" in all cases, mainly in the SCM region, but not exclusively [25]. Five of the 30 volunteers showed an exclusive increase of P_{AV} in the DIA region. This confirms many statements that "the neck region is more prone to fatigue than the intercostal one" [26, 27]. In his book, Rakimov [24] summed up the feelings of more than a thousand volunteers to the physiological answer to breath-holding. His conclusion supports our findings, as he claims

Table 1. The overall results for the entire group of 30 volunteers

No.	P^{SC} rest	P^{SC} bump	P^{D} rest	P^{D} bump	ΔP^{SC}	ΔP^{D}	AP^{max}	T_{RLX} (ms) Tra.x (ms)
1	9	34.5	36	36	283.33%	0%	283.33%	800
2	7	38	500	1550	442.86%	210%	442.86%	1800
3	10	120	48	350	1100%	629.17%	1100%	1200
4	10	29.50	11	35.5	195%	222.73%	222.73%	750
5	6	21	40	40	250%	0%	250%	1100
6	23	51	200	200	121.74%	0%	121.74%	700
7	5	45	100	180	800%	80%	800%	600
8	18	49	18	110	172.22%	511.11%	511.11%	1500
9	5	33	25	32	560%	28%	560%	2100
10	32	42	20	70	31.25%	250%	250%	2050
11	2	22	60	20	1000%	-66.67%	1000%	2000
12	5.2	18.3	4.5	4.50	251.92%	0%	251.92%	1900
13	20.3	99.8	50	50	391.63%	0%	391.63%	800
14	100	30	37	72	-70%	94.59%	94.59%	1200
15	12	23	42	42	91.67%	0%	91.67%	1800
16	2.30	50	15	15	2073.91%	0%	2073.91%	1200
17	7	120	90	120	1614.29%	33.33%	1614.29%	700
18	8	41	5	23	412.5%	360%	412.5%	1700
19	9	72	200	160	700%	-20%	700%	1800
20	12	23.5	25	17	95.83%	-32%	95.83%	1100
21	6	19.5	10	10	225%	0%	225%	1400
22	20.5	28.5	38.5	13200	39.02%	242.86%	242.86%	1800
23	21	120	120	120	471.43%	0%	471.43%	600
24	26	14	20	106	-46.15%	43%	430%	1400
25	8	8	10	120	0%	1100%	1100%	1100
26	5.80	11.80	35	34	103.45%	-2.86%	103.45%	900
27	4	12	10	4	200%	-60%	200%	800
28	7	41	160	130	485.71%	-18.75%	485.71%	1900
29	4	29	30	30	625%	0%	625%	600
30	9	21	24	25	133.33%	4.17%	133.33%	400
AVG	13.80	42.25	66.13	127.93	425.16%	133.19%	509.5%	1256.67
				SD	489.23%	255.4%	467.4%	523.21
				Δ + min	91.67%	94.59%	91.67%	400
				Δ + max	2073.91%	1100%	2073.91%	2100

The column P^{SC}_{rest} depicts the rest and P^{SC}_{bump} the P_{AV} value during the "bump" period in the sternocleidomastoid (SCM) region, while similarly P^{D}_{rest} is the rest and P^{D}_{bump} is the "bump" value of P_{AV} in the diaphragm (DIA) region, according to the labeling by the Japanese group [31]; the P_{AV} influx in percentages for the SCM and the DIA regions are denoted by ΔP^{SC} and ΔP^{D}, respectively; the maximum influx for each volunteer is given in the following column, depicted as ΔP^{MAX}; T_{RLX} is the relaxation period in milliseconds after the P_{AV} was returned to the values equal to the initial state; the raw AVG shows the simple average value for all columns, while SD shows the standard deviation for the last four columns on the right; the most important values in the first (No.), sixth (ΔP^{SC}) and seventh (ΔP^{D}) columns are in bold; while Δ_{MIN} shows the minimal increase, Δ_{MAX} shows the maximum increase for the last two columns on the right. However, Δ-raws for the ΔP^{SC} and ΔP^{D} columns are given for the bold values

that "... most people feel the sensation in the neck rather than in the diaphragmatic region..."

We have already mentioned that it is possible to prolong the breath-holding even after a physiological response for a certain period of time, which was expected to happen during our experiment [28].

Recently, professor Lejun's group published papers on changing the pedaling performance of elite cyclists, showing changes in the average power output of the sEMG signals of different locomotor muscles due to fatigue, as well as during the recovery period [29]. Their result showed significant changes in two of the four measured groups.

Our result of 16.6% of the volunteers showing a significant influx exclusively in the DIA region is in a range of human left-handedness. "There has been very little change in the proportion of left-handers since the Upper Paleolithic Age, about 10,000 years ago, and it is estimated to be around 10%," although "subtle prejudice against this minority group is still present and visible," showing finally "that the prevalence of left-handedness is lower in Serbia than in Western Europe (5–10% *vs*. 11–14%)" [30].

Statistical analysis of the three pairs of signals can be considered as follows. The lack of statistical significance for the DIA region implies that the results from this region would solely be insufficient and would not be credible if performed independently. On the other hand, a statistical difference measured between the two SCM signals ("bump" state *vs.* rest state) of $p < 0.001$ cannot give a false result, but seems to be able to miss some positive cases. The newly formed ΔP^{D} variable depicts the dominant group, defined as the maximum increase of ΔP^{SC} and ΔP^{D} columns. It can report every case with minimal time delay, without false reports.

The practical development of a dominant group would not be a difficult task. The core of the electronic device should contain one digital comparator followed by the collecting register of the higher signal.

CONCLUSION

Our research shows the influx in P_{AV} of 91% minimally in at least one measured region, SCM or DIA, with the return to the initial values in less than 3 seconds during the prolonged breath-holding. Simultaneous measurement of both regions is necessary to observe changes in the average power of sEMG in each case.

This indicates that the physiological response of the respiratory center in the medulla to a prolonged breath-holding can be observed by approximately doubling P_{AV} in one of SCM or DIA regions.

It would be beneficial to repeat this research on a larger population, as well as on different cases of health etiology.

ACKNOWLEDGMENT

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia.

Conflict of interest: None declared.

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Промена снаге површинског електромиограма при задржавању даха

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САЖЕТАК

Увод/Циљ Бројне студије површинских електромиографских (*sEMG*) сигнала као одговор на промене различитих параметара дисања, нарочито на стерноклеидомастоидним мишићима (*SCM*) и дијафрагми, указале су на обећавајуће предности њиховог истовременог праћења са могућим применама у анализи њихове корелације. Ово је мотивисало детаљну статистичку анализу просечне снаге (P_{AV}) на *sEMG* сигналима током продуженог задржавања даха, истовремено мерених у областима *SCM* и дијафрагме.

Методе Физиолошка метода задржавања даха примењена је на 30 здравих добровољаца, и то *sEMG* мерењем области *SCM* и дијафрагме пре, током и после вежбе задржавања даха. Сви испитаници су седели у усправном положају, а носнице су биле затворене десним кажипрстом и палцем током задржавања даха. Ради синхронизације записа, корисник би притиснуо посебан прекидач другом руком на почетку и на крају експеримента задржавања даха. Просечна снага *sEMG* (P_{AV}) измерена је за сваки сигнални прозор од 500 *ms*.

Резултати P_{AV} остаје непромењен пре и три секунде после вежбе. Током завршетка задржавања даха, бар једна област имала је P_{AV} прираштај од минимално 91%. Студентов *t*-тест између сигнала *SCM* показује значајну разлику од $p < 0,001$, док код дијафрагме изостаје. Мада су резултати показали да је *SCM* доминантна област у 76,67% случајева, ексклузивни P_{AV} прираштај у области дијафрагме откривен је у тачно пет случајева (16,67% укупног броја испитаника).

Закључак Наше истраживање води закључку о неопходности истовременог мерења *SCM* и дијафрагме како би се уочиле доминантне промене *sEMG* током задржавања даха. Физиолошки одговор респираторног центра може се приметити приближно удвострученим P_{AV} у једној од области *SCM* или дијафрагме.

Кључне речи: површински електромиограм; задржавање даха; стерноклеидомастоидни мишић

DOI: https://doi.org/10.2298/SARH190925042E
UDC: 616.89-008.454:615.84

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Attitudes towards repetitive transcranial magnetic stimulation among depressive patients and medical students

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SUMMARY

Introduction/Objective Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and safe brain stimulation method for the treatment of therapy resistant depression in adulthood. The German S3 guideline for unipolar depression recommends the use of high frequency rTMS of the left dorsolateral prefrontal cortex for depressive patients who did not respond primarily to antidepressant pharmacotherapy. Although a number of meta-analyses demonstrated its antidepressant efficacy on a high evidence level, rTMS is rarely offered to patients with mental disorders in German psychiatric hospitals.

Methods We introduced a questionnaire-based survey examining patients' (n = 122) and medical students' (n = 53) attitude towards rTMS. The questionnaire consisted of 10 questions with a 5-point Likert-scale. When testing for group differences, we conducted χ^2 tests.

Results The majority of students and patients are not aware of rTMS as a psychiatric treatment of depression, with more patients than students not being aware ($\chi^2(1) = 9.462$, $p = 0.002$; 39.3% *vs*. 17%). However, participants wish to be informed in more detail about rTMS. In general, positive attitudes cover the assumption of safety, while negative attitudes show concerns regarding the efficacy and a lack of trust in the method, mainly due to the fear of irreversible brain damage. Most participants would rather take psychiatric medication than rTMS. rTMS was assumed to be a helpful [$\chi^2(2) = 16.710$, $p < 0.001$ (patients: 32.8% *vs*. students: 5.7%)] and well-tolerated treatment [$\chi^2(1) = 9.110$, $p = 0.003$ (36.1% *vs*. 15.1%)] significantly more often by patients than by students.

Conclusion Our results show a clear need for more information on rTMS as a psychiatric treatment for patients and medical students to fight present prejudices and negative assumptions so that this treatment method with fewer side effects than medication may be used more often.

Keywords: repetitive transcranial magnetic stimulation; attitudes; depression

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and safe treatment option for patients with treatment resistant depression in adulthood [1, 2]. The antidepressant efficacy of high-frequency rTMS (10–20 Hz) over the left dorsolateral prefrontal cortex (DLPFC) has been suggested in a large number of studies and meta-analyses [3–6]. It is recommended by the German S3-guidelines for unipolar depression as a possible treatment for patients who are unresponsive to antidepressants [3].

Despite these promising results, rTMS was the rarest treatment presented to patients with mental disorders in Germany in 2012 [7]. Only 9% of German psychiatric clinics offered rTMS, making it even more infrequent than electroconvulsive therapy (ECT), which was used in 43% of institutions [7].

Based on these results, there appears to be a discrepancy between the evident antidepressant efficacy and tolerability of rTMS and its application in everyday psychiatric practice. One possible reason for this may include issues with health insurance coverage, as costs of an rTMS treatment on an outpatient basis are currently not covered by the German statutory health insurance. Therefore, a reimbursement is restricted to patients who are insured privately with adequate cover as well as self-payers. However, it is possible to offer rTMS as a treatment covered by German statutory health insurance for inpatients free of further costs, thus insurance coverage alone might only partly explain why this treatment is used so rarely. Lack of public knowledge about rTMS, as well as patients' and medical staffs' experiences, opinions and attitudes towards the treatment may also explain why it is so infrequently employed.

Though it is widely known that physical treatments in psychiatry such as ECT are stigmatized in the public opinion, it is less clear how the public and patients perceive rTMS [8, 9]. Walter et al. [8] conducted a study examining experience, knowledge, and attitudes of recipients of rTMS regarding the treatment. They found that significantly fewer patients remembered adverse side effects (muscle aches, nausea or vomiting, confusion and

Received • Примљено: September 25, 2019
Revised • Ревизија: June 22, 2020
Accepted • Прихваћено: June 24, 2020
Online first: June 29, 2020

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memory impairments) after rTMS than after ECT and psychopharmacological treatment [8]. Experience and opinions about rTMS were found to be generally positive compared to psychopharmacological treatment and ECT [8]. Moreover, there is a first questionnaire based study focusing patient's attitudes towards rTMS, which found that most of the study patients (suffering from treatment resistant depression) recommended the use of rTMS in case of depression [10]. Though these results are promising, further research is necessary to solidify these findings and to establish how patients and medical staff perceive this therapy. Thus, we set out to examine medical students' and patients' awareness and opinion about rTMS, in the hope that this knowledge will explain the current lack of interest in this treatment and to help promote it as a safe and effective way to treat depression.

METHODS

To examine patients' and students' attitudes towards rTMS treatment for depression a questionnaire was developed and used in a preceding study employing a sample of 150 depressive patients, 150 health workers and 150 healthy controls [11]. In the current retrospective questionnaire-based study, 122 depressive inpatients were recruited at the LVR Psychiatric Clinic in Düsseldorf. The patients received their diagnoses by common clinical assessment using the Diagnostic and Statistical Manual of Mental Disorders -IV criteria [12]. The patients were given the questionnaire to fill in at their own responsibility. Moreover, 53 medical students of the medical facility of the Heinrich Heine University of Düsseldorf were recruited within a university course. They filled out the questionnaire at the end of a randomly chosen medical lecture. No further inclusion or exclusion criteria were applied. There was no further randomization because of the design of the study. The questionnaire consisted of 10 questions, where answers have to be given on a five-point Likert scale with the extremes "totally agree" and "totally disagree". The questionnaire was handed to the patients by the nursing staff and collected anonymously in sealed envelopes to eliminate potential bias. Medical students filled out the questionnaire after a university course and the patients during their inpatient stay. All participants gave their informed consent and the institutional Committee on Ethics of the Heinrich Heine University of Düsseldorf (No. 2807) approved the study protocol. When testing for group differences, we conducted χ^2 tests on our (originally Likert-scaled) data, which is appropriate for categorical data such as our Likert-scaled data. For χ^2 tests have no assumption of normal distribution, no further pre-tests for testing it were conducted. For reasons of presentation, data is displayed using percentages. However, χ^2 tests were used on our Likert-scaled data. Percentage scores were calculated summing up "totally agree" and "agree" into "yes" and "totally disagree" and "disagree" into "no." Therefore, some values do not add up to 100% due to neutral answers, which generally contains little information.

RESULTS

The students consisted of 69.2 % women and were aged between 18 and 69 years (M = 43.5, SD = 12.2). Moreover, the medical students (60.4 % women) were aged between 23 and 44 years (M = 26, SD = 4.63). Our results show, that the majority of students and patients are not aware of rTMS as a psychiatric treatment for depression, with patients being significantly more aware than students [$\chi^2(1) = 9.462$, $p = 0.002$; 39.3% *vs*. 17%]. However, most students and patients would apply it in case of acute depression, although the majority of participants do not trust rTMS. Most patients and students seem to assume that rTMS causes irreversible brain damage and brain manipulation as an adverse side effect and only 34% of students and 41% of patients are unafraid of rTMS. Medication seems to be preferred over rTMS despite fewer side effects of the latter. Most medical students do not perceive rTMS as a helpful treatment, whereas patient attitudes appear to be more polarized: about one third perceive it as helpful and one third have the opposing opinion. This difference is significant: $\chi^2(2) = 16.710$, $p < 0.001$ (patients: 32.8% *vs*. students: 5.7%). Moreover, significantly more patients than students think that rTMS as a treatment for depression is a well-tolerated method [$\chi^2(1) = 9.110$, $p = 0.003$ (36.1% *vs*. 15.1%]. Altogether, it appears that patients have a more positive attitude towards rTMS than the students do. A larger proportion of patients than students are aware and willing to receive more detailed information about rTMS. Table 1 contains detailed distribution of answers concerning attitudes towards rTMS for students and patients.

DISCUSSION

rTMS is a safe, evidence-based brain stimulation technique for patients who do not primarily respond to psychopharmacotherapy [13]. rTMS is regularly used less often than psychopharmacotherapy and even than ECT in German psychiatric hospitals [96% standard therapy (psychopharmacotherapy) *vs*. 41% standard therapy (ECT) *vs*. 4% sometimes used (rTMS)] [7]. In the German population, ECT is generally not well known and is associated with negative attitudes [14]. Still, it is used more often than rTMS, although more negative side effects are reported under ECT than under rTMS application [8]. In an existing report the majority of participants would prefer psychopharmacotherapy over an application of rTMS, although patients experience fewer side effects through rTMS than through the medication [8].

In our study, we aimed to further explore the reasons for the low application rate in German psychiatric hospitals using a questionnaire assessing attitudes of patients and medical students toward rTMS. The results show that the majority of students and patients are not aware of rTMS as a psychiatric treatment for depression. Significantly more patients compared to students were not aware of rTMS. However, participants wish to be informed in more detail about rTMS. In general, positive attitudes

Table 1. Distribution of answers (in %) concerning attitudes towards repetitive transcranial magnetic stimulation (rTMS) for students and patients; positive and negative answers were combined to "yes" and "no"; values do not add up to 100% due to neutral answers

Answers	Students		Patients		p
	Yes	No	Yes	No	
1. rTMS is an efficient method.	39.5	54.7	50	43.5	0.175
2. rTMS is a well-tolerated method.	15.1	35.8	36.1	20.5	0.003*
3. rTMS is a safe method.	62.3	30.2	61.4	33.6	0.740
4. rTMS treatment has few side effects.	86.8	1.9	73	9	0.075
5. rTMS is a helpful treatment.	5.7	64.2	32.8	37.8	< 0.001*
6. I am afraid of rTMS treatment.	11.3	34	18.8	41	0.154
7. I have confidence in rTMS treatment.	18.9	58.5	24.6	50.8	0.592
8. I am afraid that rTMS treatment can manipulate my brain.	22.6	35.8	26.2	44.3	0.328
9. I am afraid that rTMS treatment can cause irreversible brain damage.	39.6	11.3	44.3	18.9	0.221
10. I would prefer to apply rTMS rather than medication.	13.2	66.1	22.9	49.2	0.117
11. I would apply rTMS in the event of acute depression.	56.6	15.1	44.3	26.3	0.206
12. I am aware of rTMS as a psychiatric treatment of depression.	17	83	39.3	56.6	0.002*
13. I would like to have more information about rTMS.	49	18.9	57.4	21.4	0.249

p – value of χ^2 test;
*statistically significant

include the assumption of safety, while negative attitudes show concerns regarding the efficacy and a lack of trust in the method, mainly due to the fear of irreversible brain damage. Most participants would rather take psychiatric medication than rTMS. Our results could show a significant need for more information about rTMS as a psychiatric treatment for patients and medical students to fight present prejudices and negative assumptions so that this antidepressant method with fewer side effects than medication may be used more often following the guidelines.

Positive attitudes cover the assumption of safety of the method, which stands in line with the findings of multiple randomized controlled trials and meta-analyses [2, 3]. However, in general participants showed a more negative attitude toward rTMS, which contradicts the findings of Singh, Sharma [15]. Our participants stated that they lack trust in the method and its efficacy, and that they are afraid of rTMS application, mainly due to irreversible brain damage. The reason might be the information deficit about rTMS as a psychiatric treatment in most participants, which was likely replaced by common prejudices connected with other brain stimulation techniques such as ECT [15]. The patients in our sample have a more positive attitude towards rTMS compared to medical students, with significantly more assumptions about the treatment being helpful and well tolerated than students. Our findings stand in line with a finding that patients who were treated with either sham or verum rTMS would recommend rTMS to others [10]. In their study AlHadi et al. [16] found that only 53% of the psychiatrists would agree to receive rTMS if they experienced a psychotic depressive condition, but 93% would refer their patients for rTMS. However, they could show in their study that psychiatrists had a more positive attitude towards rTMS if they had a family member or relative who was treated with rTMS. Meta-analyses constantly concluded that a patient's experience with a brain stimulation technique (ECT) has a positive impact on attitudes toward it [9, 17]. This emphasizes the necessity of familiarity with the method and therefore a need for more detailed information for patients, but also medical staff in clinics [14, 18]. Possible limitations of the study include the small number of questions within the questionnaire, the non-standardized testing conditions, and the limited restricted variety in participant characteristics (only depressive patients and medical students). Therefore, the results of our study cannot be generalized to other groups without further research. Thus, future research could examine the public attitudes towards rTMS, other patient groups, and medical staff.

CONCLUSION

Our results show that there is still an obvious need for more information about rTMS as a psychiatric treatment for patients and for medical students. Only a small number of patients and medical students are aware of rTMS as a treatment for depression and they wish to have more information about it. This mirrors existing results about the lack of public awareness of rTMS as a treatment alternative for depression. Therefore, the issue of rTMS and other brain stimulation techniques has to be covered in university lectures to expand the treatment horizon of future practitioners. Awareness of rTMS should be raised via advanced training for medical and nursing staff in hospitals, so they can offer these economical and efficient treatment options to relevant patients. Patients' doubts, prejudices, and fears need to be addressed by well-informed staff or by other patients, who have already experienced rTMS.

Source of funding: Since 2015 JC has been involved in studies sponsored by Boehringer Ingelheim Pharma GmbH, Otsuka Pharmaceutical Europe Ltd., EnVivo Pharmaceuticals, Bundesministerium für Gesundheit, BMBF, and Deutsche Forschungsgemeinschaft (DFG).

All other authors (CE, MJ, EI, KL, and MK) report no biomedical financial interest.

Conflict of interest: None declared.

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Испитивања ставова студената медицине и депресивних болесника о репетитивној транскранијалној магнетној стимулацији

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САЖЕТАК

Увод/Циљ Репетитивна транскранијална магнетна стимулација (рТМС) јесте метода неинвазивног и безбедног лечења одраслих болесника оболелих од терапијски резистентне депресије. Немачки С3 водич за униполарну депресију препоручује третирање леве стране дорзолатералног префронталног кортекса високо фреквентним ТМС-ом код депресивних болесника који нису претходно одреаговали на антидепресивну фармакотерапију. Упркос томе што је више метаанализа указало на висок степен њеног антидепресивног дејства, рТМС се ретко примењује код болесника са менталним поремећајима у немачким психијатријским установама.

Методе Истраживање ставова по питању лечења рТМС-ом спроведено је у форми анкете, а укључило је 122 болесника и 53 студента медицине. Упитник се састојао од 10 питања, док су одговори рангирани према петостепеној скали Ликерт. За тестирање разлика у групама спровели смо тестове χ^2.

Резултати Већина испитаника није упозната са рТМС-ом као могућом методом лечења депресије, што је израженије код болесника него код студената ($\chi^2(1) = 9{,}462$, $p = 0{,}002$; 39,3% наспрам 17%). Међутим, учесници су показали интересовање да буду детаљније обавештени о рТМС-у. Уопштено, позитивни ставови се углавном заснивају на претпоставци о безбедности методе, док негативни ставови указују на забринутост по питању ефикасности и недостатак поверења у ову методу, углавном због страха од неповратних можданих оштећења. Већина учесника би радије узимала психијатријске лекове него се подвргла рТМС-у. Болесници, у већој мери него студенти, виде ТМС као корисну методу лечења [$\chi^2(2) = 16{,}710$, $p < 0{,}001$ (болесници 32,8% наспрам студенти 5,7%)], која се добро подноси [$\chi^2(1) = 9{,}110$, $p = 0{,}003$ (36,1% наспрам 15,1%)].

Закључак Наши резултати јасно указују на то да постоји потреба за бољим информисањем о рТМС-у, како болесника, тако и студената медицине, чиме би се утицало на смањење предрасуда и сумњи везаних за употребу ове методе. Узимајући у обзир препоруке водича, ова антидепресивна метода, која има мање нуспојава него лекови, требало би да је чешће заступљена у лечењу него што је то тренутно случај.

Кључне речи: репетитивна транскранијална магнетна стимулација; ставови; депресија

DOI: https://doi.org/10.2298/SARH200301029M
UDC: 616.718.19-001.5-089.23

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Hip function and health-related quality of life in intramedullary and extramedullary internal fixation of trochanteric fractures

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SUMMARY

Introduction/Objective There are extramedullary and intramedullary methods of trochanteric fractures' internal fixation with implants having a lag screw. The objective of this study was to examine the difference in impact of these fixation types on final hip function and health-related quality of life.

Method There were 75 patients treated for a trochanteric fracture, using self-dynamisable internal fixator (SIF group), as an extramedullary method, or gamma nail (GN group), as an intramedullary method. These patients were called for the evaluation of Harris Hip Score (HHS) and SF-12 questionnaire at least two years after surgery. The SF-12 questionnaire has dual expression – physical component score (PCS) and mental component score (MCS).

Results There were no significant differences between the SIF group and the GN group regarding HHS, PCS, and MCS. Positive correlation was confirmed between HHS, PCS, and MCS, with the strongest relation between HHS and PCS. Negative correlation was confirmed between age and HHS.

Conclusion There was no difference in final hip function and health-related quality of life between SIF and GN methods in trochanteric fractures treatment ($p > 0.05$). These parameters of outcome were confirmed to have positive interrelation ($p < 0.05$). Both submuscular presence of extramedullary implant with dimensions of SIF and the need for bone reaming in cephalomedullary fixation were considered not to have significant impact in HHS and SF-12 scores after trochanteric fractures treatment by internal fixation.

Keywords: self-dynamisable internal fixator; gamma nail; hip function; health-related quality of life

INTRODUCTION

Trochanteric fractures occur in the proximal part of the femur between the greater and the lesser trochanter. These fractures are mostly treated with internal fixation with lag screws if the lateral wall is preserved ("no lateral wall – no hip screw"). There are intramedullary and extramedullary implants containing lag screws [1, 2, 3]. In this way, self-dynamisable internal fixator (SIF) with trochanteric unit [4, 5, 6], as an extramedullary method, and gamma nail [6–11], as an intramedullary method, are in routine use in trochanteric fractures' treatment at the Clinic for Orthopaedics and Traumatology of the Clinical Center of Niš. There are two types of SIF with trochanteric unit – the type with multiple (up to three, mostly used two) non-cannulated lag screws and the type with a single cannulated lag screw [12].

It is desired to compare intramedullary and extramedullary methods regarding final hip function, general physical health, and mental health at the end of the trochanteric fracture treatment, due to specificities in some of these methods – position of the implant or the need to ream the bone [13, 14, 15].

The literature refers to health-related quality of life in cephalomedullary as well as dynamic hip screw (DHS) fixation of trochanteric fractures. There are no results about health-related quality of life after the use of SIF. The aim of this study was to compare the two methods in trochanteric fractures' treatment – the third generation of gamma nail and SIF with trochanteric unit, regarding final results in hip function and health-related quality of life.

METHODS

Two groups of patients treated for unilateral trochanteric fracture were analyzed. There were 75 cases – 42 cases (the SIF group) were treated with SIF with trochanteric unit, having two non-cannulated lag screws (Figure 1) and 33 cases (the GN group) were treated with third-generation gamma nail (Figure 2). The excluding criteria were an implant presence in the other hip, other fracture or polytrauma at the same time as the trochanteric fracture, malignant tumor, disfunction of the parathyroid gland. Consecutive patients who were available for clinical examination and interview at least two years after surgery (surgery was performed in 2012 or later) were analyzed in this study. All the patients were treated for trochanteric fracture with internal fixation at the Clinic for

Received • Примљено: March 1, 2020
Revised • Ревизија: May 16, 2020
Accepted • Прихваћено: May 17, 2020
Online first: May 20, 2020

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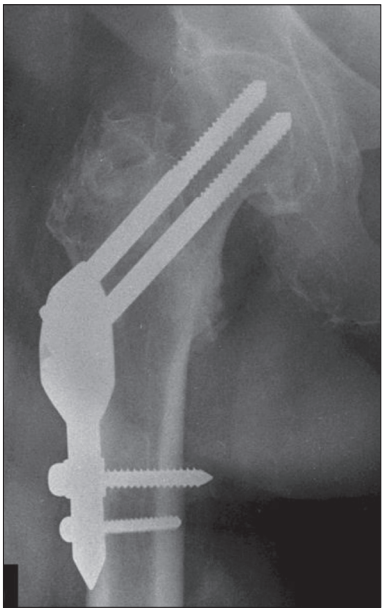

Figure 1. Self-dynamisable internal fixator with trochanteric unit, having two lag screws, used in a case with a trochanteric fracture

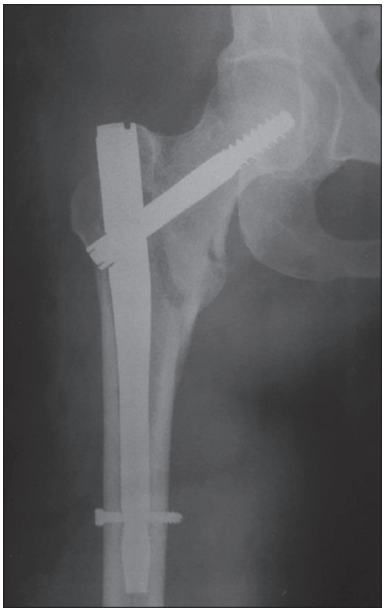

Figure 2. Gamma nail third generation, used in a case with a trochanteric fracture

Table 1. Age, hip function (HHS) and health-related quality of life (SF-12: PCS and MCS) at least two years after surgery

Parameter	SIF	GN	t/z/χ^2	p
Sex	13 M, 29 F	13 M, 20 F	$\chi^2 = 0.581$	0.446
Age	76.3 ± 11	73.3 ± 12.2	z = -1.213	0.225
HHS	72.1 ± 17.3	76.3 ± 17.8	t = 1.041	0.301
PCS (SF-12)	63.1 ± 24.8	68.2 ± 24.3	t = 0.880	0.382
MCS (SF-12)	67.0 ± 24.8	70.7 ± 17.6	z = -0.710	0.477

HHS – Harris Hip Score; PCS – physical component score; MCS – mental component score; SIF – self-dynamisable internal fixator; GN – gamma nail

Table 2. Correlations between age, hip function (HHS) and health-related quality of life (SF-12: PCS and MCS) at least two years after surgery

Parameter	HHS	PCS	MCS
Age	$r_s = -0.503$ $p < 0.001$	$r_s = -0.238$ $p = 0.090$	$r_s = -0.184$ $p = 0.113$
HHS		$r = 0.701$ $p < 0.001$	$r_s = 0.582$ $p < 0.001$
PCS			$r_s = 0.687$ $p < 0.001$

HHS – Harris Hip Score; PCS – physical component score; MCS – mental component score

Orthopaedics and Traumatology of the Clinical Center of Niš. According to the AO classification, there were A1 and A2 types of proximal femoral fractures.

There were 26 male and 49 female patients. Hip function was assessed using Harris Hip Score (HHS), which is based on both the questionnaire and clinical measures of hip movements and leg length [13, 14]. Bone union was achieved in all cases and there were no mechanical complications. The SF-12 questionnaire had been used to assess health-related quality of life. This questionnaire is used in many clinical conditions, including patients treated for hip fractures and has been accepted as a good alternative for previously defined SF-36 questionnaire, if just dimensions of health-related quality of life have to be analyzed – physical components score (PCS) and mental component score (MCS). More detailed analysis in health-related quality of life, including its subdimensions evaluation, requires SF-36 questionnaire though [16, 17, 18]. Age was considered for the time of the clinical assessment mentioned above.

Both HHS test and SF-12 questionnaire values (PCS and MCS) can have values between 0 and 100, with higher value signifying better outcome.

Regarding statistical analyzes, t-test and Mann–Whitney U-test were used for differences in average values, while χ^2 test was performed to compare distributions between the groups. The relation between measured parameters was assessed by bivariate correlations. The level of significance was 0.05.

This study was approved by the Board of Ethics of the Clinical Center of Niš.

RESULTS

Average values and distributions of followed parameters, with their statistical differences, are listed in Table 1. There were no significant differences between the groups regarding age, sex distribution, hip function, and health-related quality of life after trochanteric fracture union ($p > 0.05$).

Statistics of the correlation between measured parameters are listed in Table 2. Significant correlation was confirmed for HHS to PCS, MCS, and age ($p < 0.05$). It was also confirmed for PCS to MCS ($p < 0.05$). Correlation was not confirmed for age to PCS and MCS ($p > 0.05$). Confirmed correlations were both positive and negative and they were moderate ($\pm 0.5 \leq r < \pm 0.7$) and high ($\pm 0.7 \leq r < \pm 0.9$).

DISCUSSION

It could be considered that sex and age did not have any influence on relations between the groups regarding final hip function and health-related quality of life after trochanteric fracture treatment, because there was no significant difference in average age and in sex distribution.

Average final functional result of the treated hip was fair (HHS had values 70–79) in both groups [19]. There was no significant difference between the groups neither in hip function nor in the quality of physical life (PCS) or mental life (MCS) ($p > 0.05$) at least two years after internal fixation of a trochanteric fracture. These results suggest the following:

– submuscular presence of an extramedullary implant with dimensions of SIF does not significantly influence final functional results of the treated hip and health-related quality of life in trochanteric fractures internal fixation;
– the need for bone reaming in cephalomedullary fixation does not significantly influence final functional results of the treated hip and health-related quality of life in trochanteric fractures' internal fixation.

There was a significant correlation between hip function (HHS) and the age of the patients ($p < 0.05$). This correlation was negative; thus, it could be considered that older age means lower function of the hip. It could be explained by the influence of different comorbidities and osteoarthritic changes on gait and hip function in the older population. This correlation was accepted, but the strength of relation between hip function and age is not strictly defined, due to the moderate correlation ($-0.7 \leq r_s < -0.5$) [20]. The age of patients was not significantly correlated to PCS and MCS ($p > 0.05$). These results mean that in older population poorer final hip function can be expected, but the quality of life is not necessarily lower at the end of the trochanteric fracture treatment.

There was significant correlation between hip function (HHS) and PCS ($p < 0.05$). This correlation was positive and high ($r \geq 0.7$), meaning that the strength of the relation was higher than between age and HHS. This result confirms the importance of the gait (that is directly related to the hip function) in general physical health, thus in the physical component of the health-related quality of life.

Correlation between HHS and MCS was also confirmed ($p < 0.05$). This corelation was positive and moderate ($0.5 \leq r_s < 0.7$). It could mean that hip function has influence on the quality of both physical and mental health, with more defined relation to the quality of physical health (PCS). Additionally, there could be concluded that quality of mental life can be kept more stable although the hip function is weaker. There was significant positive correlation between qualities of physical (PCS) and mental health (MCS) ($p < 0.05$) with almost high strength ($p \approx 0.07$). These results could point to the explanation that the quality of general physical health has higher influence on the quality of mental health than just hip function and gait.

Vaquero et al. [13] analyzed the treatment of trochanteric fractures by gamma nail. Their reported results of HHS were similar, while PCS and MCS were lower than those in our study, 12 months after surgery. Li et al. [14] reported values of HHS after trochanteric fracture treatment that were higher in cephalomedullary (PFNA) and similar in the extramedullary fixation method (DHS) compared to our study. Saarenpää et al. [15] found that hip function was better in the extramedullary (DHS) than in the cephalomedullary method (gamma nail) after four months, but authors concluded that both implants are useful in the treatment of trochanteric femoral fractures.

CONCLUSION

Final hip function and health-related quality of life are expected to be similar between SIF with trochanteric unit and third generation gamma nail methods in trochanteric fractures' treatment. Furthermore, these parameters of outcome were confirmed to have positive interrelation.

ACKNOWLEDGEMENT

This work is a part of the project titled "Virtual human osteoarticular system and its application in preclinical and clinical practice" (No. III41017), funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia.

Conflict of interest: The author Milorad B. Mitković at the moment of writing the paper has an agreement with Traffix d.o.o., producer of SIF implants, on temporary assignment to the use of the patent. Other authors declare no conflict of interest.

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Функција кука и квалитет живота повезан са здрављем код интрамедуларне и екстрамедуларне фиксације трохантерних прелома

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САЖЕТАК

Увод/Циљ У унутрашњој фиксацији трохантерних прелома се често користе екстрамедуларне и интрамедуларне методе са клизним завртњима. Циљ ове студије је био да се испита разлика у утицају ових врста фиксације на функцију кука и квалитет живота повезан са здрављем после завршеног лечења трохантерних прелома.

Методе Анализирано је 75 болесника са трохантерним преломом, који су лечени унутрашњом фиксацијом самодинамизирајућим унутрашњим фиксатором, као екстрамедуларном методом, и гама клином, као интрамедуларном методом. Код ових испитаника је извршено бодовање према бодовном систему за кук по Харису и према упитнику СФ-12, најмање две године после операције. СФ-12 упитник је био исказиван кроз двојак резултат – физичка компонента и ментална компонента.

Резултати Није било значајне разлике између група по питању бодовног система за кук по Харису, физичке компоненте нити менталне компоненте. Између ова три параметра је потврђена линеарна корелација позитивног смера, при чему је ова веза била најјача између бодовног система за кук по Харису и физичке компоненте. Између старости испитаника и бодовног система за кук по Харису потврђена је линеарна корелација негативног смера.

Закључак Између самодинамизирајућег унутрашњег фиксатора са трохантерном јединицом и гама клина треће генерације није потврђена значајна разлика по питању утицаја на функцију кука и квалитет живота повезан са здрављем на крају лечења трохантерног прелома ($p > 0,05$). Потврђена је повезаност између праћених параметара ($p < 0,05$). Додатно се закључује да субмускуларно присуство имплантата величине самодинамизирајућег унутрашњег фиксатора, као и потреба за римовањем медуларне кости не утичу значајно на крајњи резултат лечења трохантерних прелома унутрашњом фиксацијом.

Кључне речи: самодинамизирајући унутрашњи фиксатор; гама клин; функција кука; квалитет живота повезан са здрављем

DOI: https://doi.org/10.2298/SARH200517047I
UDC: 616.75-007.43

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prognostic model of clinical scores in evaluation of treatment outcome in patients with acute Achilles tendon rupture – surgery vs. immobilization

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SUMMARY

Introduction/Objective When choosing the appropriate treatment for Achilles tendon rupture, there may be a dilemma when choosing the optimal treatment.
The objective of this study was analyzing groups of patients with acute closed Achilles tendon injury, comparing early recovery and functional parameters in relation to treatment and first choice treatment suggestion.

Methods The prospective study included 80 patients with acute Achilles tendon rupture. The treatment was surgery or immobilization.

Results There is a difference in the mechanism of injury between surgically and non-surgically treated ($p = 0.026$). In total, 50 (62.5%) patients were operated and 30 (37.5%) patients were treated with circular plaster. The difference ($p = 0.000$) between the groups in the duration of treatment, The American Orthopaedic Foot and Ankle Society (AOFAS) score and Visual Analogue Scale of pain (VAS) was shown. Patients undergoing surgery in the first two days had better clinical results in terms of The Achilles tendon Total Rupture score (ATRS), AOFAS and VAS. Higher satisfaction was achieved in younger people ($p = 0.036$). Patients whose treatment lasted shorter were more satisfied with their status ($p = 0.001$). ATRS and AOFAS score are higher in patients who are more satisfied with their own status (ATRS $p = 0.301$; AOFAS score $p = 0.001$). Six months after the treatment, 78.75% (63/80) of patients were fully functional.

Conclusion The therapy of choice in the treatment of acute Achilles tendon rupture is surgical, as surgical treatment is shorter; rehabilitation is faster and shorter, and the total costs associated with treatment and absence from work are lower.

Keywords: Achilles tendon; scores; ATRS; AOFAS score; VAS pain

INTRODUCTION

The Achilles tendon is the thickest and strongest tendon in the human body. Rupture of the Achilles tendon accounts for 35% of all acute tendon ruptures [1, 2, 3]. Over a period of 30 years, a tenfold increase has been recorded in the rates of incidence from18 to 21 per 100,000 inhabitants per year [1, 2, 3]. Acute Achilles tendon rupture (ATR) is not only common in professional athletes, but occurs in 61% of individuals who play informal recreational sports. Bilateral ATR occurs in about 25–30% of cases [4].

Research shows that ATRs occur at a rate of 75% for people between the ages 30–40 [3]. It has registered a significant rise in ruptures in the 40–59 demographic. It is more common in males, non-obese and obese patients. The frequency ratio of acute ATR between men and women is 3: 1 [1, 2, 5, 6].

Achilles tendon injuries are associated with risk factors ranging from inflammatory and degenerative changes, to the long-term use of corticosteroids, testosterone, growth hormones, and quinolone antibiotics [4, 6]. The tendon connects *musculus triceps surae* for calcaneus on the back of the lower leg, and actively plantar stretches the foot and raises the heel and the entire body to the toes. During physical exertion, it exposes her to a large load on stretching, especially with insufficient physical preparation and warm-up.

The weakest part of the Achilles tendon is 2–6 cm above the attachment on the calcaneus; approximately 80% of rupture cases occur here; and a limited portion of the blood supply comes from the tendon. Tendon ruptures are caused by a potent dorsiflexion force applied to calf and/or foot [3].

The clinical picture includes a very strong pain and impossibility of plantar flexion, especially standing on the toes of the injured foot. The diagnosis is made by clinical examination (normally confirmed by the Thompson Test or a palpation test), an ultrasound examination, or by magnetic resonance imaging [1, 4, 6].

The treatment options for acute Achilles tendon injury comprise both initial care and

Received • Примљено: May 17, 2020
Revised • Ревизија: July 1, 2020
Accepted • Прихваћено: July 6, 2020
Online first: July 8, 2020

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further non-surgical and surgical rehabilitation. Initial care includes the P.R.I.C.E. procedure (protection, rest, ice, compression, and elevation). Although identifying treatment is challenging, there are several modalities, from conservative therapy to open surgical reconstruction, available to patients. No matter what the technique is, relatively good, functional outcomes are likely.

Surgical treatment has a lower rate of re-rupture compared to conservative therapy (4% *vs.* 10%, respectively), and fewer working days, but records higher rates of complication. Minimally invasive percutaneous techniques are an alternative to traditional treatment. And despite similarly low rates of re-rupture and early complications compared to open surgery, it is accepted that percutaneous techniques be used with caution because sural nerve lesions are possible [2, 6, 7].

Surgical treatment, for instance, also involves joining the ends of the tendon with one of several surgical techniques. This method of treatment has several advantages, namely for the anatomical restitution of the tendon and preservation of its length, the reduction of the tendon scar tissue at the site of adhesion, and primary healing of the tendon at the optimal time. Some scholars maintain that surgical treatment is superior only if done within the first 48 hours of rupture, while others argue for surgical treatment, best performed within the first week of rupture [8].

Non-operative, conservative treatment, however, involves wearing a knee-length circular cast with the foot in a gravitational equinus and the knee in a slight flexion of about 10°, for 6–8 weeks. As physicians, we reserve this method of treatment for people who lead a sedative lifestyle and more comorbidities because patients recover more slowly and are at higher risk of Achilles tendon rerupture by up to 50%, perhaps more [6, 9, 10]. Although each method of treatment has its advantages and disadvantages, there is no consensus on which option is the best. Surgical treatment appears to reduce the risk of rerupture and give a better functional outcome compared to non-surgical treatment. The percentage of re-ruptures in operated patients is 0–11% [7–13].

There are several approaches to surgical techniques for treating a fresh tendon ruptures. The operative approach is posteromedial, recommended with a relief incision in the shape of an elongated letter "S", along the inner edge of the tendon. The posterior medial and posterolateral approaches are less commonly used. They show the best results in younger athletes among those with early surgery; among older recreationists, surgery can be avoided by immobilizing the lower leg for 6–8 weeks, depending on the severity of the injury [8].

After 12 weeks, the patient should be able to walk without an immobilization boot, have a near complete range of motion, and a certain level of muscle strength. Complete recovery from ATR surgery takes 6–9 months, depending, a great deal, on the quality of physical therapy experienced by the patient. Research has shown that accelerated postoperative protocol, with gradual loading and mobilization of the joint results in better general health and vitality in the six months immediately following surgery [14].

The aim of this study was to analyze the population with the acute ATR treated at the Clinic for Orthopedic Surgery and Traumatology of the Clinical Centre of Serbia in Belgrade, over a two-year period. We compared early recovery after acute ATR in operated and conservatively treated patients to the parameters of functionality relative to treatment, to suggest the treatment of first choice regarding the acute rupture of the Achilles tendon in our population.

METHODS

We designed this research as a prospective study at the Clinic for Orthopedic Surgery and Traumatology of the Clinical Centre of Serbia in Belgrade, Republic of Serbia from January 2017 to November 2019, in accordance with the standards of the institutional Committee on Ethics. The study included 80 patients of both sexes with acute ATR. All patients experienced sudden pain in the heel area, difficulty walking and were unable to lift their heel. Participation criteria for the study included: patients with acute ATR within two weeks of injury; a palpable gap at the ruptured Achilles tendon and a positive Thompson test; and a B-mode ultrasound that proved an acute ATR. All patients agreed to complete the questionnaire and provide the data for the scores and follow-up over the next six months.

Exclusion criteria from the study were chronic ATR, open ATR, incomplete clinical data, and a history of long-term corticosteroids or quinolones use, those who, although necessary, wished not to have the operation. Patients who lost to follow-up, or were followed for a period less than six months, were excluded from the study. Informed consent was not signed for reasons of confidentiality and the confidentiality of data. Instead, informed consent was oral. All operated patients signed surgical and anesthetic consent, which is in accordance with the Ethics committee principles.

Questionnaire collected research data, involving two parts. The first part was socio-demographic data (age, sex, body weight, comorbidities, occupation, mechanism of injury and lateralization of the injured Achilles tendon), and the second part of the survey contained data used for scores [The American Orthopaedic Foot and Ankle Society (AOFAS) score, the Achilles tendon Total Rupture score (ATRS), and Visual Analogue Scale of pain (VAS)].

The same specialist clinically examined all patients (palpation test and Thompson test). They performed basic laboratory and radiographic diagnostics, after which a decision was made on the method of further treatment.

Surgery was performed under spinal or regional block anesthesia, under ultrasound control. Non-operative, conservative treatment involved wearing a circular plater cast (immobilization of Paris). All patients continued physical therapy for six months. Steps of surgery are shown in Figure 1.

Modern methods of descriptive (tabulation, graphical representation, measures of central tendency and

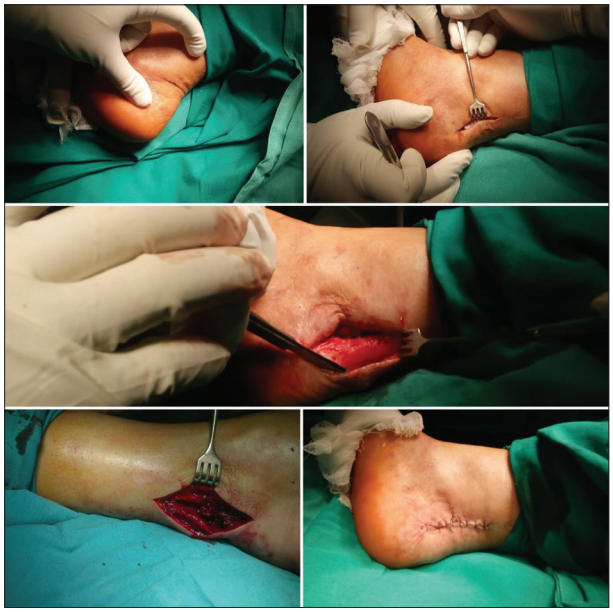

Figure 1. Steps in surgery: position for surgery; surgical approach; Achilles tendon location; Achilles tendon rupture; postoperative suture

variability analyzed data; odds ratio, probability) and analytical statistics (distribution normality test Kolmogorov–Smirnov test; χ^2 test; t-test; linear and logistic regression; linear correlation; one way ANOVA; ROC analysis) using the SPSS, software package version 26.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set as the value of $p < 0.05$.

RESULTS

Follow-up of our patients, who were divided into two groups, lasted up to 180 days. The average follow-up of patients who were surgically treated was 177 ± 11 days, and conservatively treated 175 ± 11.5 days, which is without a statistically significant difference (p = 0.437).

Table 1 shows the demographic characteristics of patients. Table 2 shows data on treatment and functionality of patients with acute ATR.

Table 1. Demographic data

Variable	Open surgery (n = 50)	Immobilization of Paris (n = 30)	p
Age (years)	42.42 ± 8.23	45.93 ± 8.91	0.077
Sex			0.021
Female	11	14	
Male	39	16	
Weight	81.28 ± 11	78.53 ± 12.41	0.305
Comorbidity			0.568
Diabetes mellitus	12	6	
Others	7	5	
Absent	31	19	
Affected side			0.358
Left	21	10	
Right	29	20	
Profession			0.568
Professions without physical activity	43	23	
Housewife/ unemployed	3	3	
Worker	4	4	
Mechanism of injury			0.026
Recreation	27	9	
Work	4	2	
Daily activities	13	12	
Does not know	6	7	

Table 2. Treatment and functionality data

Variable	Open surgery (n = 50)	Immobilization of Paris (n = 30)	p
Type of anesthesia			0.002
Spinal anesthesia	38	NA	
Regional block anesthesia	12	NA	
Duration of treatment (in days)	10.42 ± 11.42	69.17 ± 12.84	0.000
Complications			0.642
Infection	1	0	
Delayed wound healing	3	0	
Paresthesia	5	4	
Absent	41	26	
ATRS score (0–100)	89.1 ± 11.9	87.5 ± 2.97	0.473
AOFAS score (0–100)	90.18 ± 4.23	83.63 ± 6.22	0.000
VAS pain (0–10)	8.92 ± 0.6	7.93 ± 0.78	0.000
Palpation test			0.606
Positive	43	27	
Negative	7	3	
Thompson test			0.809
Positive	32	20	
Negative	18	10	
Plantar flexion (degrees)			0.007
0 (0 °)	3	0	
1 (0–10°)	15	5	
2 (11–20°)	29	15	
3 (21–30°)	3	10	
Dorsiflexion (degrees °)			0.866
3 (7–10°)	19	12	
4 (11–15°)	28	17	
5 (16–20°)	3	1	
Toe gait			0.008
No difficulties	27	25	
Mild difficulties	23	5	
Satisfaction rate (1–10)			0.000
6 (acceptable)	2	12	
8 (satisfied)	30	16	
10 (very satisfied)	18	2	
Re-rupture			0.712
No	49	29	
Yes	1	1	
Duration of treatment (days)	8.82 ± 1.32	69.1 ± 16.84	0.000
Physiotherapy	All underwent		
Full functionality after six months			0.009
Yes	44	19	
No	6	11	

ATRS – The Achilles Tendon Total Rupture Score; AOFAS – The American Orthopedic Foot and Ankle Society; VAS – visual analogue scale

Table 3. The impact on clinical outcomes over time

Interval between ATR and surgery (days)	AOFAS score (0–100)	ATRS (0–100)	VAS pain (0–10)	Satisfaction rate (1–10)
0–2 (n = 19)	90.58 ± 3.82	91.29 ± 2.81	8.95 ± 0.62	8.42 ± 0.84
3–7 (n = 31)	89.94 ± 4.5	87.77 ± 12.9	8.9 ± 0.6	8.78 ± 1.22
Significance	0.606	0.319	0.804	0.276

ATRS – Achilles Tendon Total Rupture Score; AOFAS – American Orthopedic Foot and Ankle Society; VAS – visual analogue scale

Table 4. The prediction of a positive treatment outcome by groups

Full functionality after six months	Open surgery (n = 50)	Immobilization of Paris (n = 30)	All patients (n = 80)
Predicted outcome	84% (42/50)	63.4% (19/30)	76.3% (71/80)
Observed outcome	88% (44/50)	63.4% (19/30)	78.8% (63/80)

ATRS is a composite patient-reported instrument with high reliability, validity, and sensitivity that measures symptom-related outcomes and physical activity after treatment in patients with a total ATR. ATRS is self-administered and comprises 10 questions, each valuated 0–10 points. ATRS ranges 0–100, 100 being the highest score. It tests the following in the calf/Achilles tendon/foot: strength, fatigue, stiffness, and pain. It also measures limitations in daily activities, walking, climbing stairs, jumping, and hard physical labor [2, 15].

In 1994, AOFAS established rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. Originally published in *Foot Ankle International*, the Ankle-Hindfoot Rating System incorporates subject and objective evaluations of the ankle-hindfoot. Patients report their pain and physicians assess alignment. Scores range 0–100, with healthy ankles receiving 100 points. This score may assess the ankle, subtalar, talonavicular, and calcaneocuboid joint levels and may be useful for fractures, arthroplasty, arthrodesis, and instability procedures [16].

Table 3 shows the impact on clinical outcomes over time, typically from the time of ATR and surgery. Patients who received surgical treatment of the Achilles tendon within the first two days of trauma showed better clinical results in relation to ATRS, AOFAS score, and VAS pain. Assessments of satisfaction with treatment and functional status (self-evaluation) proved to show slightly better results in the second group, but without a statistically significant difference between the groups.

We analyzed patient satisfaction in relation to the age of the patient ($F = 3.470$; $p = 0.036$). We concluded that the prevalence of higher satisfaction was in younger patients. The treatment and satisfaction duration analysis ($F = 7{,}763$; $p = 0.001$) was also performed. Results further concluded that those whose treatment lasted shorter reported greater satisfaction with their status.

The results of ATRS and AOFAS score are higher in patients who are more satisfied with their own status (ATRS $p = 0.301$; AOFAS $p = 0.001$). The AOFAS score is a significant predictive indicator. VAS pain does not show statistical significance in relation to self-evaluation ($p = 0.070$)

Logistic regression analyzed the outcome of treatment aiming at full functionality through predictive variables that proved significant in statistical analysis. In our series, 78.75% (63/80) of patients were fully functional six months after acute ATR and treatment.

We made predictions using the following variables: length of treatment, ATRS, and AOFAS scores that showed a significant association with outcome.

Table 4 shows the prediction of a positive treatment outcome by groups (probability of an excellent outcome).

There is a statistically high correlation between predicted and observed numbers. Our logistic regression model used treatment duration in which the ATRS and AOFAS score had a significant predictive value, as (Wald $\chi 2 = 8.406$; $p = 0.004$) was also analyzed using ROC analysis. Exemplary models for prediction have a value above 0.5 (if less than 0.5, model is no better than a random prediction). Predictive values are shown in Figures 2 and 3 and Table 5.

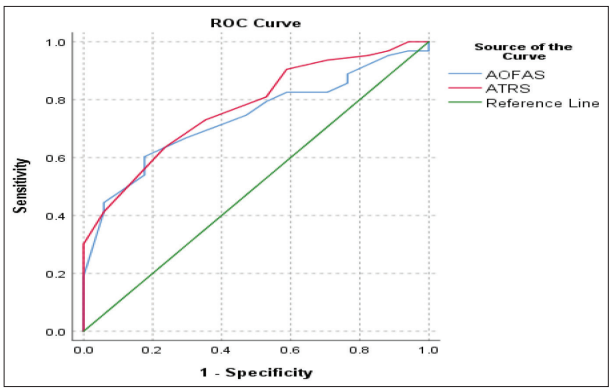

Figure 2. The area under the receiver operating characteristic curve for the following the Achilles Tendon Total Rupture Score (ATRS) and American Orthopedic Foot and Ankle Society (AOFAS) prognostic scores for the patients who fully functionally recovered within six months after acute total rupture of the Achilles tendon

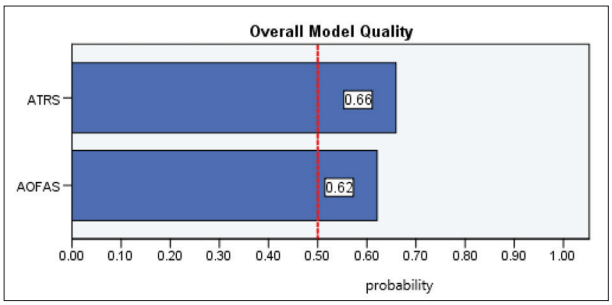

Figure 3. Overall power of prognostic model; both the Achilles Tendon Total Rupture Score (ATRS) and American Orthopedic Foot and Ankle Society (AOFAS) scores are highly reliable and internally consistent (Cronbach alpha p = 0.001)

Table 5. Predictive strength of Achilles Tendon Total Rupture (ATRS) and American Orthopedic Foot and Ankle Society (AOFAS) scores analyzed by receiver operating characteristic (ROC) curve

Predictive variables	Area under the ROC	p	CI 95%
ATRS	0.773	0.000	0.659–0.886
AOFAS	0.736	0.000	0.621–0.852

DISCUSSION

Despite increased incidences of ATR, the best strategy for treatment remains a topic of debate. Surgical treatment is preferred options for many authors, as it decreases the time needed to go back to work after injury, better quality of life and full functionality.

Knobe et al. [11] compared percutaneous treatment to standard open surgical treatment. The mean age of patients with acute ATR treated with standard surgery was 44.8 ± 14.1 years. Similar to the average age of our patients who were treated with standard open surgical treatment and conservative, our work is in line with the current state of the literature, which shows an increased trend in the 40–59 age group [11]. One domestic study, conducted by Vidić et al. [17] 15 years ago, found a preference for the surgical treatment of acute ATR over a more conservative treatment where the average age of patients was 38.8 ± 2.79 years [17]. Considering these data, we can say that in Serbia there is a tendency to move the age group with the highest frequency of acute ATR.

According to the current literature, sex distribution shows a higher incidence of acute ATRs in males. The frequency ratio of acute ATR between men and women in literature is 3:1. In the systematic review done by Abubeih et al. [3] in 2018 we were able to find different men to women ratio raging from 1:1 to 2:1, as well results in compliance with ours.

Overall, a higher frequency of injury to the left Achilles tendon was noted. This differs from our study, where the frequency of acute rupture of the right Achilles tendon is higher [6, 11, 12].

Grubor and Grubor [4], analyzed the treatment of acute ATR, where the frequency of surgical treatment is higher, 81% of patients were operated upon (45% by percutaneous technique; 36%, surgical technique). Our study identifies a statistically significant difference in the treatment of acute ATR. Our study analyzed the mechanism of Achilles tendon injury, and found that the most common injury was observed during recreational sports activities, and in our study, those were treated surgically, while the highest frequency of injuries of those conservatively treated in our study, occurred during daily activities, which is a statistically significant difference.

On average, all patients treated surgically or conservatively within two days of injury, according to the study, which is approximately the same as our results (3.82 ± 1.20 days for surgically treated and 2.67 ± 14.48 days for patients with immobilization). All patients who underwent an open surgical technique were under spinal anesthesia. In our study, besides spinal anesthesia, local infiltrative anesthesia was used. There is also a statistically significant difference compared to our research [4].

The complications of Knobe et al. [11], were present in 34% of cases while in our study they were present in 16.25% of cases; the most common in both studies were paresthesias. Paresthesias can be the result of surgical treatment or diabetes mellitus [11]. Grubor and Grubor [4], had a similarly low frequency of ATRs as early complications (one surgically treated; another, conservatively treated). There were two reversals of the Achilles tendon registered in the group of patients treated with open surgical treatment, four re-ruptures occurred in those conservatively treated [4]. We registered one case of Achilles tendon re-rupture in a group of conservatively treated patients. In the study of Vidić et al. [17], they applied a percutaneous surgical treatment in the control group.

Much like our study, the average duration of treatment of operated and conservatively treated patients in the study of Grubor and Grubor [4], and is nine days in open surgery patients. In Serbia, the average duration of treatment is 8.82 ± 1.32 days, and 9.6 weeks in conservatively treated, while in Serbia, 69.17 ± 12.84 days [4]. This is important owing to the ability to return to work, but also the impact on one's quality of life, and the impact of both the direct and indirect costs of treatment.

In a ten-year follow-up study post-acute ATR surgery, Seker et al. [1] estimated the extent of movement and the mean value of dorsiflexion of the foot on the side of the operated Achilles tendon to be 18° (10–20°). In our study, the highest frequency of patients ranged 10–15° (median 14°). The mean value of plantar flexion in study by Seker et al. [1] was 30° (ranging 20–40°); in ours, the highest frequency was 20–30° (with a median of 28°) in surgery patients. In the same study, they averaged the AOFAS score 98.5 and the VAS pain was 0 for all patients. We find this to be statistically significant vis-à-vis the range plantar flexion among the conservatively treated.

While the finds of several studies differ from ours, monitoring in the aforementioned research is far longer. This may account for the range of difference among findings [1]. Manegold et al. [2] investigated and followed-up on post percutaneous surgical treatment of acute ATR complications. They found that where ATRS was 85.4 ± 14.8, the AOFAS score was 95.3 ± 6.6 and VAS pain 0.6 ± 1, they performed analysis on the impact of the time elapsed, starting the ATR to surgery on the clinical outcome. Patients operated on in the first two days of rupture showed poorer clinical results in terms of AOFAS score. ATRS and VAS pain showed better clinical results in those operated on in the first two days of rupture. In our study, patients who underwent surgery in the first two days of an ATR showed better clinical results vis-à-vis their ATRS, AOFAS score, and VAS pain.

In Knobe et al. [11], the AOFAS score was compatible with ours and was 90 ± 8 in open surgery patients. In the same study, a self-evaluation of patients who underwent open surgical technique was performed, which was 8.40 ± 1.3 on the Likert scale, which is compatible with our results (8.42 ± 0.84 for those operated on in the first two days; 8.78 ± 1.22 for patients operated on in the period 3–7 days).

A prospective study, comparing surgical and non-surgical treatment of acute ATR followed by a physical rehabilitation protocol, showed acceptable outcomes in both groups of patients. The group of operated patients with a statistically significant difference in functionality after six months was significantly better compared to conservative patients treated.

Our study has certain limitations. The number of patients in the study is relatively small. Larger, more

multi-centric study would be recommended to generalize conclusions and give recommendations for good clinical practice.

CONCLUSION

The therapy of choice in the treatment of acute ATR should be primarily surgical, even if both methods of treatment have given reliable results. We should base the choice of treatment on the patient's characteristics and the physical therapy protocol. Surgical treatment is shorter, conditions for better and shorter rehabilitation are more favorable, and the total costs are related to treatment and duration of the absence from work is lower.

Conflict of interest: None declared.

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Прогностички модел клиничких скорова у процени исхода лечења болесника са акутном руптуром Ахилове тетиве – оперисаних и неоперисаних

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САЖЕТАК

Увод/Циљ Код избора одговарајућег третмана руптуре Ахилове тетиве понекад могу постојати недоумице у избору оптималне процедуре.

Циљ ове студије је анализа групе болесника са акутном затвореном повредом Ахилове тетиве, поређење раног опоравка и параметара функционалности у односу на третман и предлагање лечења првог избора.

Методе Проспективно истраживање је обухватило 80 болесника са акутном руптуром Ахилове тетиве. Лечење је изведено хируршком интервенцијом или имобилизацијом.

Резултати Постоји разлика у механизму повређивања између оперисаних и конзервативно лечених ($p = 0,026$). Педесет (62,5%) болесника је оперисано, а 30 (37,5%) болесника је лечено циркуларним гипсом без анестезије. Показана је разлика ($p = 0,000$) између група у дужини трајања лечења, скора Америчког ортопедског друштва за скочни зглоб и стопало (*AOFAS*) и визуелно-аналогне скале (ВАС) бола. Боље клиничке резултате у погледу скорова руптуре Ахилове тетиве (*ATRS*), *AOFAS* и ВАС бола имали су болесници који су подвргнути операцији у прва два дана. Већа сатисфакција је била постигнута код млађих особа ($p = 0,036$). Болесници чији је третман трајао краће били су задовољнији својим статусом ($p = 0,001$). *ATRS* и скор *AOFAS* су виши код болесника који су задовољнији сопственим статусом (*ATRS* $p = 0,301$; скор *AOFAS* $p = 0,001$). Шест месеци после лечења било је потпуно функционално 78,75% (63/80) болесника.

Закључак Терапија избора у лечењу акутне руптуре Ахилове тетиве је хируршка, јер је хируршко лечење краће, повољнији су услови за бржу и крађу рехабилитацију, а укупни трошкови повезани са лечењем и одсуством са посла су мањи.

Кључне речи: Ахилова тетива; скорови; *ATRS*; скор *AOFAS*; ВАС бола

DOI: https://doi.org/10.2298/SARH190918017I
UDC: 159.946.4.072-056.49-053.2; 616.89-008.47-053.2

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Writing kinematics and graphic rules in children with ADHD

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SUMMARY

Introduction/Objective The aim of this study was to compare kinematic features and graphic rules of writing between children with attention deficit/hyperactivity disorder (ADHD) (with and without medical treatment) and typically developed children (TDC).

Methods In total, 55 children (26 with ADHD/ten subjects were on methylphenidate treatment and 29 TDC) completed a writing task on a digitizing board (in three repetitions; using non-inking stylus) which included a semicircle tracing, triangle, and letter copying. Kinematic features of movements in all tasks and graphic rules during a semicircle tracing were analyzed. Graphic rules were observed as expected movements (selecting the starting point and direction of tracing).

Results The values of kinematic parameter jerk were significantly larger in TDC group compared to all ADHD subjects (regardless of treatment) and increased constantly with semicircle task progression and repetition in both groups. Children with ADHD without methylphenidate treatment used overall slower movements compared to TDC. The tracing of children with ADHD taking methylphenidate was more automated (with less change in movement velocity and acceleration) compared to TDC. In ADHD group only, those with treatment traced faster and more automated compared to those without treatment. The majority of subjects used expected movements in semicircle tracing and this percentage increased with the task repetition (without difference between ADHD and TDC).

Conclusion Both children with ADHD and TDC used similar approach in the tracing task and were compliant with graphic rules. Methylphenidate treatment may positively influence writing kinematics in children with ADHD. Task repetition also influences writing.

Keywords: writing; ADHD; kinematic parameters; graphic rules; methylphenidate

INTRODUCTION

Writing is a sophisticated skill that combines cognitive, affective, and biomechanical processes [1, 2]. Writing skill develops with age and masters during elementary and high school [2, 3, 4]. Writing is still an important part of learning and education, and writing difficulties can negatively influence development [1, 2]. Due to its complexity, writing is very sensitive to different intrinsic (e.g., fine motor control, sensory modalities, attention, or working memory) and extrinsic factors (e.g. sitting position, chair height, writing surface color, or verbal instructions) [2, 3].

Writing movements can be divided into basic portions called strokes. A single stroke is defined as the time segment between two subsequent changes in direction during writing [5]. Specific kinematic parameters of writing can be derived from strokes and these are: on surface pressure, stroke speed, stroke duration, velocity, acceleration, jerk, number of velocity/acceleration direction alteration, hand in-air/on-surface time, horizontal/vertical/tangential velocity (acceleration/jerk) and others [6–10]. Various psychiatric and neurological disorders often have their own unique combination of kinematic parameters in particular writing task in which they deviate from healthy controls [6–11].

Certain rules are observed during writing, copying or tracing. These rules are observed as predictable movements, which form a sequence in writing simple or more complex shapes. They are called graphic rules and include starting (a preference to initiate writing by selecting certain location point), progression (a preference to write a segment in some direction), and horizontal rule (a tendency to draw horizontal line after the vertical or oblique) [12, 13]. Using these rules, we can predefine order/sequence of writing or tracing movements in writing task execution and potentially reveal which cognitive strategies children use in writing. By this approach, it is possible to detect children with writing difficulties [12].

Attention deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders among children and adolescents with a worldwide prevalence ranging 5–7%, being more frequent among males [14]. Children with ADHD may have motor performance difficulties including writing

Received • Примљено: September 18, 2019
Revised • Ревизија: February 15, 2020
Accepted • Прихваћено: February 28, 2020
Online first: March 4, 2020

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impairment [1, 15, 16, 17]. Problems with attention span, fine motor control, error processing, visual-motor integration, motor planning, and working memory can all contribute to poorer writing performance in ADHD [1, 18, 19, 20]. Subjects with ADHD write less legible, poorer scaled, with more interruptions, using higher on-surface pressure and less automated movements for age compared to TDC, while writing can be influenced with stimulant medication [1, 18].

Both kinematic analysis and graphic rules are potential ways to assess writing characteristics, but only one study so far had combined these to detect children with writing difficulties [12]. Our research was organized in order to further analyze this particular approach in developmental disorders like ADHD. The aim was to determine whether and how writing of children with ADHD differs from TDC in kinematic features and graphic rules. In addition, we tested the influence of stimulant medications and task repetition onto writing performance.

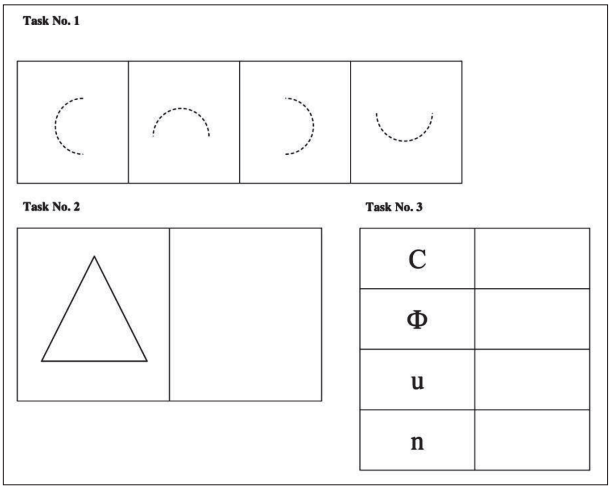

Figure 1. Examples of writing tasks; Task No. 1 – semicircle tracing task (semicircles from 1 to 4 with radius of 1.9 cm rotated in clockwise direction by 90°); Task No. 2 – triangle copying task (a – left edge, b – base and c – right edge); Task No. 3 – letter copying task (C – capital Cyrillic letter s, Ф – capital Cyrillic letter f, u and n are small latin leters)

METHODS

Participants

Data for the present study was collected from a clinical and community sample. The clinical sample, constituting the experimental group, included 26 children (mean age 10.5 ± 1.5 years; 21 (80.8%) boys; 24 (92.3%) right-handed) to whom was confirmed the diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM–5) [21]. The experimental group was divided regarding medical treatment with psychostimulant drugs. Ten children (38.5 %) in the experimental group were taking extended-release methylphenidate (MTX) (OROS formulation; at dose 18 or 36 mg per day) and 16 subjects did not take medications. The community sample, constituting the control group, included 29 TDC (mean age 10.2 ± 0.4 years; 16 (55.2%) boys; 26 (89.7%) were right-handed). The majority of subjects preferred Serbian cursive Cyrillic script during writing. The exclusion criteria were the total IQ < 80 and the presence of any other neurological or psychiatric comorbidity.

An informed consent from parent/guardian was provided for all subjects. The study was approved by the Institutional Committee on Ethics.

Procedure

Following the previous study of Khalid et al. [12], 2010, this study considered a similar combination of tracing and copying tasks of semicircles, shapes, and letters and a digitizing writing board. The writing task considered the following (Figure 1): (1) a tracing of four semicircles (SC) rotated in clockwise direction (CW) by 90°, (2) a triangle copying, and (3) a letter copying, namely writing the capital Serbian Cyrillic letters S (C) and F (Ф), and small Serbian Latin letters u (y) and n (н) (selected to resemble previous semicircles by their shape). Tasks were repeated three times and each time with a different task order. For left-handed subjects, the test battery was adapted not to overlay their hand over the writing material ("mirror image"). In order to familiarize participants with the procedure, all subjects were first instructed to write (e.g. their name) on the writing board surface. The writing tasks were performed on a digitizing board (Intuos4 XL, sampling rate – 200 Hz, resolution – 0.25 mm) (Wacom®, Kazo, Japan) with stylus without ink trace. An A4 white paper sheet with printed tasks was placed on the writing surface under the transparent foil. A customized software platform for data acquisition was previously created using the LabVIEW® (National Instruments Co. Austin, TX, USA) software environment [22]. All subjects from the experimental group (ADHD) were tested in conditions resembling those in school, while the control group (TDC) was tested during school classes.

Data analysis

Kinematic parameters were analyzed from the data related to all writing tasks (Figure 1): the semicircle tracing (for each semicircle for three repetitions), triangle coping (for all triangle edges: a – left edge, b – base and c – right edge; in three repetitions), and letter coping (for all letters together only for the first repetition). The following kinematic parameters were analyzed (mean values and standard deviations): on surface pressure (P), velocity (V), acceleration (A), jerk (J), stroke time (ST), stroke speed (SS), number of changes in velocity (NCV) and number of changes in acceleration (NCA). For V, A and J, three vector components were analyzed: x – horizontal, y – vertical and t – tangential (Table 1). Kinematic parameters were extracted using a customized algorithm in Matlab® (Mathworks, Novi, MI, USA) [8, 9].

The difference in mean values for kinematics parameters between the experimental and control group were tested by the t-test for two independent groups (when the normality assumption is satisfied) and the Mann–Whitney

Table 1. Kinematic parameter details

Parameters	Abbreviation	Details
Pressure	P	The force that a stylus tip creates over the writing surface
Velocity*	V	The rate at which the position of a stylus changes with time
Acceleration*	A	The rate at which the velocity of a stylus changes with time
Jerk*	J	The rate at which the acceleration of a stylus changes with time
Stroke duration (time)	ST	The duration of the basic unit of writing movements
Stroke speed	SS	The length of a single stroke divided by the stroke time
Number of changes in velocity	NCV	The mean number of local extremes of the velocity
Number of changes in acceleration	NCA	The mean number of local extremes of the acceleration

* – velocity, acceleration, and jerk have three vector sub-components: x – horizontal; y – vertical; t – tangential [7]

U test (when the normality assumption is not satisfied). Categorical parameters were analyzed with χ^2 test. The level of statistical significance was set at a two-tailed p-value of 0.05. In addition, sustainability of statistically significant difference between groups through task repetitions was particularly addressed for each kinematic parameter.

In addition, graphic rules were analyzed from the data related only to the semicircle tracing task and included the starting point and the direction of tracing for each semicircle in each of the three task repetitions. These were called "expected movements" and were predefined for each of the semicircles [12]: for the first semicircle from top to the bottom – Counter Clock Wise (CCW), for the second from left to the right – Clock Wise (CW), for the third from top to the bottom – CW, and for the fourth from left to the right – CCW (Figure 2). Expected movement usage was considered as compliance with graphic rules.

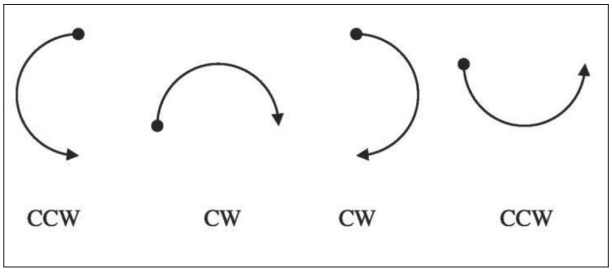

Figure 2. Expected movements in semicircle tracing; starting points (dots) and tracing directions (arrowheads) are shown; CW – clockwise; CCW – counter clockwise

RESULTS

Kinematic features

Semicircle tracing task

Compared to TDC, children with ADHD (all subjects regardless of stimulant treatment) traced semicircles with a lower NCA and had a lower Jt (tangential jerk) in each of the three task repetitions. Children with ADHD receiving MTX (n = 10) had lower NCA, NCV and Jt in comparison to TDC, where only NCA difference sustained through all three task repetitions (Table 2, section A). Children with ADHD not receiving MTX traced with lower SS, Vt and At and higher ST in the first two repetitions compared to TDC (Jt was lower in ADHD group in all repetitions) (Table 2, section A). In addition, in ADHD group only, those taking MTX wrote with higher Vt and lower ST, NCV and NCA compared to subjects without MTX (in all repetitions except for NCV) (Table 2, section B).

The Jt had sustainable trend of augmentation through semicircles and task repetitions in both ADHD (regardless of stimulant treatment) and TDC group (Figure 3; test statistics for the Mann–Whitney U test ranged from $U = 127$, $p < 0.001$ to $U = 429.5$, $p = 0.02$). Difference in Jt value between groups was reducing with task progression (Jt value rose faster in ADHD group).

Table 2. Kinematic parameter relations between study groups in semicircle tracing task

	Parameter		TDC														
			P	SS	ST	NCA	NCV	V			A			J			
		Rpt.						x	y	t	x	y	t	x	y	t	
A)	ADHD (all)	I	/	/	/	▼	/	/	/	/	/	/	/	/	/	▼▼	
		II	/	/	/	▼	/	/	/	/	/	/	/	/	/	▼	
		III	/	/	/	▼▼	/	/	/	/	/	/	/	/	/	▼	
	ADHD 1	I	/	/	/	▼	/	/	/	/	/	/	/	/	/	▼	
		II	/	/	/	▼	▼	/	/	/	/	/	/	/	/	/	
		III	/	/	/	▼▼	▼	/	/	/	/	/	/	/	/	/	
	ADHD 2	I	/	▼	▲	/	/	/	/	▼	/	/	▼	/	/	▼▼	
		II	/	▼	▲	/	/	/	/	▼	/	/	▼	/	/	▼▼	
		III	/	/	/	/	/	/	/	/	/	/	/	/	/	▼	
B)	Parameter		ADHD 2														
			P	SS	ST	NCA	NCV	V			A			J			
		Rpt.						x	y	t	x	y	t	x	y	t	
	ADHD 1	I	/	/	▼	▼	▼	/	/	▲▲	/	/	/	/	/	/	
		II	/	/	▼	▼	▼	/	/	▼	/	/	/	/	/	/	
		III	/	/	▼	▼	/	/	/	▼	/	/	/	/	/	/	

A) ADHD (all), ADHD 1 and ADHD 2 compared to TDC; B) ADHD 1 compared to ADHD 2 during successive semicircle tracing in three task repetitions; ADHD – attention deficit/hyperactivity disorder (all – all ADHD subjects, 1 – ADHD receiving methylphenidate treatment, 2 – ADHD without methylphenidate treatment); TDC – typically developed children; Rpt. – task repetition; shaded fields indicate statistically significant difference ($p < 0.05$); / - no statistically significant difference ($p > 0.05$); ▲ (▼) – indicates that parameter value is statistically higher (or lower) compared to A) TDC and B) ADHD 2; ▲▲ (▼▼) – indicates substantial statistical difference ($p < 0.01$); parameter abbreviations are defined in Table 1

Triangle copying task

In the first repetition, for b and c triangle edges, ADHD subjects (regardless of stimulant treatment) applied significantly larger pressure on the writing surface ($U = 511$, $p = 0.02$ and $U = 579$, $p = 0.01$ respectively) compared to TDC. This was not the case in second and the third task repetition where no statistically significant difference in pressure was documented ($p = 0.06$ - 0.14). Regarding other kinematic parameters, no significant difference was observed between study groups in neither task repetition.

Letter copying task

Only the first repetition was analyzed, and all ADHD subjects (regardless of stimulant treatment) were compared to TDC. It was found that Vt, SS and P were significantly higher in ADHD group compared to TDC ($U = 80798$, $p = 0.004$; $U = 80680$, $p = 0.004$; and $U = 81169$, $p = 0.002$ respectively).

Graphic rules

Comparing ADHD subjects (regardless of stimulant medication treatment) to TDC, those ADHD subjects taking stimulant medication to TDC and those ADHD without medical treatment to TDC; no statistically significant differences were observed regarding usage of expected movements. The same was observed when comparing ADHD subjects with stimulant medication to ADHD subjects without stimulants. There was a certain trend observed with task repetition where an increased number of subjects used expected movements (the most evident in TDC for the first and third semicircle and in ADHD with MTX treatment in the second semicircle). The usage of expected movements was the highest for the fourth semicircle and the lowest for the third semicircle in all groups (Figure 4).

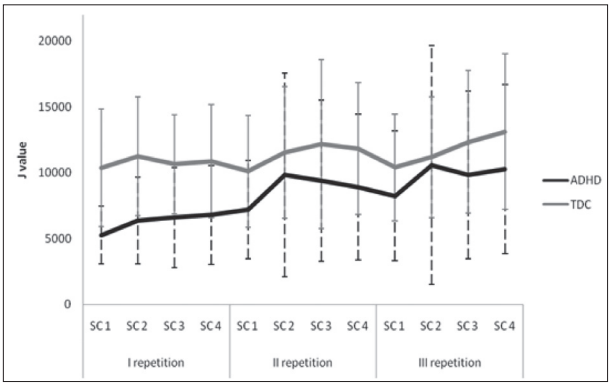

Figure 3. Observed increment in tangential jerk value with successive semicircles and task repetition; mean values and standard deviations are presented; there is a statistically significant difference between groups ($p < 0.05$); ADHD – attention deficit/hyperactivity disorder; TDC – typically developed children; J – jerk; SC – semicircle

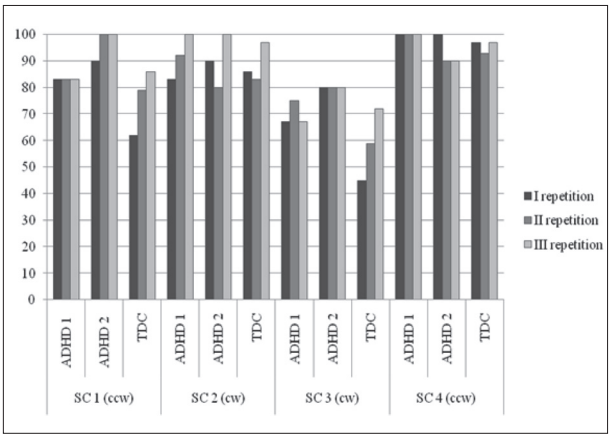

Figure 4. Percentage of subjects used expected movements for semicircle tracing in each task repetition; there is no statistically significant difference between groups ($p > 0.05$); ADHD 1 – subjects receiving methylphenidate treatment; ADHD 2 – subjects without methylphenidate treatment; TDC – typically developed children; SC_i i=1-4 – semicircles; cw – clockwise; ccw – counter clockwise.

DISCUSSION

In both ADHD (regardless of medication treatment) and control group, the Jt had sustainable trend of augmentation through semicircles and task repetitions (values were significantly higher in the control group but raised faster in the ADHD group). We could assume that, based on previous research, with the lack of visual guidance (no inking trace) TDC would be more careful during writing task, making saccadic ("jerky") movements with increased jerk value and in this manner decreasing possibility for error (missing tracing lines, under- or overwriting preset boundaries) [7, 15]. This could also result in decreased writing automation. In addition, the automation of writing movement is observed through changes in velocity and acceleration profile of writing movements (NCV and NCA values). The bigger NCV and NCA values are the lower writing automation is [7]. The opposite would be expected in ADHD group, less saccadic ("smoother"; with lower jerk) and more automated movements (with lower NCA and NCV) which could be due to disturbances in error monitoring [2, 15]. This was shown in our results for all ADHD subjects (regardless of stimulant medication treatment) and similar for ADHD taking stimulant medication. It was also observed that, with repetition, difference in jerk between study groups tends to decrease and ADHD subjects tend to trace as "jerky" as TDC. This could be in partial explained by better error processing with time and repetition. However, recent study has shown that ADHD subjects make from the beginning jerkier large-scale writing movements compared to TDC [19].

ADHD subjects without stimulant medication treatment traced semicircles with movements that were slower and of longer duration, but less saccadic compared to TDC. When these subjects were compared to ADHD subjects with a stimulant medication, they traced with the movements of longer duration and with lower velocity, but also less automated. Stimulant medication in subjects with ADHD modified writing kinematics compared to TDC improving overall movement speed, and this was not the case in group of ADHD subjects without stimulant medication.

This could be explained with the previous data showing that stimulant treatment could alleviate fine motor control impairment seen in ADHD with possible repercussion to writing movements [18, 23]. However, there is not much data on the influence of stimulant medications on motor functioning in ADHD, and should be interpreted with caution [18, 24]. MTX does improve ADHD symptoms in overall, but motor performance problems could remain [18, 25].

In the triangle-copying task, in the first repetition, subjects with ADHD applied significantly more pressure on writing surface (P) compared to TDC (but not in later repetitions). Although larger axial pressure on the writing surface was seen in ADHD [18], our result was not consistent with task repetition. Since no sustainable difference between groups was observed regarding all triangle edges and task repetition, we can assume that kinematic profile of shape copying in ADHD is similar to TDC.

In the letter-copying task, our results showed that V, SS, and P were significantly larger in ADHD group. This is to some instance in accordance with earlier research showing faster, poorly scaled writing movements with larger pressure in ADHD [17, 18]. Earlier research of writing in children with ADHD revealed that writing difficulties associated with attention problems are the consequence of both impaired graphemic buffer and kinematic motor production, and not of linguistic nature [26]. Based on this, we could assume that subjects with ADHD tend to make faster movements with more pressure on the surface compared to TDC and not due to the possibly accompanied dyslexia or dysgraphia, or the presence of comorbid developmental coordination disorder (DCD) [26, 27].

Our findings showed that there were no differences between children with ADHD and TDC when considering the expected movement usage (starting point and the direction of tracing as the main graphic rules). The lowest percentage of fulfilling graphic rules was in the third semicircle tracing. This result could be explained with greater "degrees of freedom" in tracing this semicircle as at the same time being a part of some letters (e.g. b or p, or Cyrillic small letter f – ф or r – р), which offers a possibility to start tracing from either end [13]. On the other hand, the highest percentage of fulfilling graphic rules was in the tracing of the fourth semicircle. It could be explained with the fact that the fourth semicircle resembles small cursive shape for the Cyrillic letter "i" (*и*). This letter is written and connected to other letters in words from left to right during writing (in Serbian language writing is from left to the right). In addition, most of our subjects preferred cursive script Cyrillic.

Subjects in both ADHD and TDC groups fulfilled expectations proposed by graphic rules with an observed increment of usage of expected movement with a task repetition [12]. This increment with task repetition in both ADHD and TDC groups represent a novel result in studies dealing with writing analysis. The largest percentage of non-preferred movement (opposite to graphic rules) seen in the first attempt can also be explained with the poor visual feedback (lack of inking trace). This finding could lead us to conclusion that both ADHD and TDC subjects have similar writing movement strategy in dealing with a simple tracing task.

Our study has some limitations. The writing was done using writing stylus without ink trace. It could influence results to some extent due to poor visual feedback during writing. Correlation between attention, behavior issues, and writing performance was not analyzed. The writing accuracy and overall legibility were not analyzed in the relations to the graphic rules and kinematic parameters.

CONCLUSION

Children with ADHD tended to make more automated writing movements with less jerk compared to TDC. It appeared that MTX treatment improved writing movement speed and automation in ADHD subjects, however these are preliminary data from a small number of subjects and should be further assessed. In more complex tasks, like triangle and letter copying, the kinematic difference was evident but not consistent. Both ADHD and TDC children were compliant with graphic rules in semicircle task. This study also showed importance of task repetition and its influence on writing. These specific kinematic traits found in children with ADHD could be used in clinical practice as an additional method in defying more subtle clinical presentations of ADHD, as well as to monitor effects of stimulant therapy. Addressing the limitations of the present study, further research is needed among children with ADHD in order to better understand specific cognitive approaches to writing and how to implement these in regular clinical practice.

ACKNOWLEDGMENTS

Special thanks for the contribution to the paper: Marina Grbić-Ivančević, Vladimir Kojić, Blažo Nikolić, Janko Samardžić and Milena Janjić.

Founding: partially supported by project #175016 of the Ministry of Education, Science and Technological Development of the Republic of Serbia.

Conflict of interest: None declared.

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Кинематика писања и графичка правила код деце са хиперкинетским поремећајем са недостатком пажње (*ADHD*)

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САЖЕТАК

Увод/Циљ Циљ ове студије био је да упореди кинематичке карактеристике и графичка правила приликом писања деце са хиперкинетским поремећајем са недостатком пажње (*ADHD*) (са терапијом стимулансима и без ње) и код типично развијене деце (*TDC*).

Методе Анализирано је укупно 55 испитаника (26 са *ADHD*, од којих је 10 добијало метилфенидат, и 29 *TDC*). Испитаници су радили задатак са писањем на дигитализованој графичкој табли (у три понављања; писаљком без мастила). Задатак је укључивао подебљавање полукругова, прецртавање троугла и преписивање слова. Анализиране су кинематичке карактеристике свих покрета, као и графичка правила приликом подебљавања полукругова. Графичка правила су сагледавана кроз очекиване покрете писања (одабир почетне тачке и правац подебљавања).

Резултати Вредности параметра „трзај" биле су статистички значајно веће код *TDC* у поређењу са децом са *ADHD* и константно су расле у обе групе са израдом и понављањем задатка са полукруговима. Деца са *ADHD* без терапије метилфенидатом имала су спорије покрете писања у поређењу са *TDC*. Покрети подебљавања су били аутоматизованији (мање промена у брзини и убрзању) и са мањим трзајем код деце са *ADHD* на метилфенидату у поређењу са *TDC*. У групи деце са *ADHD*, она деца која су била на терапији подебљавала су брже и аутоматизованије у поређењу са децом без терапије. Већина испитаника користила је очекиване покрете за подебљавање полукругова и овај проценат је растао са понављањем задатка (није било разлике међу испитиваним групама).

Закључак Деца са *ADHD* као и *TDC* користе сличан приступ у подебљавању полукругова и придржавају се графичких правила. Третман метилфенидатом може утицати позитивно на кинематику писања код деце са *ADHD*. Понављање задатка такође утиче на писање.

Кључне речи: писање; *ADHD*; кинематички параметри; графичка правила; метилфенидат

DOI: https://doi.org/10.2298/SARH191119044P
UDC: 616.34-007.44-036-053.2

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prevalence and significance of transient enteroenteric intussusceptions in children with recurrent colic abdominal pain

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SUMMARY

Introduction/Objective Recurrent colic abdominal pain (RCAP) is a common complaint in children. Children with this complaint are often referred to abdominal ultrasound (US). Examining the children with RCAP by US in our outpatient clinic we occasionally noticed transient enteroenteric intussusceptions (TEIs) with spontaneous resolution.

The objectives of our prospective observational study were to determine the prevalence and evaluate the significance of TEIs in children with RCAP.

Methods From January 2016 to December 2017 we examined 358 children with RCAP by US. Age range was 1–17 years (mean age 7.7 years). TEIs were detected and the prevalence determined. The sensation of pain at the time of the US examination was noted.

Results We detected TEI in 41 children; the prevalence was 11.5%. Abdominal pain at the time of the presence of TEI was reported in 17.1% of these children. In the group of children without TEI detected, pain at the time of the examination was reported in only 6%. A statistically significant relationship was found between the presence of TEI and the pain at the time of the examination ($p = 0.046$). No child had other significant abdominal pathology.

Conclusion TEIs happen more commonly in children than previously thought. A rather high prevalence of TEIs in our study group of children with RCAP and the fact that higher percentage of children with detected TEI experienced pain at the time of the examination, are suggestive that TEIs may be one of the causes for the RCAP in children.

Keywords: intestinal invagination; intussusception; ultrasound; ultrasonography; abdominal pain

INTRODUCTION

Recurrent colic abdominal pain (RCAP) is a common complaint in children. The differential diagnosis of RCAP is fairly extensive; however, most children do not have a serious or even identifiable underlying illness causing the pain [1]. In general, abdominal pain is the most common type of pain in younger children and the second most common type in older children and adolescents [2]. In a study, which included around 15,000 children, 20% of the children reported at least two episodes of abdominal pain in a three-month period [3]. Children with abdominal pain are often referred to abdominal ultrasound (US) examination. Improvements in resolution and the quality of US images now allow detection of small pathologic changes in the abdomen, including bowel intussusceptions. Most often diagnosed and reported intussusceptions were ileocolic ones; enteroenteric intussusceptions were reported much less frequently [4, 5].

Examining children with RCAP by US in our outpatient clinic over a period of several years, we occasionally detected enteroenteric intussusceptions, which were transient and usually spontaneously resolved during the time of the examination. When an intussusception was present, some children experienced pain. We wondered how common TEIs are, as well as how significant they are in the context of managing children with RCAP. Therefore, we decided to conduct a study with the objective to determine the prevalence and evaluate the significance of TEI in children with RCAP.

METHODS

All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Patients

From January 2016 to December 2017, we examined 358 children referred to our outpatient clinic for abdominal US with the only complaint of RCAP. The pain, as reported by children and parents, was spastic, short lasting, occurring in repeated episodes, and located in the periumbilical region. There was no history of vomiting, rectal bleeding or other warning

Received • Примљено: November 19, 2019
Revised • Ревизија: June 24, 2020
Accepted • Прихваћено: June 25, 2020
Online first: July 1, 2020

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Table 1. Baseline characteristics of the study population

Number of patients	358		
Sex		162 boys	196 girls
Age range [years]	1–17	1–17	1–17
Mean age [years]	7.7	7.4	8.1

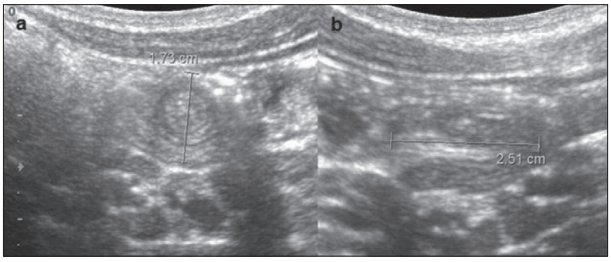

Figure 1. Ultrasound image of a transient enteroenteric intussusception (TEI) in the transversal (a) and the longitudinal (b) plane; the image shows a typical appearance of a TEI: small outer diameter – less than 2.5 cm (in the image of the transversal plane), short bowel segment – less than 3 cm (in the image of the longitudinal plane), and no lead point

signs of underlying illness. On physical examination there were no pathologic findings. Basic laboratory studies were normal. Baseline characteristics of the study population are listed in Table 1.

Ultrasound

US examinations were performed on a DC-8 scanner (Mindray Medical International Limited, Shenzhen, China), using a 7–3 MHz convex-array transducer and a 12–4 MHz linear-array transducer. All examinations were performed by an experienced pediatric radiologist well-skilled in the use of US.

During the examination, the entire abdomen was thoroughly scanned with both transducers and evaluated for the presence of any pathology. Special attention was paid to the potential signs of small bowel intussusception. The duration of examinations ranged 15–20 minutes.

To determine that a small bowel intussusception was transient in its nature, we used the criteria for transient small bowel intussusception described by Kim et al. [6]. These criteria are as follows: 1) small outer diameter (less than 2.5 cm); 2) short (less than 3 cm) segmental intussusception; 3) peristaltic wall motion, and 4) absence of a specific lead point. A typical US appearance of a TEI is shown in Figure 1. Rarely, when we were not certain of the diagnosis of a TEI, because of an unusual location or due to a less typical appearance, a follow-up US was performed after 30–60 minutes. Beside US, no other diagnostic imaging studies were needed for this group of children.

At the start of each US examination, the child was asked about the presence of pain at that time. For younger children, the parents were asked to evaluate whether the child was in pain.

Statistical analysis

Descriptive statistics were obtained to describe characteristics of the study group. χ^2 test was used to evaluate the relationship between the presence of TEI and the pain at the time of the US examination. Significance was set at $p < 0.05$. Statistical analysis was performed with IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA).

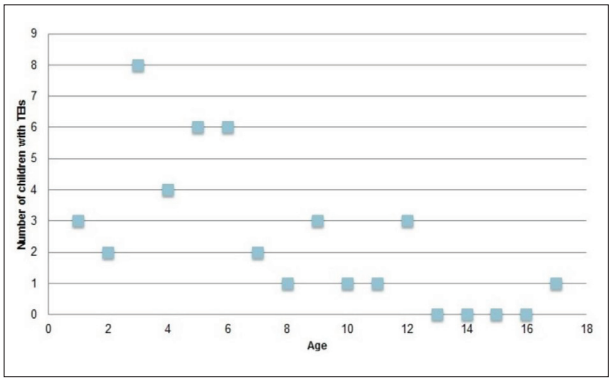

Figure 2. Distribution of transient enteroenteric intussusceptions (TEIs) by age; the chart of distribution of TEIs by age shows that TEIs are the most common in children aged 3–6 years; this group of children represented 58.5% of the diagnosed cases; TEIs were rarely found in children aged < 3 years and aged 7–12, and very rarely in children > 13 years (only one child in our study)

Table 2. Results

Parameter	Total n (%)	Boys n (%)	Girls n (%)
No. of patients	358 (100)	162 (45.3)	196 (54.7)
No. of children with TEI (prevalence) boy:girl ratio	41 (11.5)	30 (18.5)	11 (5.6)
	2.73:1		
Age with TEI (range; mean) [years]	1–17; 5.8	1–17; 6.1	1–12; 4.7
Children with TEIs by age (years)			
< 3	5 (12.2)	4	1
3–6	24 (58.5)	15	9
7–12	11 (26.8)	10	1
> 13	1 (2.4)	1	0

TEI – transient enteroenteric intussusception

RESULTS

We examined 358 children with RCAP referred to our outpatient clinic for abdominal US. Girls represented 54.7% of the study group and boys made up 45.3%. The mean age of the children was 7.7 years. TEIs were detected in 41 of the 358 children, so the prevalence was 11.5%. Most of the TEIs were detected in children aged between 3–6 years (58.5 %). The distribution of TEIs by age is presented in Figure 2. Intussusceptions were more frequently found in boys: boy to girl ratio was 2.73:1. The mean age of the children with TEI was 5.8 years (age range: 1–17 years). Eight children had multiple TEIs (19.5%); in one boy there were four concurrent TEIs. Nearly all TEIs were located in the mid-abdomen or in the left hemiabdomen; only four TEIs were located in the right lower quadrant of the abdomen (7.7%). The results are summarized in Table 2.

Some of the children (17.1%) reported abdominal pain at the time of the presence of TEI and the majority did not. In the group of children that did not have a TEI detected at the time of the US examination, the pain at the time of

the examination was reported in only 6%. A statistically significant interaction was found between the presence of TEI and the pain at the time of the examination (χ^2 (1) = 3.98, p = 0.046).

A lead point was not present in any of the TEIs. There was no evidence of other significant abdominal pathology in any of the children. None of the children returned for a follow-up US examination or for any other additional diagnostic imaging study.

DISCUSSION

The objectives of our prospective study were to determine the prevalence of TEIs in the group of children with RCAP referred to our outpatient clinic for abdominal US and to evaluate the significance of TEIs. The group consisted of 358 children. The prevalence of TEIs was 11.5%.

The prevalence of TEIs in our study is considerably higher than the prevalence previously reported in the literature, in which we found only two studies reporting the prevalence of TEIs in children. In the study by Doi et al. [7], the authors examined 550 children with acute abdominal symptomatology. TEIs were found in 21 cases and the prevalence was 3.8%. The intussusceptions were more common in boys (boy to girl ratio was 1.63:1), similar to our study. The mean age of the children with TEI was 6.2 years, also similar to our study. In the study by Strouse et al. [5], the authors retrogradely reviewed approximately 6000 reports of abdominal computed tomography (CT) scans in children. TEIs were reported in 25 cases; the prevalence was 0.4 %. TEIs were more common in boys (boy to girl ratio was 1.8:1), similar to our and Doi et al. [7] study. The mean age of the children with TEI was 11.2 years, more than in our study. In both studies, all enteroenteric intussusceptions were transient in nature (as diagnosed by a follow-up CT scan, US, barium swallow study, or surgery) and there was no presence of lead points in any of the intussusceptions, the same as in our study. The reason for the higher prevalence of TEIs in our study could most likely be due to the differences of the study groups. Our study group only consisted of children who all had the history of RCAP, while Doi et al. [7] study group consisted of children who all had acute abdominal symptomatology, and Strouse et al. [5] group consisted of children who all had abdominal CT scan indicated for diverse abdominal problems. Because of higher incidence of TEIs in our homogenous group of children with RCAP, we suspect that TEIs could be one of the reasons for the RCAP in children.

It is known that there are chemical and mechanical nociceptors in the enteric wall [8]. Based on this fact, two pathophysiologic mechanisms could explain the occurrence of the colic abdominal pain caused by enteroenteric intussusceptions. Firstly, intussusceptions that last a longer period of time and/or have a strong peristaltic activity may cause so much bowel wall compression and vein strain that it potentially leads to some degree of hypoxia or even ischemia, which in turn leads to pain through activation of the chemical nociceptors in the bowel wall. And vice versa – intussusceptions that do not cause ischemia do not cause the pain. This most likely happens in the intussusceptions with weaker peristaltic activity and/or in the intussusceptions that last a short period of time. Secondly, intussusceptions that cause more bowel wall extension could lead to pain through the activation of stretch mechanic nociceptors in the bowel wall of the intussuscipiens. These two mechanisms may also explain the fact that in our study some children complained of the pain when TEI was present, while some did not. The same finding was noted and reported by other authors [9].

The complaint of pain at the time of US examination additionally strengthens our theory that TEIs could be one of the causes of RCAP in children. During our study, 17.1% of the children with RCAP that had a TEI diagnosed on US examination reported pain at the time, while in the group of children with RCAP and no TEI diagnosed during the examination, the pain during the examination was reported in only 6% of the children. The relationship between the presence of TEI and pain at the time of the US examination was found to be statistically significant ($p < 0.05$).

In 2020, Goel et al. [10] published a study which included 90 children with clinical suspicion of intussusception. All included children had acute abdominal pain. In 15 of those children, a TEI was the only pathologic finding. This fact affirms the finding from our study that some TEIs cause acute abdominal pain. Additionally, in all those cases, the TEI involved a short bowel segment (less than 3 cm in length) and had small outer diameter (less than 2.5 cm), which is also in line with findings from our study [10].

To diagnose a TEI, we used the criteria set by Kim et al [6]. The criteria turned out to be reliable and easy to use. The criteria were also useful to distinguish between ileocolic intussusception and enteroenteric intussusception when the intussusception was located in the right hemiabdomen. Nevertheless, in these cases we did a follow-up US in 30–60 minutes. In none of the children TEIs were present on these follow-up US examinations. This confirmed that these intussusceptions were correctly diagnosed as TEIs by the diagnostic criteria by Kim et al [6]. Other authors also report that US can reliably differentiate between ileocolic and enteroenteric intussusception [10, 11]. In contrast, Bartocci et al. [12] recently reported that it can be difficult to distinguish between an ileocolic intussusception and enteroenteric intussusception by US, and pointed out that the accuracy of the diagnosis very much depends on the experience of the examiner [12].

Concerning the clinical significance of RCAP in childhood, we turned to the pediatric Rome classifications for Childhood Functional Gastrointestinal Disorders [13]. According to the most recent Rome IV classification, published in 2016, TEIs in relation to the RACP are not included in any specific category. By clinical symptomatology, TEIs would fit into the category of the "Functional abdominal pain disorders – not otherwise specified." The diagnostic criteria for the "Functional abdominal pain – not otherwise specified" are as follows: 1) at least four

episodes of abdominal pain per month that do not occur solely during physiologic events (e.g. eating, menses); 2) insufficient criteria for irritable bowel, functional dyspepsia, or abdominal migraine, and 3) exclusion of other medical conditions that fully explain the abdominal pain [13]. TEIs could be one of the medical conditions that fully explain the occurrence of the abdominal pain of the category of the "Functional abdominal pain disorders – not otherwise specified." The reason that TEIs are not included in the Rome classification may be due to the facts that it is not possible to diagnose TEIs by clinical examination or laboratory studies, their spontaneously resolving nature, and their low rate of detection by radiologic imaging in the past. Thus, the TEIs were simply considered to be rare and of low importance.

Abdominal pain can be caused by a severe disease, in which case it requires direct treatment. On the other hand, the pain can have a harmless cause, like TEIs, when no direct treatment is needed. Nevertheless, repeated episodes of pain due to TEIs, though not endangering, cause anxiety, impair the child's self-perception of health, interfere with everyday activities of the child and the family, and can considerably worsen the quality of their life. According to the pediatric guidelines concerning the treatment, in the category of the "Functional abdominal pain disorders – not otherwise specified," into which the pain associated with TEIs could fit, indirect treatment only is said to be beneficial. Pharmacotherapy is not recommended [14]. When the symptoms persist for a longer period of time, consultations with a pediatric psychologist may be helpful. The goal of the treatment is not total elimination of the symptoms, but rather the acquisition of strategies for coping with the pain and getting on with life. For school-age children, getting back to school is a prime objective [15]. Cognitive behavioral therapy reduces pain, general stress, and reduces passive and avoidant behavior [16].

US examination is important for the group of children with RCAP. Firstly, for medical reasons, since TEIs can be diagnosed as the cause for the RCAP, and other potential causes for the RCAP can be diagnosed or excluded by US. US is also important in the psycho-social context. Though TEIs do not endanger children and do not require specific medical treatment, as already mentioned, RCAP interferes with everyday activities of the child. When we detect a TEI by US, we explain to the parents what TEI is, its pathophysiological mechanism, and its association with RCAP. We inform them that RCAP caused by TEIs does not endanger the child. We also advise the child and parents how to cope with the pain. We suggest that the child, when experiencing pain, stops with the current activity and lays down if possible. The parents can gently massage the abdomen and soothe the child by gentle communication and maybe by reading to the child. The approach to the child and parents must be done with empathy. Even in the group of children with RCAP in whom we do not detect a TEI during US examination, due to the same symptomatology, we simply assume that TEIs do occur at other times and could be the cause for the RCAP. Therefore, we provide the parents the same possible explanation and advice as in the group of children in whom we detect TEIs. We believe that this holistic approach is helpful, as, by our experience, the return rate of these children for the repeated US examination is low.

Our study was limited by the lack of pathological correlation in TEIs, since no surgery is needed for TEIs due to their spontaneously resolving nature. Another limitation of our study is the lack of a control group. It is difficult to get a referral for abdominal US examination for a comparable group of healthy children without any symptoms.

CONCLUSION

The occurrence of TEIs is a more common phenomenon in children than previously thought. In our group of children with recurrent colic abdominal pain examined by ultrasound, the prevalence of TEIs was 11.5%. This rather high prevalence in our study and the fact that a higher percentage of children with detected TEI experienced pain at the time of an intussusception suggest that TEIs can be the cause for the recurrent colic abdominal pain in children.

Recurrent colic abdominal pain can interfere with everyday activities of the child and family and worsen the quality of their life. Empathic explanation to the parents that TEIs may be the cause for the recurrent colic abdominal pain, and the explanation of the pathophysiology of TEIs in association with recurrent colic abdominal pain is relieving for the parents and the child, and can help them return to a more normal everyday life.

ACKNOWLEDGEMENT

Early results of this study were presented at the Annual meeting of the European Society of Pediatric Radiology in Berlin in June 2018 with an abstract and a short presentation.

Conflict of interest: None declared.

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Учесталост и значај пролазних ентероентеричних инвагинација код деце са понављајућом абдоминалном боли

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САЖЕТАК

Увод/Циљ Понављајућа абдоминална бол (ПАБ) честа је појава код деце. Деца са ПАБ често се упућују на ултразвук абдомена, уз помоћ којег смо код такве деце запажали ентероентеричне инвагинације, које су током прегледа обично спонтано регредирале.

Циљеви наше проспективне опсервацијске студије су били утврђивање учесталости и значаја пролазних ентероентеричних инвагинација (ПЕИ) код деце с ПАБ.

Методе Од јануара 2016. до децембра 2017. ултразвучно смо прегледали 358 деце старости 1–17 година (средња старост 7,7 година). Дијагностификовали смо ПЕИ и утврдили њихову учесталост. Регистровали смо осећај бола у време претраге.

Резултат ПЕИ смо открили код 41 детета (учесталост 11,5%). Болове у тренутку присуства ПЕИ имало је 17,1% те деце. Само 6% деце без ПЕИ је имало бол. Испоставило се да је веза између бола за време прегледа и присуства ПЕИ статистички значајна ($p = 0,046$). Ниједно од 358 прегледане деце није имало другу значајну патологију.

Закључак ПЕИ се појављује чешће него што се досад мислило. Прилично висока учесталост ПЕИ (11,5%) код наших болесника и чињеница да је већи број деце са откривеним ПЕИ у часу прегледа имао болове указује да би ПЕИ могле бити један од узрока за ПАБ код деце.

Кључне речи: ентероентерична инвагинација; интусусцепција; ултразвук; бол у трбуху

DOI: https://doi.org/10.2298/SARH190109129D
UDC: 618.146-006.6-084(497.11)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The prevalence and factors associated with cervical cancer screening among women in the general population – evidence from the National Health Survey

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SUMMARY

Introduction/Objective Serbia has been burdened with one of the highest cervical cancer incidence and mortality rates in Europe.
The objective of the study was to estimate the prevalence and factors associated with compliance to cervical cancer screening among women in the general population.

Methods The study used the data from 2013 National Health Survey of the population of Serbia. Logistic regression analysis was further used to examine demographic and socio-economic factors which affect the disparities in cervical cancer screening practices among the female population.

Results Every third woman (35.4%) has never done a Pap test in her lifetime. The highest percentage of respondents did their Pap tests after they were recommended by doctors (52.3%); 45% of women did it on their own initiative, and only 2.7% did it after they had been summoned to participate in an organized screening by their doctor. The multivariate logistic regression analysis revealed that the most important factors in women who had never undergone Pap tests were the following: age (being within the youngest or the oldest age group), rural residence and low level of education, poor socio-economic status, and marital status (have never married).

Conclusion Further strategies and interventions for improving cervical cancer incidence and mortality rates should be focused on socially and economically endangered population groups in order to reduce disparities in cervical cancer screening more effectively.

Keywords: cervical cancer screening; Pap test; socioeconomic inequalities

INTRODUCTION

Cervical cancer is one of the most common causes of cancer death in women worldwide [1, 2]. Incidence and mortality rates have decreased in high-resource countries. Nowadays, approximately 87% of cervical cancer deaths occur in developing and low-resource countries due to the lack of awareness within their female populations and certain difficulties in running cervical cancer screening programs (Pap test) [3, 4].

Serbia has been burdened with one of the highest cervical cancer incidence and mortality rates in Europe. According to the Cancer Registry of the Republic of Serbia for 2015, the age-adjusted incidence rate was 18.1 and the mortality rate 6.1 per 100,000 women [5]. Regular screenings are the most effective way to reduce the cervical cancer incidence and mortality rates [6, 7]. Following the recommendations of the European Union Council, almost all European governments have made political decisions to introduce cervical cancer screenings in their health systems. However, the levels of implementation are uneven. The majority of developed countries use organized screening models recommended by the relevant international professional organization while the others organize periodic screenings. There are considerable variations in screening strategies (i.e. age limit, screening intervals, etc.) and the extents to which they cover the target population [8].

Certain socio-demographic and cultural characteristics have been recognized as barriers to cervical cancer screening, including low income, low education level, marital status, rural residence, lack of knowledge and awareness of the importance of Pap tests, cultural beliefs, traditions, and fear of cancer [9, 10, 11]. The health care providers fail to inform and encourage women to get tested, which is also a common obstacle to the provision of adequate services. The main systemic barriers are the inaccessibility to healthcare services and thus the inaccessibility to Pap test execution facilities [12].

The objective of the study was to estimate the prevalence and factors associated with compliance to cervical cancer screening among women in the general population.

Received • Примљено: January 9, 2019
Revised • Ревизија: October 31, 2019
Accepted • Прихваћено: November 26, 2019
Online first: November 28, 2019

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METHODS

This study used the data from the 2013 National Health Survey for the population of Serbia (without data from Kosovo and Metohija). This was the third population-based cross-sectional survey conducted by the Ministry of Health of the Republic of Serbia. In this survey, the research tools (methodology, questionnaires, instructions) were harmonized with the instruments of the European Health Survey second wave (EHIS wave 2) taking into account the defined, internationally accepted indicators [13]. The aim was to obtain the results that would be comparable with the results obtained in the EU member countries. The study used a national representative probability sample; two-stage stratified sample with known probability of the sample unit selection at every sampling stage. Three types of questionnaires were used in the survey.

Ethical Standards in Health Research were harmonized with the international World Medical Association Declaration of Helsinki. The study was approved by the Ethics Committee, which covers four major regions in Serbia based in Dr Milan Jovanovic Batut Public Health Institute of Serbia in Belgrade, Institute of Public Health in Novi Sad, Institute of Public Health in Kragujevac, and Institute of Public Health in Niš. All necessary steps were taken, in accordance with the Law on Personal Data Protection (Off. Gazette of RS No 97/08, 104/09) [14], to ensure the protection of privacy and confidentiality of collected information.

The study used only the data on respondents aged 15 and above and their respective households. The final sample for analysis included 7864 women. Demographic characteristics (i.e. age, marital status, settlement type, region) and socioeconomic status (i.e. education, employment, and well-being index) are used as independent variables. The cervical cancer screening practices were taken as dependent variables.

The data of interest were analyzed with the mathematical-statistical methods suitable for the data type. χ^2 test was applied to examine the differences in the frequencies of categorical variables. Logistic regression analysis was used to examine demographic and socio-economic factors associated with the disparities in cervical cancer screening habits. All results with the probability equal to or less than 5% ($p \leq 0.05$) were considered statistically significant. Statistical analysis was performed in a commercial standard software package IBM SPSS Statistics, Version 19.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The 62.1% of the respondents had done a Pap test prior to the study; 42.6% of them had undergone cervical cancer screening in the previous three years (22.7% during 12 months and 13.7% one or two years prior the survey). Every third subject (35.4%) had never had a Pap test.

During the three years prior to the survey, a Pap test had been executed most frequently on women aged 25–34 (68.4%), married women (52.7%), Belgrade residents (57.1%) and other urban dwellers (47.8%), highly educated (66.6%), employed (69.5%), and women belonging to the richest population group (62.8%) (Table 1).

The highest percentage of respondents did the Pap test after it had been recommended by a doctor (52.3%); 45% of subjects did it on their own initiative, and only 2.7% did it after being summoned by medical professionals to attend organized screenings.

The analysis shows that there is a statistically significant correlation between all the observed demographic

Table 1. The frequency distributions of the last Pap test based on the demographic and socio-economic characteristics of the respondents

Variables	In the last 12 months	1–2 years ago	2–3 years ago	≥ 3 years ago	Never	No answer	p*
Age							
< 24	15.5	6.1	1.4	1.1	75	0.9	< 0.001
25–34	39.1	21.7	7.6	5.8	25.2	0.6	
35–44	37.7	19.7	8.7	13.1	20	0.8	
45–54	29.3	20.5	9.8	19.7	19.2	1.5	
55–64	21.6	13.5	6.1	29.8	26.7	2.3	
≥ 65	5.7	5.4	3.7	30.5	48.7	6	
Marital status							
single	18.9	9.5	2.7	3.4	64.2	1.3	< 0.001
married	27.4	17.3	8	20.4	25.1	1.8	
widow	9.9	5.6	3.1	29	46.5	5.9	
divorced	27.8	15.8	6.9	25.9	21.8	1.8	
Type of residence							
city	26.7	14.6	6.5	21.9	28.4	1.9	< 0.001
other	17.2	12.4	5.7	16.6	44.8	3.3	
Region							
Vojvodina	22.9	12.9	5.6	21.5	35.4	1.9	< 0.001
Belgrade	33.2	16.9	7	23.8	16.8	2.3	
Šumadija and W. Serbia	18.6	12.8	5.5	16.9	43.6	2.6	
S. and E. Serbia	17.8	12.6	6.6	17.2	42.2	3.6	
Education							
primary school	9.4	6.8	4	20.2	54.5	5.1	< 0.001
high school	27.4	17.4	7.7	20	26.5	1	
university	40.8	19.2	6.6	17.1	15.4	1	
Employment status							
employed	40.5	20.9	8.1	13	16.8	0.7	< 0.001
unemployed	25.5	18.1	6.6	15.3	32.8	1.7	
inactive	13.1	8.4	5	24.6	45.2	3.7	
Financial status							
I (the poorest)	10.7	7.4	4.8	18.7	53.6	4.8	< 0.001
II	17.3	13.6	6.3	20.9	40.3	1.6	
III	22.4	14	7.4	20.5	33	2.7	
IV	28	17.3	5.7	20.1	26.9	2	
V (the wealthiest)	38.7	17.4	6.7	17.6	18.4	1.2	

*χ^2 test

and socio-economic features and the screening initiatives. Highly educated subjects were most likely to take screening examinations voluntarily (60.6%). For the women with the lowest education level the percentage amounted to 29.1%; these respondents (with elementary or lower education) were significantly more likely to undergo Pap testing after being recommended to do so by a doctor (66.8% to 37.2%). The same pattern is revealed for financial statuses. The wealthy respondents did their Pap tests more frequently on their own initiative (57.1%) than the poorest (30.9%) ones. The opposite correlation was determined for screenings performed at doctors' recommendations. The poorest respondents were most likely to get tested in suchlike manner (64.3%). In terms of employment, the analysis reveals that employed women were most likely to get tested at their own request (50.7%); 43.9% of unemployed and 38.7% of inactive respondents reported the same practice. The respondents from Belgrade (50.3%) and other urban areas (50.1%) were more likely to take the Pap test on their own initiative, while women from rural areas (60.3%) and other regions were more likely to get tested after doctors had recommended them to do so (Table 2).

The multivariable logistic regression analysis shows that the most important factors in women who have never done a Pap test are as follows: age (being within the youngest or the oldest age group), rural residence and low level of education, poor socio-economic status, and marital status (never have married). The respondents with the lowest education level were four times less likely to take a Pap test than those with the highest education level (OR = 4.203). Those who belong to the poor group, based on the index of well-being, did their Pap smear tests 2.8 times less frequently than those who were classified as wealthy (OR = 2.856). Women who have never been married were significantly less likely to get tested than those who have been married (OR = 2.761). The same applies to economically inactive women (OR = 1.632). The youngest subjects, i.e. those who were less than 24 years old, did Pap tests least frequently (OR = 1.816).

Table 2. Frequency distributions for Pap test initiatives based on the demographic and socio-economic characteristics of the respondents

Variables	Personal initiative	Doctor's recommendation	Summoned to screening (by a doctor)	p*
Age				
< 24	41.1	57.9	1	< 0.001
25–34	46.6	52	1.4	
35–44	52.7	45.1	2.2	
45–54	43.5	53.1	3.4	
55–64	41.7	54.2	4.1	
≥ 65	39.1	56.4	4.5	
Marital status				
single	57.7	41	1.3	< 0.001
married	42.1	54.9	3	
widow	41.9	56	2.1	
divorced	58.2	39.5	2.3	
Type of residence				
city	50.1	47.9	2	< 0.001
other	35.7	60.3	4	
Region				
Vojvodina	46.7	51.9	1.4	< 0.001
Belgrade	50.3	48.9	0.8	
Šumadija and W. Serbia	42	53.8	4.2	
S. and E. Serbia	39	55.9	5.1	
Education				
primary school	29.1	66.8	4.1	< 0.001
high school	43.5	53.9	2.6	
university	60.6	37.2	2.2	
Employment status				
employed	50.7	46.7	2.6	< 0.001
unemployed	43.9	54	2.1	
inactive	38.7	58	3.3	
Financial status				
I (the poorest)	30.9	64.3	4.8	< 0.001
II	35.1	62.1	2.8	
III	43	53.9	3.1	
IV	48.2	49.9	1.9	
V (the wealthiest)	57.1	40.7	2.2	

*χ^2 test

DISCUSSION

Every third women had never had a Pap test in her life. The most important factors in women who had never undergone Pap tests were the following: age (being within the youngest or the oldest age group), rural residence and low level of education, poor socio-economic status, and marital status (have never married).

The results of our study show that 62.1% of the subjects had done a Pap smear at some point in time prior to the survey. Only 42.6% of our respondents had done it during the three years prior to the study. Compared to our results, higher rates of screening were recorded in the national research in Brazil in 2013 on a sample of 31,845 respondents (78.8%) [15]. Similar rates were also recorded by the Cancer Barometer surveys in France; however, they also noted a declining trend from 75.3% in 2006 (n = 3820) to 71.9% in 2010 (n = 3727) [16]. Quite contrary to this, the data obtained in population-based cross-sectional surveys within Lithuanian Health Behaviour Monitoring that included 4248 women aged 25–60 years revealed a constant increasing trend – from 60% in 2006 to 74.2% in 2014. The likelihood of not being screened for cervical cancer was lower among older than among younger women (OR = 0.70; 95% CI = 0.61–0.82) [17].

Developed countries reported even higher screening rates. For example, 83% of women reported having a Pap smear test performed during the previous three years in the United States [18]. The analysis of a cross-sectional survey from Great Britain indicates that 91% of women aged 40–74 years had had a cervical smear test; 3% of women aged 53–74 years had never undergone cervical screening [19].

Several Latin American countries reported the screening rates that are lower than ours. In all countries in

Table 3. The cross ratios (OR) and 95% confidence intervals (CI) for women who have never done the screening, based on the demographic and socio-economic characteristics

Variables	Univariate model		Multivariate model	
	OR (95% CI)	p	OR (95% CI)	p
Age				
< 24	2.899 (2.424–3.468)	< 0.0005	1.816 (1.397–2.362)	< 0.0005
25–34	0.317 (0.268–0.375)	< 0.0005	0.505 (0.406–0.628)	< 0.0005
35–44	0.236 (0.199–0.280)	< 0.0005	0.472 (0.383–0.582)	< 0.0005
45–54	0.226 (0.192–0.267)	< 0.0005	0.401 (0.330–0.488)	< 0.0005
55–64	0.350 (0.303–0.404)	< 0.0005	0.491 (0.417–0.579)	< 0.0005
≥ 65	1		1	
Marital status				
single	1		1	
married	3.603 (3.094–4.196)	< 0.0005	2.761 (2.231–3.416)	< 0.0005
widow	1.183 (0.888–1.576)	0.25	1.347 (0.994–1.826)	0.055
Type of residence				
city	1		1	
other	1.524 (1.334–1.741)	< 0.0005	1.006 (0.849–1.192)	0.945
Education				
primary school	1		1	
high school	2.113 (1.760–2.548)	< 0.0005	1.656 (1.339–2.049)	< 0.0005
university	8.334 (6.575–10.563)	< 0.0005	4.203 (3.164–5.583)	< 0.0005
Employment status				
employed	1		1	
unemployed	5.202 (4.342–6.233)	< 0.0005	1.632 (1.302–2.045)	< 0.0005
inactive	1.989 (1.702–2.324)	< 0.0005	1.249 (1.049–1.487)	0.012
Economic well-being index				
wealthy	1		1	
middle	1.838 (1.557–2.171)	< 0.0005	1.639 (1.339–2.005)	< 0.0005
poor	4.117 (3.272–5.181)	< 0.0005	2.856 (2.121–3.846)	< 0.0005

question, the ratio of a recent Pap smear test was below 55%; for example, 49% (95% CI, 49–50%) in the Dominican Republic, 42% (95% CI, 41–43%) in Bolivia, and 52% (95% CI, 51–53%) in Peru. There have been indications that the percentage of women with Pap test awareness was growing in both Bolivia and Peru, with the level consistently higher in the latter country [20].

The results obtained for the countries in the region vary significantly. In Greece, women aged 40–69 years were recruited for the Pap smear screening program. About 7% of them reported that they had never done a Pap test before they entered the program and 28.8% had not done it during the previous three years [21]. Reportedly, cervical cancer screening rates in Hungary amount to 74%. On the other hand, the screening coverage among women in their reproductive age in Albania is extremely low. It is the lowest detected rate in the region with only 3.2% of women 15–44 years old tested. The organized cervical cancer screening program in Bosnia and Herzegovina has not improved significantly and the country still lacks national cervical cancer registries and Pap test databases. In Bulgaria, there is no national program for cancer prevention. Currently, North Macedonia also lacks the national cancer registry. However, several countries in the region have managed to establish organized cervical cancer screenings that are functioning relatively well. The others are still in the early or preparatory stages of suchlike screening practices. In countries where cervical screening is performed, plans and strategies have been established for switching to organized screenings in the near future [22].

The results of our analysis show that only 2.7% of women responded to a doctor's call to attend organized screening. The Ministry of Health of the Republic of Serbia appointed a special working group for the prevention of cervical cancer in June 2006 as an official response to high incidence of cervical cancer. The group's task was to establish a national program for the prevention of cervical cancer. The program was adopted in 2008, but the results have still not been satisfactory, primarily because of the low response from the women whose health culture is low. In addition, the implementation of health promotion programs has been insufficient, probably due to disregarding the recommendations from the appointed group, as well as the incompetence in managing suchlike programs.

The current literature on the topic reports that recent medical visits are a significant indicator of recent cervical cancer tests [20]. The results of this study show that the highest ratio of respondents did their Pap test after they had been advised by a doctor to do so (52.3%). Women from Latin America who had recently visited their doctor were 1.47–3.44 times more likely to have a recent Pap smear test than those who had not visited a doctor recently [20]. The probability of having a Pap test in this manner was 48% higher in Bolivia (95% CI, 39–59%), 241% higher in Brazil (95% CI, 182–312%), 98% higher in the Dominican Republic (95% CI, 85–113%), 77% higher in Guatemala (95% CI, 36–125%), and 94% higher in Nicaragua (95% CI, 67–129%). In summary, women were 47–244% more likely to receive a recent Pap smear screening after they had recently visited a doctor than those who had not. These data were adjusted to other socioeconomic covariates. Even the poorest women with the recent medical visit were more likely to get tested than the richest women who had not recently visited a doctor. The relations between a recent visit to a doctor and cervical cancer screening may operate through different pathways. Screening may coincide with prenatal or postnatal care or the treatment of any illness as opposed to seeking preventive care directly [23, 24].

Cervical cancer screening habits in Serbia exhibit significant disparities in women based on socioeconomic and demographic characteristics. The multivariable logistic regression analysis shows that the most important factors in women who have never done a Pap test are the following: age (being within the youngest or the oldest age group), rural residence and low level of education, poor socioeconomic status, and marital status (have never married).

Some studies suggest that the participation in the cervical screening is significantly higher in younger women

who belong to higher social classes, are better educated and financially better off, who live in urban areas and visit their gynecologist on a regular basis. In contrast, women of lower socioeconomic status and education, unemployed and disabled women, and women who do not have a habit of visiting a gynecologist regularly are less likely to enter a screening program [25].

Some previous studies in the field have shown that household income is a significant predictor of cervical cancer screening practices and habits [26]. The current findings from Latin America show that the knowledge about the Pap smears and their importance in cancer prevention increases with age (reaching a plateau in the age group 31–35 years) and with education levels. In Bolivia, women with no formal education were 19% (95% CI, 16–22%) less likely to be familiar with Pap smear tests than those with primary education. The subjects with secondary and higher education were 11% (95% CI, 10–13%) and 15% (95% CI, 14–17%) more likely to be informed, respectively. The results from Ecuador, Nicaragua, Peru, and Trinidad and Tobago show that the probability of cervical cancer screening was significantly higher in the urban than in the rural population. The opposite pattern has been recorded in Bolivia [20]. In Brazil, the screening prominence was higher in the subjects with households in urban regions, with partner cohabitation, with better education and with private health insurance. Also, those who regularly underwent screenings with established protocols had healthier lifestyles, including healthier behavior patterns in terms of cervical cancer prevention [27].

Our results are in accordance with other findings reported for European countries. For example, in Lithuania, the non-attendance to cervical screenings was associated with lower education, being single, and having rare contacts with doctors [17]. The survey conducted in Italy revealed that the age group 55–64 years (OR = 2.11, 95% CI: 1.76–2.53) and divorce (OR = 1.32, 95% CI 1.02–1.71) were important factors [28].

The current literature suggests that participation in cervical screenings of those individuals with lower income can be enhanced with adequate interventions at the primary health care level, where an additional focus should be placed on the members of vulnerable groups. Therefore, it is important to keep monitoring how the current public health policies, like expanding the scope of free cervical cancer examination of women whose households are in the lower 50% of the income bracket, impact the participation rates over time [26].

Our study has several limitations. The main limitation is its cross-sectional design, which does not permit inferences about potential causal relations between the explanatory variables and disorders of interest. In addition, self-reporting is always prone to recall biases in describing past screening experiences or socioeconomic variables. Several factors that may influence the rate of participation in cervical cancer screenings, such as accessibility and availability of screening facilities, were not included in this study. These factors should be examined in the future. The further research in the field is also needed in order to explore longitudinal trends and identify other potential factors of inequalities in cervical cancer screening. For better understanding and more efficient implementation of public health strategies, focusing on women with low socio-economic status, we need comprehensible studies to be conducted constantly in the future.

CONCLUSION

Cervical cancer is a preventable disease. When regular screening is properly implemented, early detection and appropriate treatment are possible. In developing countries like Serbia, a great deal more has to be done to improve the screening rates. The measures should focus on increasing the accessibility and availability of cervical cancer screening facilities and services and on decreasing health expenditure. Also, the infrastructure has to be improved. Health care providers must be better educated and equipped.

Educational programs and strategies for raising awareness about cervical cancer, cervical cancer screening and prevention, are crucial steps in deepening and expanding the knowledge of the female population about the issue. As we have shown in this paper, health care service providers have a major impact on the decisions their patients make about their health care and prevention. Their role is crucial in addressing the lack of knowledge, cultural barriers, shame, and fear of pain. Thus, they may have a huge impact on the success of all preventive measures and interventions. Finally, health care system and its health care centers should incorporate cervical cancer screening into their health services at the primary health care level.

The results of this study may be helpful to decision makers, health care providers, and the whole community in designing proper strategies to handle Serbian unfavorable cervical cancer statistics. The findings of this study emphasize the need to explore continuously the reasons why women do not attend regular cervical cancer screenings and to constantly examine the potential ways of supporting and encouraging vulnerable groups to take part in regular screenings. All the strategies and interventions should place an additional emphasis on those population groups that are socially and economically vulnerable and thus most endangered. Only by doing so, we can effectively reduce the current disparities in cervical cancer screenings and diminish the inequalities in the diagnosis stage and treatment, and eventually in survival rates.

ACKNOWLEDGMENT

The study is a part of the 2013 National Health Survey for the population of Serbia (excluding Kosovo and Metohija) that was carried out by the Ministry of Health of the Republic of Serbia with professional support of the Dr. Milan Jovanović Batut Institute of Public Health of Serbia.

Conflict of interest: None declared.

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Учесталост и фактори повезани са скринингом рака грлића материце код жена у општој популацији – докази из Националног истраживања здравља

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Увод/Циљ Србија доживљава високу оптерећеност карциномом грлића материце и има једну од највећих стопа инциденције и смртности у Европи.
Циљ студије је процена преваленције и фактора повезаних са коришћењем скрининга на карцином грлића материце у општој популацији жена.
Методе Коришћени су подаци из националног Истраживања здравља становништва Србије 2013. Логистичка регресиона анализа је примењена за испитивање повезаности демографских и социо-економских фактора са неједнакостима приликом коришћења скрининга на рак грлића материце.
Резултати Свака трећа жена (35,4%) никада није урадила Папаниколау тест током живота. Највећи је проценат испитаница које су Папа тест урадиле по савету лекара (52,3%), а затим самоиницијативно – 45% жена, док позив лекара у оквиру организованог скрининга наводи свега 2,7% жена. Мултиваријантна логистичка регресија као најзначајније факторе за жене које никада нису урадиле Папа тест издвојила је најмлађу и најстарију добну групу, ванградска насеља, низак ниво образовања, сиромашну класу и жене које никада нису биле у браку/ванбрачној заједници.
Закључак Ефективне стратегије и интервенције треба да буду усмерене на социјално и економски угрожене групе како би се ефикасно смањили диспаритети у скринингу карцинома грлића материце.

Кључне речи: скрининг на карцином грлића материце; Папа тест; социо-економске неједнакости

DOI: https://doi.org/10.2298/SARH200519045G
UDC: 616.995.121-089; 616.36-022.1-089

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Laparoscopic approach in the treatment of echinococcal liver disease – case report and literature review

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SUMMARY

Introduction Cystic echinococcosis or hydatid disease is a parasitic disease, zoonosis, and is most commonly caused by *Echinococcus granulosus* larvae. It mainly occurs in endemic areas. The most common localization is the liver.

Case outline In this paper, we will present our experience with a 67-year-old female patient diagnosed with an echinococcal cyst in the right lobe of the liver, as confirmed by computed tomography examination of the abdomen. The patient underwent laparoscopic partial pericystectomy with omentoplasty. The operation went without complications, as well as the postoperative period.

Conclusion Laparoscopic partial pericystectomy is a safe and effective treatment of available hepatic hydatid cysts. Considering all the benefits of minimally invasive surgery, laparoscopic partial pericystectomy of hepatic hydatid cysts may be the treatment of choice, over the classical open surgery approach.

Keywords: *Echinococcus granulosus*; liver cyst; laparoscopy; hydatid cyst; laparoscopic fenestration

INTRODUCTION

Cystic echinococcosis or hydatid disease is a parasitic disease, zoonosis, and is most commonly caused by *Echinococcus granulosus* [1]. Hepatic echinococcosis is the most common localization of echinococcal disease in man. There are other rare causative agents of echinococcal disease: *E. multilocolaris*, *E. vogeli*, and *E. Oligarthus*. The most common in humans is a cystic form of the disease that is caused by *E. granulosus*, much rarer is the alveolar form, which is caused by *E. alveolaris*. It can affect all organs and tissues. The most commonly affected are the liver (70–80%) and lungs (10–25%), while rarely, in about 5% of cases, it can be found in the spleen, kidneys, mesentery, pancreas, brain, heart, muscles and skeleton [2].

Echinococcus granulosus is common in the endemic and sheep breeding regions of the Mediterranean, the Middle East, Australia, New Zealand, South Africa, and South America.

The symptoms are nonspecific. Usually, the infection occurs at a young age and years before the disease is diagnosed. In clinically manifested disease, there are cysts usually large in diameter, which exert a compressive effect and cause problems in the form of dull pain under the right costal arch, discomfort, and this is the reason why the clinical trials are started. The appearance of jaundice, cough, hemoptysis, and severe abdominal pain with fever are signs of advanced disease with consequent complications and the spread of the disease.

It can be diagnosed in several ways: in addition to a well-processed medical history, clinical status, and clinical testing (X-ray, ultrasound, nuclear magnetic resonance, computed tomography, laboratory analyses, and serological tests for the presence of anti-*E. granulosus* antibodies by ELISA test) are also important [1]. The disease is mainly diagnosed incidentally [3].

It is treated with albendazole preoperatively, and also postoperatively, then surgically, as well as with the aspiration of the cyst and injection of scolecid (PAIR: puncture, aspiration, injection, and reaspiration procedure method) in cysts smaller than 5 cm in diameter, in patients who refuse surgery, or have contraindications to surgery due to other comorbidities. Some papers also describe the thermal destruction of echinococcal cysts by using the radiofrequency ablation [4].

In surgical treatment, we have the classic open-approach and laparoscopic approach in resolving echinococcal cysts. Insight into the expert literature shows us that nowadays the number of patients undergoing laparoscopic method in hydatid disease is increasing, due to many advantages in the form of shorter hospitalization of patients, faster recovery, and aesthetic benefits [5]. The laparoscopic approach is mainly performed as the partial pericystectomy with omentoplasty, although larger procedures in the form of partial resections of the liver may be performed laparoscopically. The first described laparoscopic surgery for a hydatid cyst was performed by Katkhouda in 1992 [6].

Received • Примљено: May 19, 2020
Accepted • Прихваћено: June 28, 2020
Online first: July 2, 2020

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This paper aims to present a laparoscopic approach as a safe procedure in resolving hepatic echinococcal cysts.

CASE REPORT

A 67-year-old female patient, who was radiologically diagnosed in May 2019 with the hepatic echinococcal cyst, was admitted to the Clinic for Digestive Surgery, Clinical Center of Serbia, in January 2020. The inspection of the medical records showed that the patient was treated with four cycles of albendazole. Repeated multidetector computed tomography examination confirmed an echinococcal cyst sized 58 × 51 × 42 mm in the sixth liver segment, which is slightly larger compared to the previous finding of three months prior (Figure 1). The ultrasound examination verified the echinococcal cyst type III according to the Gharbi classification. Serological tests for the presence of anti-*E. granulosus* antibodies performed by ELISA test were positive.

Due to the radiological (multidetector computed tomography) progression in echinococcal cyst growth, with positive serological blood analyzes, we decided to perform laparoscopic surgery on February 3, 2020. Because of the prevention of thromboembolic complications, the patient preoperatively received low molecular weight heparin, as well as a prophylactic dose of antibiotics.

After the placement of working ports and the laparoscope, the preoperative finding of the echinococcal cyst in the sixth liver segment on the basic surface was confirmed. After lifting the right lobe of the liver by the use of one gauze holding instrument to prevent hepatic injury, one approaches a cyst which is previously enclosed with gauze soaked in a scolicidal solution (hypertonic or 10% NaCl) (Figure 2). Then a small fenestration was made and suction was placed in the cavity of the cyst where a portion of the content was aspirated without spilling it out (Figure 3). After that, a partial pericystectomy with the evacuation of the content of the cyst (daughter cysts and germinative membrane) was performed. The content was placed in the endo-bag and then removed from the abdomen (Figure 4).

Then, the cavity of the cyst was carefully inspected, cleaned with clean gauze to check for possible biliary fistula. Since the gauze was bile-free, the operation was completed by placing a previously developed part of the large omentum into the cyst cavity, fixed by a pair of sutures

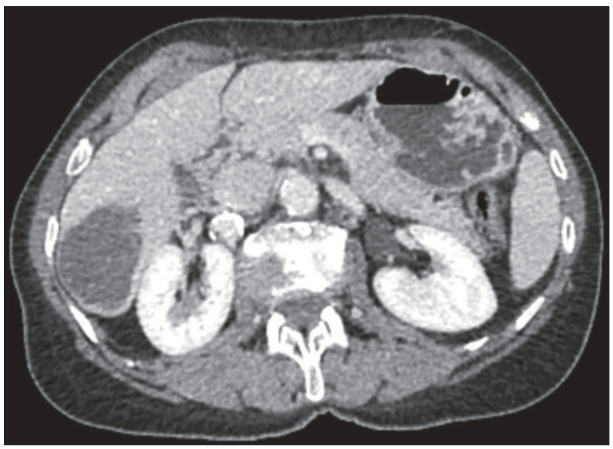

Figure 1. Abdominal computed tomography scan showing a hydatid cyst in segment VI of the liver

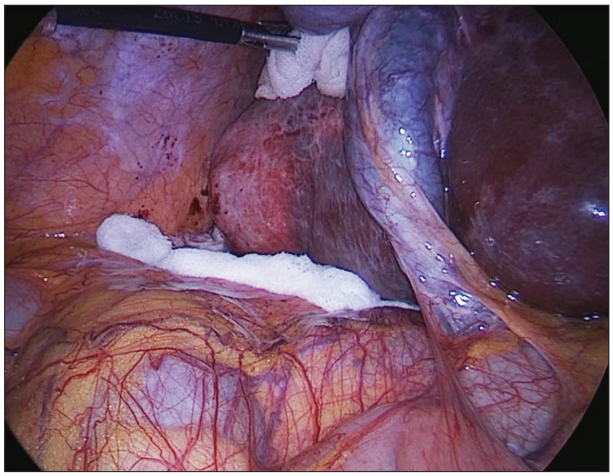

Figure 2. Right lobe of the liver pulled up with forceps; a gauze soaked with scolicidal solution used for operative field packing and also as protection of instrumental liver injury

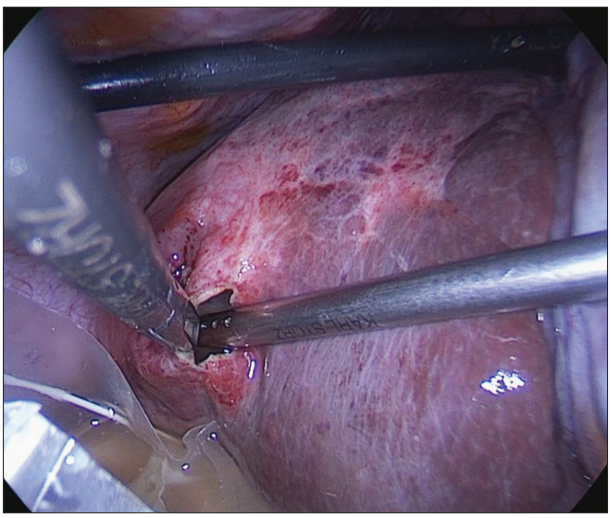

Figure 3. Aspiration of the cyst content

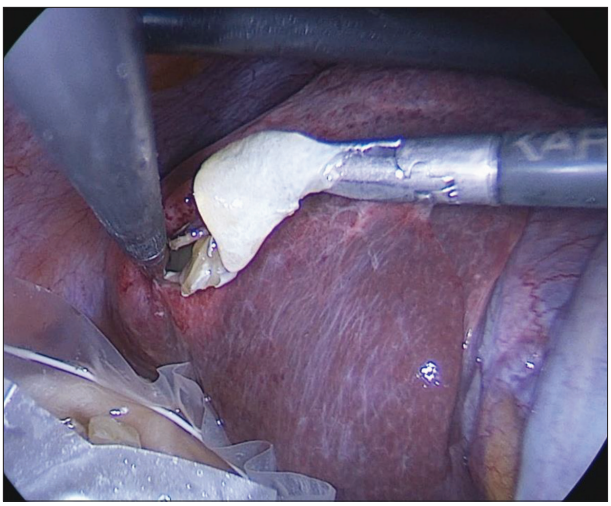

Figure 4. Evacuation of the daughter cysts in to the bag

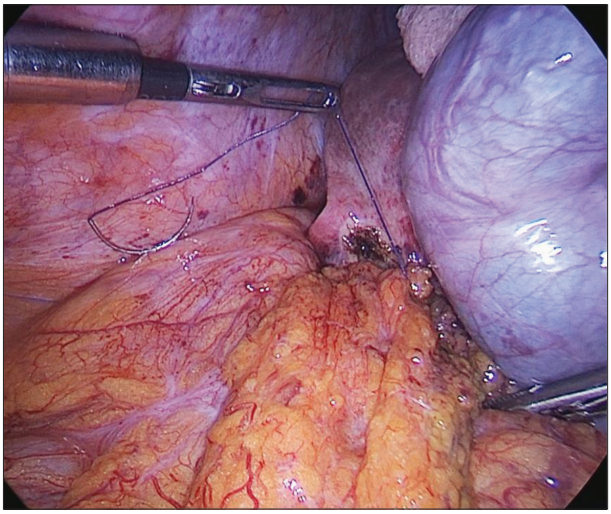

Figure 5. Omentoplasty – omental patch placed in the cyst cavity

(omentoplasty) (Figure 5). After the revision of hemostasis, an abdominal drain was placed. The preparation was sent for histopathological examination, which subsequently confirmed that it was a hydatid hepatic disease.

There were no postoperative complications. The nasogastric probe was removed immediately after the surgery and the abdominal drain was removed on the second postoperative day. The patient was discharged from the hospital on the third postoperative day with prescribed antibiotic therapy and albendazole. One month after the surgery, an ultrasound examination of the abdomen was performed, as well as the magnetic resonance cholangiopancreatography examination three months after the surgery, and both showed regular findings.

This paper was approved by the institutional Committee on Ethics, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

Katkhouda et al. [6] were the first who described laparoscopic echinococcal cyst surgery in the liver in 1992.

The goal of hepatic cystic hydatid disease surgery is to eliminate parasites, to prevent the onset of disease recurrence, and to reduce complications and morbidity to a minimum.

A good preoperative imaging technique largely indicates possible complications (e.g. the existence of a cystic-biliary fistula), as well as the decision of the type of surgery planned [7].

An insight into the expert literature here raises the question of the scope of surgery required to achieve the desired goal. Thus, there are two modalities in the surgical management of hepatic hydatid disease: conservative and radical. The choice of surgical treatment depends on the number, localization, diameter, and complexity of echinococcal cysts, as well as on the characteristics of the patient (age, comorbidities) and the experience of the surgeon.

A conservative surgical procedure is a partial pericystectomy with the removal of the roof of the echinococcal cyst and its contents (germinative membrane and daughter cysts) and placement of part of the large omentum in the cyst cavity (omentoplasty). This is an easier and simpler procedure, which is generally sufficient to deal with hydatid liver disease.

Radical surgical procedures represent two types of surgery: total pericystectomy with echinococcal cyst removal in its entirety, and the other is liver resection.

Indications for surgery are mainly echinococcal cysts type II and III, according to Gharbi's classification, although some authors include type IV, as well as uncomplicated large-sized cysts that compress the surrounding organs, cysts in which the percutaneous treatment is not possible (cysts at risk of spontaneous or traumatic ruptures due to hanging localization on the liver surface, or infected cysts) [8].

According to the current literature data, about 10% of cases remain diagnostically unrecognized disease [9].

It is considered that cysts smaller than 5 cm in diameter can be treated by an interventional radiologist under the control of the ultrasound if the cysts are easily accessible (PAIR procedure). Although this is a less invasive procedure, it also carries some possible complications such as the existence of cystic-biliary fistula after the intervention [10]. Larger diameter cysts are those that are indications for surgical treatment, as well as those, which are more difficult to access.

An indication for surgical resolution of an echinococcal cyst (rather than PAIR) is certainly a preoperatively nuclear magnetic resonance suspected cystic biliary fistula. Its resolution depends on the size and localization of the cyst, as well as the experience of the surgeon. The fistula is usually identified intraoperatively by inspection, after evacuating the cyst contents and placing of a white, clean gauze in the cavity of the cyst, after which the biliary content (bile) is observed on the gauze. Cystic-biliary fistula can be identified by intraoperative cholangiography, or by the white leakage test. Surgical resolution after identification of the fistulose orifice is by suture. Endoscopic retrograde cholangiopancreatography is a method that also may help to resolve the fistulous opening [11]. In clinical practice, endoscopic retrograde cholangiopancreatography is used for preoperatively diagnosed echinococcal cyst rupture into the biliary tract, where the hydatid content (cyst daughter) is seen in the bile ducts, or postoperatively in cases with complications including biliary fistulas or jaundice. In suspected minor cystic-biliary fistula, there is still controversy about the routine preoperative endoscopic retrograde cholangiopancreatography with sphincterotomy [12].

With the first successful laparoscopic surgery due to hepatic echinococcal cysts, begun a new era, with more series are being published and surgeons mastering the technique. However, the curve of learning and accepting the laparoscopic technique is a long process. With the advancement of the technique, the innovation of instruments and the experience of the surgeons, radical laparoscopic surgical procedures, such as pericystectomy and hepatectomy for hepatic hydatid disease in selected cases, are beginning to be reported, with diminishing morbidity and with all

the benefits of laparoscopic surgery in the form of faster recovery. Several comparative papers have been published concerning the differences between laparoscopic and classical, open surgery. The results are generally similar, although laparoscopic surgery is preferred because of the slightly lower morbidity, in selected cases of course. The surgical approach, as well as the treatment of patients with hepatic hydatid disease, should be individual and tailored to each patient individually, and thus laparoscopic surgery would be increasingly used [13].

Laparoscopic surgery, as a superior approach in resolving echinococcal cysts, is particularly preferred for cysts that are more accessible in the II, III, IVb, V, and VI segments of the liver [14].

Indications for laparoscopic echinococcal cyst surgery are, according to some authors, cysts up to 14 cm in diameter, as well as their availability, that is, accessible localization. In these cases, the laparoscopic approach is superior. In addition, the existence of a cystic-biliary fistula can be resolved laparoscopically by sutures or clips [13, 15, 16].

According to guidelines, laparoscopic surgery provides a safe and effective approach for almost all types of hepatic hydatid cysts.

This paper demonstrates that laparoscopic surgery for hepatic echinococcal cyst is safe to perform. It is recommended that a white gauze soaked in scolicid agents stands in the cavity of the echinococcal cyst for a minimum of five minutes after pericystectomy. Existence of cysto-biliary fistula can be confirmed by gauze colorization by bile. We also believe that it is desirable to place an omental patch in the cavity of the cyst as it may prevent abscess formation.

Conflict of interest: None declared.

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Лапароскопски приступ у лечењу ехинококне болести јетре – приказ болесника и преглед литературе

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САЖЕТАК

Увод Цистична ехинококоза или хидатидна болест представља паразитарно обољење, зоонозу и најчешће је узрокована ларвама псеће пантљичаре (*Echinococcus granulosus*). Углавном се јавља у ендемским подручјима. Најчешћа локализација је јетра.

Приказ болесника У овом раду приказаћемо наше искуство са болесницом старом 67 година, код које је дијагностикована ехинококна циста у десном лобусу јетре, што је и потврђено прегледом мултидетекторском компјутеризованом томографијом абдомена. Болесници је учињена лапароскопска парцијална перицистектомија са оментопластиком. Операција и постоперативни период протекли су без компликација.

Закључак Лапароскопска парцијална перицистектомија је сигуран и ефикасан третман доступних ехинококних цисти јетре. С обзиром на предности минимално инвазивне хирургије, ова процедура може бити третман избора за ехинококне цисте јетре, наспрам класичне отворене операције.

Кључне речи: *Echinococcus granulosus*; циста јетре; лапароскопија; хидатидна циста; лапароскопска фенестрација

DOI: https://doi.org/10.2298/SARH191013021M
UDC: 617.55-006

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Abdominal wall endometriosis – clinical presentation, imaging features and management of five cases

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SUMMARY

Introduction Endometriosis represents a functional endometrium outside the uterine cavity. Ectopic endometrial tissue has been identified within the pelvis, affecting both pelvic and extrapelvic organs, causing recurrent pelvic or abdominal pain corresponding to the menstrual cycle.
The incidence of abdominal wall endometriosis after Cesarean section is approximately 2%. It is often mistaken for other conditions primarily because this condition is underestimated on imaging.
The objective of this case series is to summarize possible clinical and radiological presentations of this uncommon condition.

Outline of cases The authors present a case series of five patients who developed abdominal wall endometriosis after Cesarean section. Having been diagnosed clinically, the patients underwent open abdominal surgery, and were treated by surgical resection.

Conclusion Good clinical practice and excellent surgical techniques may help in preventing endometriosis, while adequate clinical examination and proper imaging can help in presurgical planning and successful definitive treatment.

Keywords: abdominal wall; Caesarean section; endometriosis; endometrioma; imaging; surgery

INTRODUCTION

Abdominal wall endometriosis (AWE) represents a challenging and underestimated diagnosis for both clinicians and radiologists due to its rarity [1, 2, 3]. However, it seems to be the most frequent localization of the extra-pelvic endometriosis [3, 4]. In the past, imaging did not represent a significant part of presurgical assessment, providing only scarce information on general radiological features of AWE [3].

Endometriosis is reported in up to 10% of menstruating women and in up to 40% of reproductive age women who undergo gynecological procedures allowing endometrial tissue to be transplanted [5].

Anterior wall endometriosis should be taken into consideration when a painful and tender palpable abdominal wall mass appears within or near Cesarean section, hysterectomy, or laparoscopic trocar sites, with or without bleeding from Cesarean section scar and cramp [6].

Presurgical assessment of this condition should consist primarily of clinical examination followed by appropriate imaging, most commonly ultrasonography (US) or magnetic resonance imaging (MRI).

The objective of this case series is to summarize possible clinical and radiological presentations of this uncommon condition.

Received • Примљено: October 13, 2019
Revised • Ревизија: March 8, 2020
Accepted • Прихваћено: March 30, 2020
Online first: April 24, 2020

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CASE REPORTS

Case 1

A 33-year-old patient was referred to a gynecologist due to pain in the middle of Cesarean section scar that correlates with menstrual bleeding. The patient underwent two Cesarean sections 18 and 49 months before.

Clinical examination revealed two palpable tumors, being approximately 25 × 25 mm and 30 × 20 mm in size, respectively, in the abdominal wall just beneath the Cesarean section scar, that being in accordance with US findings of two irregular, heterogeneous subcutaneous nodules of 23 × 21 mm and 32 × 23 mm, respectively. MRI confirmed the diagnosis, showing two spiculated masses within the muscle of the anterior abdominal wall with imprints to the peritoneum.

Case 2

A 37-year-old patient was referred to a gynecologist due to pain in the left part of the Cesarean section scar correlating with menstrual bleeding. The patient was delivered via Cesarean section 25 months earlier.

Clinical examination revealed a palpable tumor, measuring approximately 45 × 30 mm, in the abdominal wall just beneath the healthy

Cesarean section scar, and it correlated with US findings of irregular, heterogeneous subcutaneous nodules of 50 × 30 mm with internal scattered echoes typical for scar endometriosis.

Case 3

A 32-year-old patient was referred to a gynecologist due to pain in the right part of the Cesarean section scar that correlated with menstrual bleeding. The patient had a history of one previous Cesarean section 31 months earlier.

Clinical examination revealed a palpable tumor, whose approximate size was 25 × 15 mm, in the abdominal wall just beneath the Cesarean section scar. Computed tomography (CT) confirmed the diagnosis, showing one spiculated hypodense mass lesion adjacent to the scar.

Case 4

A 31-year-old patient suffered from pain in the middle and right part of the Cesarean section scar and she was therefore referred to a gynecologist. She had undergone Cesarean section 13 months earlier.

Clinical examination revealed a palpable tumor, measuring approximately 35 × 20 mm, in the abdominal wall just beneath the Cesarean section scar, which correlated with US findings of irregular, subcutaneous nodule of 37 × 18 mm.

Table 1. Clinical information on all five cases

Patient No.	Age at diagnosis	Months after CS	Main symptom	Impression after physical examination	Imaging used for diagnosis	Year of operation for AWEC
1	33	49, 18	Painful mass in ACSS relationship with menstruation	Endometrioma	USG, MRI	2015
2	37	25	Painful mass in ACSS relationship with menstruation	Endometrioma	USG	2017
3	32	31	Painful mass in ACSS relationship with menstruation	Endometrioma	CT	2018
4	31	13	Painful mass in ACSS	Granuloma	USG	2018
5	41	94, 28	Painful mass in ACSS with cutaneous fistula relationship with menstruation	Endometrioma	USG, MRI	2019

CS – Cesarean section; ACSS – abdominal wall previous Cesarean section scar; AWEC – abdominal wall endometriosis in CS scar; MRI – magnetic resonance imaging; CT – computed tomography; USG – ultrasonography

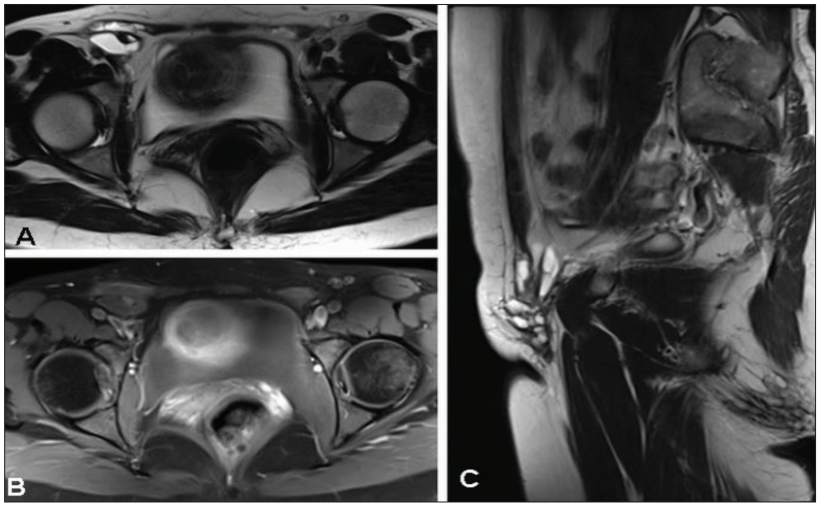

Figure 1. Abdominal wall endometriosis; a multicompartmental cystic lesion is observed at the level of right inguinum on T2W axial image (A), with slight contrast enhancement of the walls seen on T1W vibe axial image (B), extending craniocaudally below the level of anterior abdominal wall (C – T2W coronal image)

Case 5

A 41-year-old patient was referred to a gynecologist because she had complained of pain in the left part of the Cesarean section scar with cutaneous bleeding fistula that correlated with menstrual bleeding. The patient had underwent two Cesarean sections, 94 and 28 months earlier.

Clinical examination revealed a palpable tumor, its approximate size being 30 × 25 mm, in the abdominal wall just beneath the Cesarean section scar, which was in accordance with US findings of irregular, heterogeneous subcutaneous nodule of 33 × 27 mm. MRI confirmed this diagnosis, showing spiculated mass within the muscle of the anterior abdominal wall with imprints to peritoneum and associated with cutaneous fistula.

All five patients underwent mini-laparotomy with surgical approach via previous Cesarean section scar. In all cases, endometriomas were completely surgically removed. The abdominal wall defect was reconstructed by sutures placed through the anatomical layers of the abdominal wall (Table 1).

Being parts of the abdominal wall, all surgical specimens were pink-brown in color. However, after the resection of specimens, they became multicolored in appearance and of elastic consistency (Figures 2 and 3).

Pathohistological examinations of collected samples revealed a lot of coalescent foci of endometrial mucosa consisting of dilated endometrial glands, fenced by stromal cells with typical morphological characteristics. Signs of fresh and old hemorrhage were detected in examined materials (Figure 4a).

Progressive destruction of the anterior abdominal wall muscles was due to anastomosed stripes of newly developed fibrous tissue (Figure 4b).

The presence of all elements of the endometrial lining within the anterior abdominal wall as an ectopic location confirmed the PH diagnosis.

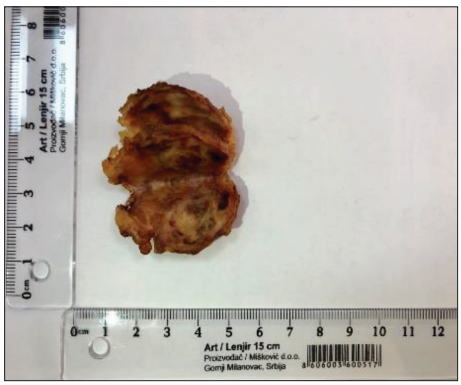

Figure 2. Anterior abdominal wall fragment with the zones of hemorrhage and fibrosis

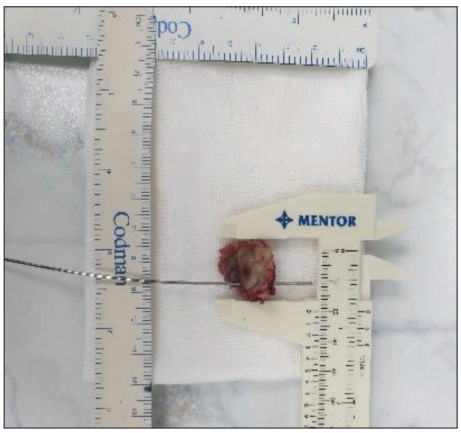

Figure 3. Resected abdominal wall with cutaneous fistula

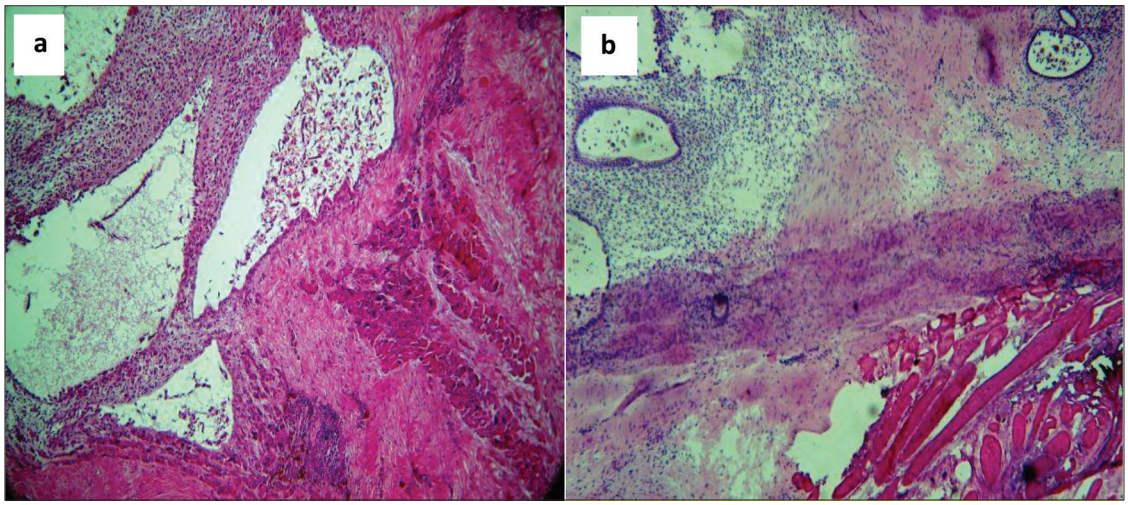

Figure 4. a) Confluent endometriosis foci in the abdominal wall tissue (H&E, 10 × 10); b) fibrous destruction of the muscular beam induced by confluent endometriosis zones (H&E, 10 × 25)

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

DISCUSSION

Anterior AWE is closely connected to Cesarean section, its reported incidence going up to 2% of all women who underwent cesarean delivery [5, 7, 8].

Conditions such as stitch granuloma, hematoma, keloids, primary or metastatic adenocarcinoma and incisional hernia create a diagnostic dilemma [5, 8].

The time period from the Cesarean section to the onset of symptoms ranges from a month to 17.5 years, the average being 30 months [8, 9].

Direct implantation is the most exploited theory of pathogenesis of AWE. Namely, during the surgical procedure that consists of opening the uterine cavity, endometrial tissue is implanted into the surgical scar and afterwards proliferates following the same hormonal influences as uterine endometrium [9]. Endometriosis of surgical scar often infiltrates not only superficial layers of the abdominal wall, but also deeper layers – including the rectus muscle and peritoneum [8].

A common clinical symptom of AWE is cyclical pain spreading within the abdominal wall, usually occurring at the time of menstruation [10].

Palpable mass at the site of maximum tenderness in the region of the surgical scar, which is sometimes multiloculated, is a typical clinical finding [8, 10].

Anterior AWE can also be asymptomatic and incidentally discovered during imaging performed for other reasons [8]. Routine imaging modality for the assessment of AWE is US, due to its availability and low cost. Endometriomas are usually found in the midline and in the left hemiabdomen. Echosonographic features of scar endometriomas are various and non-specific [2]. Most commonly, they present as solid, nodular masses, sometimes stellate clearly defined margins [1]. Recent research has confirmed that heterogenous echogenicity is most common, representing the distribution of fibrous and hemorrhagic components, and varying across the menstrual cycle

[1, 3]. Internal echogenic spots or thick strands represent the fibrotic tissue component [2]. On power Doppler examinations, the lesions show internal vascularity, peripheral in distribution. It is important to notice that US findings of scar endometriomas differ from adnexal ones, typically presenting with round cystic masses, clear margins, thickened walls, and low-level internal echoes [2].

The main role of CT and MRI is to depict the exact extent of the disease preoperatively. CT may be performed with or without the use of contrast agent – contrast studies are preferable due to higher sensitivity and specificity [2]. The CT presentation of AWE nodules is usually non-specific: solid soft-tissue masses that are of heterogenous density and directly associated with the scar tissue. Contrast enhancement of the lesions is mild to moderate, with depiction of the feeding vessels within or adjacent to the nodule [2]. Internally, it can contain blood products with variable attenuation (dependent on chronicity and the menstrual cycle phase) [3].

MRI is a preferred cross-sectional imaging method because of the best tissue characterization, the absence of ionizing radiation, and the possibility of evaluating the relationship between scar tissue and AWE, mandatory for presurgical planning. Endometrioma is usually T2 hyperintense heterogenous nodule with hemorrhagic foci (best observed on T1), directly associated with scar tissue. On T1 sequences with fat suppression, endometrial foci are seen as heterogenous hyperintense lesions, compared to the abdominal musculature, as a result of hemorrhage. Variable T2 signal intensity is associated with cyclic hormonal influences, chronic inflammation and fibrosis [11]. Contrast enhancement is usually strong, at least in a portion of AWE. Diffusion-weighted imaging is used for diagnosing this condition, but apparent diffusion coefficient values also vary across the menstrual cycle [12].

Diagnostic rates on CT and US are low, with undiagnosed endometriosis in 77–100% of the cases, while MRI establishes the correct diagnosis in 75% of the cases [3]. It seems that radiologists are in general not familiar with the spectrum of endometriosis imaging features. The most common differential diagnoses include dermoid tumors, hematomas, keloids, granulomas, metastases, and lymphoma [13, 14]. Dermoid tumors may mimic the radiological appearance of endometriomas but lack the cyclic changes. Hematomas are associated with a recent trauma, they lack typical contrast enhancement and are of a sudden onset. Keloids are usually indistinguishable from AWEs and require biopsy [15].

With emerging of new, less invasive therapeutic approaches, such as high-intensity focused US (HIFU) and radiofrequency ablation (RFA), the requirements for the adequate imaging follow-up will raise, and so should the radiological awareness of this condition and its variable presentation on imaging [16].

Only the presence of endometrial glands and stroma within the lesion can confirm the histopathological diagnosis of endometriosis [17].

Therapeutic options for AWE include surgical excision and medical therapy with hormonal agents – progestagens, danazol, oral contraceptive pills, and gonadotropin-releasing hormone analogs but with a partial response and recurrence when medications are discontinued. The only definitive treatment is a wide local surgical excision with clear margins to prevent local recurrence [8, 18, 19, 20].

CONCLUSION

Anterior abdominal wall scar endometriosis after a Cesarean section represents a challenge from both the diagnostic and the therapeutic aspect.

With a rising Cesarean section rate, anterior abdominal wall scar endometriosis is becoming more common, considering the theory of iatrogenic endometrial inoculation into the surgical wound.

Good clinical practice and excellent surgical techniques may help in preventing endometriosis, while adequate clinical examination and proper imaging can help in presurgical planning and successful definitive treatment.

Conflict of interest: None declared.

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Ендометриоза предњег трбушног зида – клиничка презентација, имиџинг карактеристике и начини решавања пет случајева

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САЖЕТАК

Увод Ендометриоза представља функционални ендометријум изван материчне дупље. Ектопично ткиво ендометријума је идентификовано унутар карлице, захвата карличне и екстрапелвичне органе узрокујући пелвични или бол предњег трбушног зида који траје истовремено са цикличним менструалним крварењем.

Учесталост ендометриозе предњег трбушног зида после царског реза је 2% и често се посумња на друга патолошка стања првенствено услед непрепознавања овог стања на имиџингу.

Циљ ове серије случајева је приказати могуће клиничке и радиолошке презентације ендометриозе.

Приказ болесника Приказана је група од пет болесница са ендометриозом предњег трбушног зида, после царског реза, која је клинички дијагностикована и подвргнута отвореној хирургији локалном ексцизијом.

Закључак Добра клиничка пракса и изврсне хируршке технике могу помоћи у спречавању ендометриозе, док адекватан клинички преглед и одговарајући имиџинг могу помоћи у хируршком планирању и успешном коначном лечењу.

Кључне речи: трбушни зид; царски рез; ендометриоза; ендометриом; имиџинг дијагностика; операција

DOI: https://doi.org/10.2298/SARH191202043S
UDC: 616.714.7-006.6; 616.24-006.6-033.2; 618.19-006.6-033.2

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Tumors of the orbit as the first manifestation of a lung and breast malignancy

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SUMMARY

Introduction Orbit is one of the rarer locations for the metastasis of malignant tumors. The symptoms of orbital tumors are nonspecific, but require detail diagnostics. Methods of visualization, such as ultrasound, radiography, computed tomography scan and/or magnetic resonance imaging of the endocranium are a mandatory step in the diagnostics in order to determine not only the spread of the malignancy but also the affliction of the surrounding structures. The orbital manifestations can be the first sign of the malignant disease.

Outline of cases The first case report presents a female patient with ocular symptomatology as a result of a metastasis of previously undiscovered breast cancer, and the second report presents a male patient with undiscovered lung cancer also presenting with ocular symptomatology.

Conclusion An orbital tumor should instigate further diagnostic procedures, as it can be the first sign of a disseminated malignant disease.

Keywords: orbit; cancer; metastasis; lungs; breast

INTRODUCTION

Tumor of the orbit is a term that encompasses a wide array of both benign and malignant processes located in the orbit or in its structures (mainly bone structures). Some of these processes are vascular malformations, inflammations, proliferation of the adipose tissue (in Graves–Basedow disease), benign and malignant tumors. The clinical manifestation of the orbital tumors is, most commonly, nonspecific, and is manifested with exophthalmos, ptosis, ocular pain, or visual disorders. Computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound are important visualization methods in the diagnostic of these tumors, as well as providing important data in choosing the best treatment options [1]. Depending of the etiology and clinical presentation, the treatment options of the orbital tumors are pharmacological, surgical, or radiational [2, 3]. We present two clinical cases where the primary manifestation of a malignant disease, whose primary localization is extraorbiral, is orbital symptomatology.

REPORTS OF CASES

Case 1

Female patient, aged 54 years, was initially treated at the Clinic of Ocular Diseases, Clinical Center of Serbia, due to double vision, ocular pain, and suddenly developed divergent strabismus. Retrobulbar mass was discovered and a biopsy was performed. The pathohistological finding was that of a metastatic adenocarcinoma. As a part of a preoperative diagnostic, a chest X-ray was performed and showed a bilateral pleural effusion. A pulmonologist was consulted, who indicated the hospitalization at the Clinic of Pulmonology. After hospitalization, a diagnostic pleural thoracentesis was performed and its pathohistological finding was that of a chronic fibrosing pleuritis. In the effusion itself, malignant cells were discovered; however, further differentiation could not have been performed. During the physical examination, enlarged lymph nodes in both axilla were found, so mammography was performed. The mammography showed a malignant lesion in the left breast, classified as T2N1Mx. In order to determine the spread of the malignant disease, radiography of the head, spine, and pelvis was performed, which showed multiple osteolytic metastases (Figure 1). After performing all of the previously stated diagnostic procedures, as well as the revision of the orbital tumor biopsy, it was concluded that the patient had primary breast cancer with the metastasis in the orbit, pleura, and the skeletal system. The patient was presented to the Council for Primary Breast Cancer at the Institute for Oncology and Radiology of Serbia. The Council suggested treatment with systemic chemotherapy – fluorouracil, Adriamycin, and Cytoxan (FAC) regimen.

Received • Примљено: December 2, 2019
Accepted • Прихваћено: June 15, 2020
Online first: June 29, 2020

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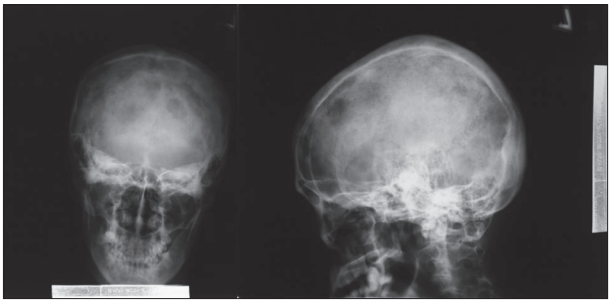

Figure 1. Radiography of the skull and spine with osteolytic metastases

Case 2

Male patient, 47 years old, was admitted to the Clinic of Ocular Diseases, presenting with a ptosis of the right eyelid. He did not have any respiratory symptoms at the time of admission. As a part of the diagnostic procedure, a CT scan of the endocranium was performed (Figure 2), which showed that the ptosis was caused by a tumor of the orbit. Additional diagnostic procedures were performed and chest X-ray showed enlarged right hilum with elements of infiltration present. This finding was further expanded with a CT scan of the thorax and the abdomen (Figure 3), which showed a primary tumor mass in the right lung with multiple osteolytic metastases in the thoracic vertebrae, left iliac bone, and in the skull. Multiple osteolytic metastases had been confirmed with scintigraphy (Figure 4), and new metastases in the sternum and ribs were detected. The patient was transferred to the Clinic of Pulmonology. Taking into consideration the state of the patient (severe cachexia, cyanosis) and a severe decrease in pulmonary function, predominantly obstructive type (FVC 44.2%, FEV1 21.4%, FEV1/FVC 38.85), further diagnostic procedures were not performed at that time, and symptomatic treatment was applied. Despite all of the therapeutic measurements, the patient suffered a lethal outcome.

Consent was obtained from the patients for publication of this report and any accompanying images.

DISCUSSION

Although rare, the signs and symptoms of the metastasis in the ocular region can be the first sign of a malignant disease [4]. As for the metastasis of the non-small cell lung cancer, the eye represents an uncommon localization [5]. Clinical symptoms evolve rather quickly, in a matter of weeks or months, and consist of exophthalmos and difficulty in moving the eye itself. Pain, double vision, and other visual problems are also frequent. It should be noted that, depending on the destruction of other nearby structures, the patient could present with an enophthalmos. Certain studies have shown a relative correlation between the localization of the metastasis in the orbit and its primary localization. Breast cancer has an affinity for the adipose and muscular tissue, prostate cancer afflicts the bone, and melanoma most commonly afflicts the muscular tissue [6].

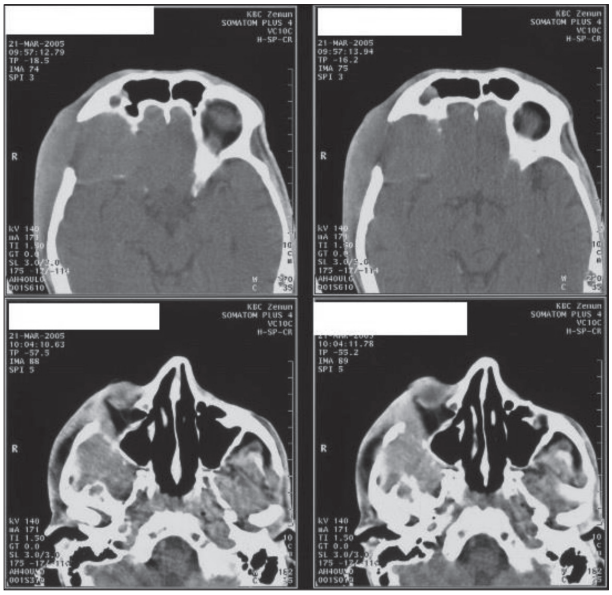

Figure 2. Computed tomography scan of the endocranium, showing a tumor infiltrating the base of the skull, zygomatic bone, and the walls of the orbit, with penetration in the endocranium

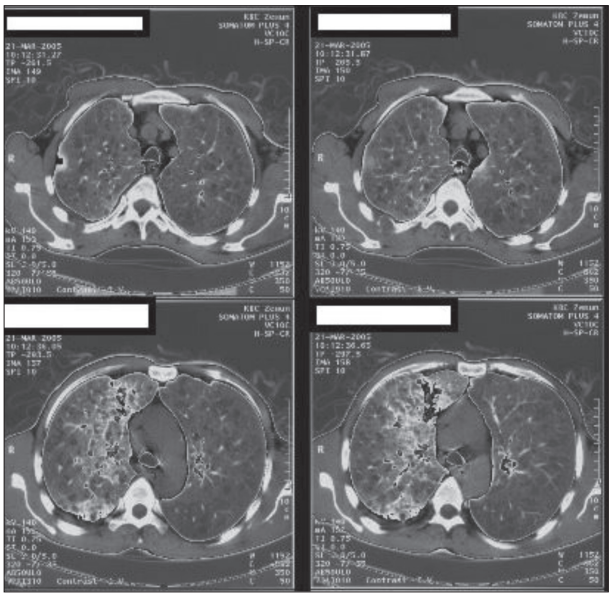

Figure 3. Computed tomography scan of the thorax, showing emphysema, tumor, and multiple metastatic changes

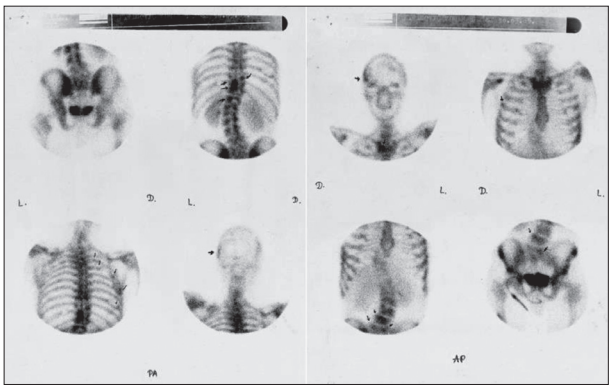

Figure 4. Scintigraphy with multiple osteoblastic changes in the vertebrae, sternum, scapula, skull, and ribs

Ocular manifestations can be the first symptoms of a malignant disease primary located elsewhere. The incidence of an ocular metastasis in lung cancer is 4–6.7% [7]. A case report at the University Hospital in Bohn has shown a patient, aged 65 years, who presented with an afferent pupillary defect in his vision. The initial diagnosis was that of an acute optic ischemia. However, after further diagnostics, it was discovered that the metastasis of the lung cancer caused the compression of the optic nerve, which in turn caused the visual deficit [8]. A patient similar to our second case report, was described by doctors in Japan. The patient, 55 years of age, had a sudden onset of double vision with no respiratory symptomatology. The initial MRI of the endocranium showed a tumor in the right orbit, with destruction of the surrounding bone structures. The finding was supplemented with a CT scan of the thorax, and the full body scintigraphy. The CT scan showed a tumor in the right lung, 4 cm in diameter. Pathohistological finding showed that the tumor is an adenocarcinoma, and scintigraphy showed multiple osteolytic metastases. Taking into consideration all of the diagnostic results, it was concluded that the patient had adenocarcinoma of the lungs with multiple metastases. The patient was treated with chemo- and radiotherapy; however, three months after the diagnosis was set, despite the therapy, the patient died [9]. A case report form Indonesia had showcased a 39-year-old woman who presented with blindness and nonproductive cough. The physicians performed a panel of diagnostic procedures similar to our own, and were able to perform a biopsy of a supraclavicular lymph node, which showed that the patient had adenocarcinoma of the lung. After a multidisciplinary approach, it was concluded that the patient had stage IV lung cancer, and was treated with chemotherapy. Unfortunately, after the first cycle, the patient passed away [10].

The orbit is not a common localization of the metastasis for malignant tumors [11]. More often than not, the ocular symptomatology is the first sign of the malignancy. Methods of visualization, such as CT scan, MRI, and full-body scintigraphy, are important to diagnose the underlying disease, as well as its spread. However, it is important to know that the lethality in these patients is significantly higher, due to the fact that these patients usually have multiple metastases. Certain tumor markers have shown promise in predicting the development of ocular metastases, although further research is needed [12]. The purpose of our case reports is to present these relatively rare forms of metastases, and to help in everyday clinical practice in diagnosing the primary malignant disease.

ACKNOWLEDGEMENT

This study was supported by the Ministry of Education and Science of the Republic of Serbia (grants no. 175046 and 175081).

Conflict of interest: None declared.

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Тумори орбите као прво испољавање малигне болести плућа и дојке

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САЖЕТАК

Увод Орбита представља једну од ретких локација метастаза малигних тумора. Симптоми тумора орбите су неспецифични, али захтевају детаљну дијагностику. Методе визуализације као што су ултразвук, радиографија лобање и компјутеризована томографија / магнетна резонантна томографија ендокранијума представљају обавезан корак у дијагностици како би се тачно одредили степен раширености метастазе и захваћеност околних структура. Треба напоменути да симптоматологија везана за метастатски тумор орбите може бити први знак малигне болести.

Приказ болесника Први приказ случаја се тиче жене са орбиталном симптоматологијом која је последица метастазе претходно неоткривеног карцинома дојке, док се у другом случају ради о мушкарцу са орбиталним испољавањима метастатског карцинома плућа, такође претходно недијагностикованог.

Закључак Малигни тумори орбите треба да подстакну даљу дијагностику код оболелог, с обзиром на то да могу бити последица дисеминоване малигне болести.

Кључне речи: орбита; карцином; метастаза; плућа; дојка

DOI: https://doi.org/10.2298/SARH191222024A
UDC: 615.33.06:616-056.3

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Amoxicillin-clavulanate prescribed in a patient with known penicillin allergy

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SUMMARY

Introduction Prescription of penicillin requires extra caution in order to avoid its administration in a person allergic to this antibiotic. We present a case of a patient allergic to penicillin, to whom a doctor prescribed this medicine by mistake.

Case outline An 18-year-old female patient turned to an otolaryngologist because of a sore throat, difficulty in breathing, and light clogging in the left ear during several previous days. The patient tolerated oral intake of only liquid foods. She reported frequent attacks of tonsillopharyngitis, and an allergy to penicillin. Tonsillopharyngitis was established by a physical examination. The doctor prescribed oral therapy, including a penicillin-based antibiotic Augmentin® (amoxicillin + clavulanate potassium) 1000 mg 2 × 1 tablet for seven days. The pharmacist in the local pharmacy knew the patient and was aware of the fact that the girl was allergic to penicillin, so the patient did not take the prescribed penicillin-based remedy. In this way, an extremely serious professional medical error did not obtain essential features of a criminal act according to the Serbian Criminal Code.

Conclusion When prescribing antibiotics, it is necessary for the physician to be extremely careful not to prescribe a medicine for which there is a *cave* warning in medical documentation, as this error can become grounds for legal prosecution against the doctor, as well as for professional sanctioning.

Keywords: penicillin; prescribing; allergy; alert

INTRODUCTION

The number of antibiotics (AB) is large, and so are the expectations of their use. In contemporary clinical practice, however, problems have been identified relating to: the use of insufficiently tested AB, non-indicated use of AB, not prescribing AB in indicated cases, side effects of AB, inadequate combinations with other drugs, prescribing and administering AB to patients who are not allowed to take them because of sensitivity [1].

When assessing the contribution of AB to health, they are one of the most important groups of drugs: the introduction of ABs, especially of penicillin, is believed to have prolonged the life span of each inhabitant of our planet for 10 years [2]. As an AB of narrow spectrum, with proven efficacy and low cost, penicillin has always been a drug of choice in treating streptococcal tonsillopharyngitis. However, it requires extra caution in order to avoid its administration in a person allergic to this AB.

We present a case of a patient allergic to penicillin to whom a medical doctor prescribed this medicine, as an illustration of a serious medical error that has all the elements of a potential criminal offence.

CASE REPORT

An 18-year-old female patient was examined by an ear, nose, and throat (ENT) specialist for sore throat, difficulty in breathing, and light clogging in the left ear during several previous days. Due to pronounced pain when swallowing, the patient was able to tolerate only liquid foods and because of that she significantly reduced oral intake of food and liquid. The patient reported frequent attacks of acute tonsillopharyngitis, as well as an allergy to pollen and penicillin, the latter being written down as a medical warning in the medical examination report of the ENT specialist: *CAVE PENICILLINI!* (Figure 1).

Physical examination showed the following: soft palate and mucous membranes were diffusely extremely hyperemic; tonsils were inflamed, moderately enlarged, juicy, pus-negative. The other findings were unremarkable.

A penicillin-based AB Augmentin® (amoxicillin + clavulanate potassium) 1000 mg 2 × 1 tablet was prescribed for the following seven days. Lemod® solu i.m. for five days, in reduction (80, 60, 40, 20, 20 mg). Tantum verde® sol. 0.15% 150 ml to gurgle several times a day. Brufen® 400 mg tablet as needed.

The pharmacist in the local pharmacy knew the patient, and was aware of the fact that the patient was allergic to penicillin, so the patient did not take the prescribed penicillin-based

Received • Примљено: December 22, 2019
Revised • Ревизија: March 29, 2020
Accepted • Прихваћено: April 29, 2020
Online first: May 6, 2020

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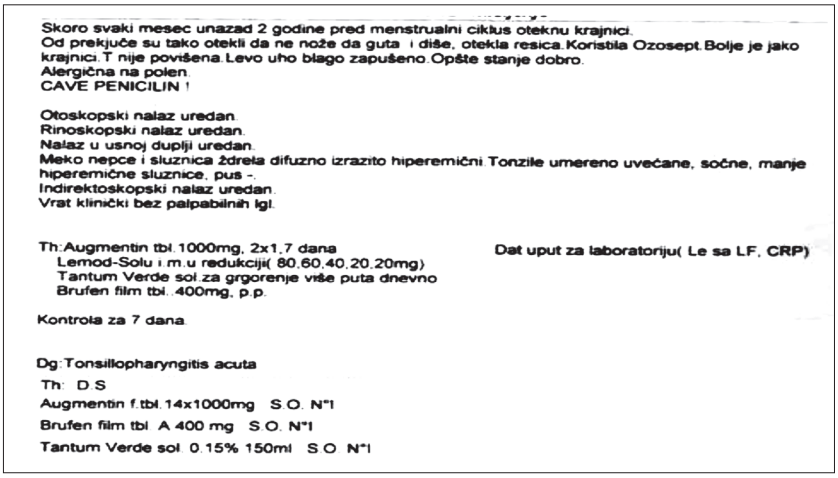

Skoro svaki mesec unazad 2 godine pred menstrualni ciklus oteknu krajnici.
Od prekjuče su tako otekli da ne može da guta i diše, otekla resica.Koristila Ozosept.Bolje je jako krajnici.T nije povišena.Levo uho blago zapušeno.Opšte stanje dobro.
Alergična na polen.
CAVE PENICILIN !

Otoskopski nalaz uredan.
Rinoskopski nalaz uredan.
Nalaz u usnoj duplji uredan.
Meko nepce i sluznica ždrela difuzno izrazito hiperemični.Tonzile umereno uvećane, sočne, manje hiperemične sluznice, pus -.
Indirektoskopski nalaz uredan.
Vrat klinički bez palpabilnih igl.

Th:Augmentin tbl.1000mg, 2x1,7 dana
Lemod-Solu i.m.u redukciji(80,60,40,20,20mg)
Tantum Verde sol.za grgorenje više puta dnevno
Brufen film tbl..400mg, p.p.

Dat uput za laboratoriju(Le sa LF, CRP)

Kontrola za 7 dana.

Dg:Tonsillopharyngitis acuta
Th: D.S
Augmentin f.tbl.14x1000mg S.O. N°1
Brufen film tbl A 400 mg S.O. N°1
Tantum Verde sol 0.15% 150ml S.O N°1

Figure 1. The medical examination report with medical warning CAVE PENICILLIN!

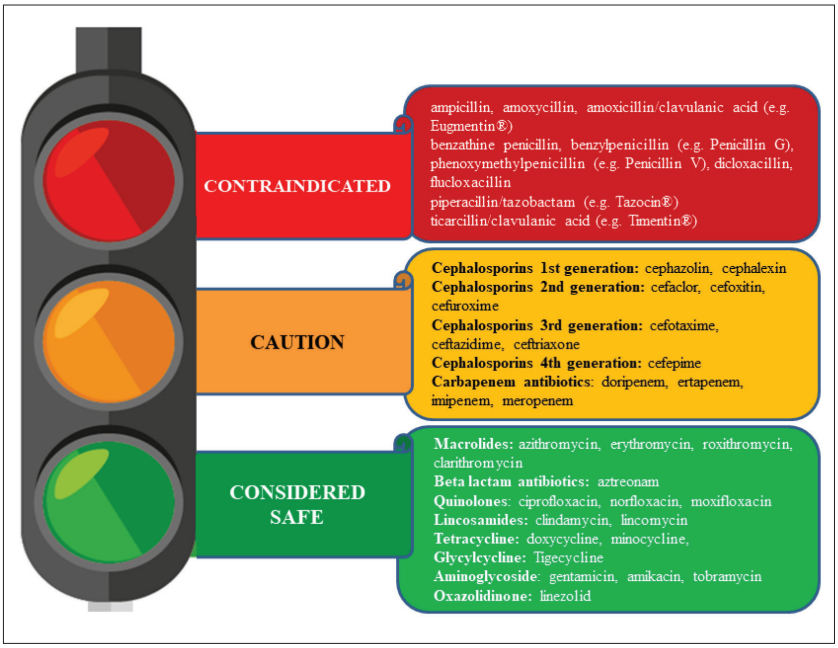

Figure 2. Penicillin allergy [7]

remedy. In this way, occurrence of potentially serious and even fatal allergic reactions to penicillin was avoided.

Consent was obtained from the patient for publication of this report and any accompanying images.

DISCUSSION

AB treatment of the acute bacterial tonsillopharyngitis is recommended, as in the presented case, in patients with severe general condition and three or four Centor criteria (fever, tender cervical lymph nodes, coatings of the tonsils, and lack of cough) [3]. The drug of choice is penicillin. The phrase *cave penicillini* is commonly seen in medical notes and records. Up to 10% of the general population report a history of penicillin allergy, more frequently in females than in males [4 ,5]. Additionally, once an allergy is recorded in the medical chart, it will most likely remain there for the rest of the patient's life.

In hospital and outpatient medical examination of the patient, a subjective patient statement (anamnesis) is the main guideline in detecting a known allergy to penicillin [6]. A positive statement should, as with our patient, be supported by a medical warning written in the health booklet, medical records, and the physician's report stating *cave penicillini*. According to the Australasian Society of Clinical Immunology and Allergy (ASCIA), record details of allergy incident including drug name, description of the reaction, severity, date, and the name of the person making the report [7]. ASCIA recommendation protocols describe different adverse reactions to the administration of penicillins, and categorizes ABs into red (contraindicated), orange (avoid in serious penicillin allergies), and green (safe) categories – a very useful reference tool. In patients with a history of clinical signs of life-threatening penicillin allergy (anaphylaxis, angioedema, laryngeal edema, wheezing/bronchospasm, diffuse erythema, urticaria), penicillins, cephalosporins, and other beta-lactam ABs should be avoided (Figure 2). In a non-severe penicillin allergy (fever, vomiting, erythema, seizures, etc.) cephalosporins and carbapenems can be used with caution. Some reactions (e.g. diarrhea, nausea) are not considered allergies and do not warrant prohibiting penicillin use [7].

Independently of the medical history, the current standards of good pharmaceutical practice also provide for taking a short "pharmaceutical anamnesis" from the patient [8]. By doing that, the pharmacist gets familiar with the patient's health and remembers those patients who are often ill and with verified allergies to drugs (in this case to penicillin). Pharmaceutical healthcare involves the co-operation of pharmacists with the patient and other healthcare professionals when issuing drugs, with the aim of achieving appropriate results and improving patients' quality of life [9, 10]. As with most other drugs, serious practical medical problems can arise in the practical application of AB, which in certain cases may raise a question about potential criminal responsibility of doctors due to mistakes and low conscientiousness at work [11].

Negligent work of a doctor does not necessarily cause a deterioration in a patient's condition. According to Article 251 of the Criminal Code of the Republic of Serbia (CCRS), a necessary condition for the existence of

a criminal offence is that a detrimental effect occurs in the form of deterioration of the health status of a person due to negligent provision of medical aid, including the use of an obviously inappropriate therapeutic agent [12].

Did the doctor commit a criminal offence of a negligent provision of medical aid by prescribing Augmentin® in this case? The pharmacist working in the local pharmacy knew the patient who came to take the prescribed medicine, and was aware of the fact that the patient was allergic to penicillin. Therefore, the pharmacist warned her and did not issue her the prescribed medicine, so that this grave professional mistake of the doctor did not lead to harmful consequences in the form of deterioration of the patient's health.

According to Article 251 of the CCRS, there is no conviction without harmful effect of the physician's negligent treatment, which practically means that if a doctor obviously behaves negligently and makes a serious professional mistake, but that does not lead to deterioration of the patient's health, there is no criminal offence [12]. In the presented case the ENT specialist, who made a serious professional error proscribing penicillin to the allergic patient, avoided legal action and a sentence owing to the appropriate procedure of the pharmacist.

What were the possible scenarios under the Criminal Code in the reported case? If penicillin is administered to a patient said to be allergic without producing subsequent allergic reaction, there will be no grounds for criminal responsibility of the treating doctor. If urticaria occurs, as a slight form of health deterioration, the sentence is up to three years in prison (YP); life threatening edema of the larynx – up to eight YP; and for anaphylactic shock with lethal outcome – up to 12 YP (severe and fatal forms of health deterioration are included in Article 259 of the CCRS, titled Grave Offences against Health). Furthermore, in cases with final court judgment for grave offences against health (Article 259 of the CCRS), the Medical Chamber of Serbia immediately permanently revokes the medical license of the sentenced physician [11].

The presented case is very interesting as an illustration of a serious medical error that has all the features of a potential criminal offence except for the final one – a harmful consequence in the form of deterioration in the patient's health status – which in this case, by pure chance, did not arise thanks to the pharmacist. Nevertheless, the doctor's practice was a serious professional failure. Therefore, when prescribing AB, it is necessary for the physician to be extremely careful not to prescribe a medicine for which there is a *cave* warning in medical documentation.

Conflict of interest: None declared.

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Амоксицилин-клавуланат прописан болеснику са познатом алергијом на пеницилин

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САЖЕТАК

Увод Прописивање пеницилина захтева додатну опрезност како се не би издао рецепт или налог за инјекцију особи алергичној на овај антибиотик. Приказујемо случај болесника алергичног на пеницилин коме је лекар грешком прописао овај лек.

Приказ болесника Осамнаестогодишња болесница обратила се оториноларингологу због гушобоље, отежаног дисања и лаке запушености левог ува током претходна два дана. Толерисала је перорални унос само течне хране. Наводи честе атаке тонзилофарингитиса и алергију на пеницилин. Физикалним прегледом установљен је тонзилофарингитис. Лекар прописује пероралну терапију, између осталог и пеницилински препарат Аугментин® (амоксицилин + клавуланска киселина) 1000 *mg* 2 × 1 таблета током седам дана. Фармацеут у локалној апотеци је познавао девојку и знао је да је алергична на пеницилин, тако да није ни добила прописани пеницилински препарат. На тај начин изузетно озбиљна професионална медицинска грешка према Кривичном законику Србије није добила суштинске карактеристике кривичног дела.

Закључак При прописивању антибиотика неопходна је изузетна пажња лекара да не препише лек за који у медицинској документацији постоји упозорење *cave*, јер та грешка може постати основа за кривично гоњење лекара, као и професионално санкционисање.

Кључне речи: пеницилин; прописивање; алергија; упозорење

DOI: https://doi.org/10.2298/SARH200128040B
UDC: 616.94-083.98

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Sepsis and septic shock – recognize early, act fast, treat right

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SUMMARY
Sepsis is a medical emergency and therefore requires early identification and immediate management, which is not a matter of hours, but minutes. Since the first definition in 1991, sepsis remains a major challenge for clinicians and scientists. Despite significant advances in technology and therapy, mortality and cost of treatment are unacceptably high. Septic shock is the leading cause of mortality in critically ill patients. Cognitive impairment and functional disability were observed after survivors' long-term follow-up.
Since its foundation in 2002, Surviving Sepsis Campaign aims to implement global strategies and to raise awareness of the challenges associated with sepsis. The implementation of guidelines and sepsis care bundles resulted in significant decrease in mortality. Hospital mortality is lower in hospitals with high versus low bundle compliance. Still, epidemiological data for sepsis are missing for low- and middle-income countries.
Keywords: sepsis; septic shock; Surviving Sepsis Campaign; sepsis bundle

INTRODUCTION

Sepsis and septic shock are life-threatening clinical syndromes due to dysregulated host responses to infection that cause organ hypoperfusion and dysfunction. Sepsis is a medical emergency, similar to polytrauma, acute myocardial infarction, and stroke, indicating that only early identification and appropriate immediate management lead to better outcomes. Septic shock is the main cause of mortality in critically ill patients [1, 2]. Mortality due to sepsis in the intensive care unit (ICU) is estimated at 30% [1, 2]. A recent study is the first to produce global estimates of sepsis incidence and mortality across 195 countries, including data from low-income and middle- income countries in the period 1990–2017. Estimated 48.9 million cases of sepsis resulted in 11 million deaths in 2017 [3]. These fascinating estimates are more than double previous global figures, which is probably due to the inclusion of more data from low-income and middle- income countries. Furthermore, cognitive impairment and functional disability were observed after long-term follow-up of survivors [4].

Since its foundation in 2002, Surviving Sepsis Campaign (SSC) aims to implement global strategies and sepsis bundle and to raise awareness of the challenges associated with sepsis. The results of the 12-year-long study of the SSC performance demonstrated a significant decrease in mortality rates of sepsis, and lower mortality in hospitals with higher bundle compliance [5].

DEFINITION AND CLINICAL CRITERIA

The diagnosis of sepsis still remains a major problem. The definition of sepsis has been changed over the time in order to include the most important criteria for early recognition of sepsis. The first definition, Sepsis-1, made in 1991, was based on the presence of systemic inflammatory response syndrome (SIRS) due to infection. Diagnostic performance of this definition was suboptimal since SIRS criteria failed to distinguish between uncomplicated infection and severe life-threatening infection leading to multiple organ dysfunctions. In 2001, Sepsis-2 definition showed high sensitivity, but low specificity [6]. On the Third International Consensus Conference in 2016, the new Sepsis-3 definition defined sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection [7]. Septic shock is a subset of sepsis with underlying circulatory and cellular/metabolic abnormalities that substantially increase mortality [7].

Organ dysfunction in sepsis is identified as an acute change of ≥ 2 points in the total Sequential (Sepsis-related) Organ Failure Assessment (SOFA) criteria (Table 1) [2]. Sepsis-3 definition propose quick SOFA score (qSOFA) as easy bedside tool to screen patients with infection for those at risk of organ dysfunction and death. A "positive" qSOFA Score (≥ 2) suggests high-risk patients who should be thoroughly assessed for evidence of organ dysfunction and to increase frequency of monitoring.

Received • Примљено: January 28, 2020
Revised • Ревизија: May 29, 2020
Accepted • Прихваћено: June 20, 2020
Online first: June 26, 2020

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Table 1. Sepsis-related Organ Failure Assessment score

System		Score				
		0	1	2	3	4
Respiratory	PaO_2/FiO_2, mmHg (kPa)	≥ 400 (53.3)	< 400 (53.3)	< 300 (40)	< 200 (26.7) with respiratory support	< 100 (13.3) with respiratory support
Coagulation	Platelet, 10^3/μl	≥ 150	< 150	< 100	< 50	< 20
Liver	Bilirubin, mg/dl (μmol/l)	< 1.2 (20)	1.2–1.9 (20–32)	2–5.9 (33–101)	6–11.9 (102–204)	> 12 (204)
Cardiovascular	MAP (mmHg)	≥ 70	< 70	Dopamine < 5 or dobutamine (any dose) [a]	Dopamine 5.1–15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1[a]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[a]
Central Nervous System	Glasgow Coma Scale (GCS)	15	13–14	10–12	6–9	< 6
Renal	Creatinine, mg/dL (μmol/l)	< 1.2 (110)	1.2–1.9 (110–170)	2–3.4 (171–299)	3.5–4.9 (300–400)	> 5 (440)
	Urine output, mL per day				< 500	< 200

FiO_2 – fraction of inspire oxygen; PaO_2 – partial pressure of oxygen; MAP – main arterial pressure;
[a]catecholamine doses are given as μg/kg/min. for at least one hour

Comparing qSOFA and SIRS, qSOFA is superior to the SIRS criteria regarding content validity and feasibility, especially outside the ICU because no laboratory tests required (Table 2) [8].

Table 2. Systemic Inflammatory Response Syndrome (SIRS) and quick Sepsis-related Organ Failure Assessment (qSOFA) score

Parameters	SIRS	qSOFA
Body temperature (C°)	< 36 or > 38	
Hearth rate (beats/min)	> 90	
White blood cell count (10^3/μL)	> 12 or < 4 or > 10% immature bands	
Respiratory rate (breaths/min)	> 20	≥ 22
Systolic blood pressure (mmHg)	-	≤ 100
Glasgow Coma Scale	-	< 13 or abnormal mental status

Two or more parameters for positive SIRS and qSOFA score

Zhang et al. [8] tested the predictive validity of SIRS criteria in patients in the Sepsis-3 cohort and concluded that the increase in the SOFA score of 2 or more has greater prognostic significance for in-hospital mortality than SIRS or qSOFA score [7, 8].

INITIAL RESUSCITATION

Numerous studies and protocols showed that the successful management in septic shock is not the matter of hours, but minutes. In addition, SSC implemented a new "sepsis bundle" in 2018 which combined the previous three hour and six hour bundles into the single one "one hour bundle" [9]:

1. Measure lactate level; re-measure if the initial lactate is > 2 mmol/L;
2. Obtain blood cultures prior to antibiotics administration;
3. Administer broad-spectrum antibiotics;
4. Begin rapid administration of 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L;
5. Apply vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mmHg.

Until 2016 SSC guidelines, early goal-directed therapy (EGDT), has been a key strategy for the resuscitation of patients with septic shock. According to EGDT protocol, initial resuscitation in the first six hours with intravenous fluids, vasopressors, inotropes, and blood transfusions are adjusted to reach pre-defined "goals" of central venous pressure, central venous oxygen saturation, mean arterial pressure (MAP) and urine output. Although this protocol was based on a single-center study, published by Rivers et al. [10] in 2001, this algorithm has changed the standards of sepsis treatment in the world.

After almost 15 years, the three large multicenter randomized controlled studies, the Protocolized Care for Early Septic Shock trial, the Australasian Resuscitation in Sepsis Evaluation trial, and the Protocolised Management In Sepsis trial, were conducted in order to test the accuracy of the Rivers protocol [11, 12, 13]. Studies compared the clinical outcomes of patients presenting with early septic shock in the emergency department with strict EGDT to patients with protocol-based standard therapy. All patients received early antibiotic therapy and appropriate hemodynamic management. Studies showed that EGDT is safe, and no harm was associated with interventional strategies. Yet, this protocol could not be recommended from its evidence base, since the cohort in the study by Rivers et al. [10] was unrepresentative (older and more severely ill patients, with higher initial serum lactate level on admission and higher mortality: 42% *vs.*10–20%) compared to control group patients from the three recent studies.

According to current guidelines, initial resuscitation during the hyperdynamic phase of septic shock begins with rapid administration of 30 ml/kg crystalloid solution in order to increase oxygen delivery during circulatory failure. Reevaluation of the response to treatment should start with clinical

examination and physiological variables, such as heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, among others. Guidelines suggest that dynamic variables (passive leg raising, stroke volume measurements, pulse pressure variation) should be used rather than static, in order to predict fluid responsiveness [2, 9]. Growing literature suggested that bedside lung ultrasound can be useful in fluid resuscitation [14, 15].

The SSC recommends targeting MAP of at least 65 mmHg to maintain critical organs perfusion in patients with septic shock requiring vasopressors. However, studies showed that in certain subgroups of patients (older than 75 years and patients with chronic kidney disease) higher MAP (75–80 mmHg) is associated with lower hospital mortality rate and reduced need for renal replacement therapy [16, 17]. On the other hand, aiming to achieve a higher MAP may be harmful due to the significantly higher risk of arrhythmias and excessive vasopressor use [16].

Randomized controlled trials (RCTs) demonstrated that lactate-guided resuscitation therapy showed significant reduction in mortality in ICU patients [18, 19]. However, serum lactate level is not a direct measure of tissue perfusion and may be increased not only in anaerobic glycolysis due to hypoperfusion, but also in other conditions that accompany critically ill patients. For example, accelerated aerobic glycolysis where pyruvate production overcomes the capacity of pyruvate dehydrogenases occurs as a response to cytokine release, excess beta-adrenergic stimulation, or the accumulation of leukocytes at the site of inflammation.

After the resuscitation phase, during the optimization phase, the goal is to maintain adequate tissue perfusion. In addition, cautious titration of fluids with reassessment of hemodynamic status aimed to avoid fluid overload is mandatory. A recent multicenter study showed that 40% of septic shock patients experienced fluid overload defined as a body weight 10% higher than the baseline [20].

ANTIMICROBIAL THERAPY

One of the main determinants for sepsis and septic shock outcome is early systemic administration of appropriate antibiotic therapy. International guidelines recommended empiric antimicrobial therapy in the first hour of recognizing sepsis [2]. Cultures must be obtained before antibiotic administration with at least two sets of samples (aerobic and anaerobic).

In 2006, a retrospective study by Kumar et al. [21] showed correlation between increased survival in adults with septic shock and effective antimicrobial administration within the first hour of documented hypotension. According to this study, only 50% of septic shock patients received appropriate antimicrobial therapy within six hours of documented hypotension. Additionally, each hour delay in the administration of antibiotic is associated with an increase in mortality. Systematic review with meta-analysis of 70 prospective cohort studies assessing the effects of appropriate empirical antibiotic treatment on mortality showed overall, 46.5% of patients were given inappropriate empirical antibiotic treatment [22]. Mortality was significantly higher with inappropriate empirical treatment.

The initial empirical regimen should be broad enough to cover all assumed pathogens [2]. Selection of antibiotics is very complex depending on the patient's medical history, clinical status, and local epidemiological map. Key patient factors include the nature of the site infection, concomitant underlying diseases, chronic organ failures, indwelling devices, the presence of immunosuppression, recent known infection, or colonization with a specific pathogen and recent administration of antimicrobials. Patients with neutropenia represent a subgroup of patients at risk for infections with atypical or resistant gram-negative bacilli and Candida species. In addition, patients with nosocomial infections and prolonged use of antibiotic can develop sepsis with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci*. Clinicians should also consider risk factors for multi drug resistant pathogen (*Pseudomonas*, *Acinetobacter*, *Klebsiella*) when deciding about the empirical antibiotic treatment.

Broad-spectrum carbapenem or extended-range penicillin/β- lactamase inhibitor combination (meropenem, imipenem/ cilastatin or doripenem) or extended-range penicillin/β- lactamase inhibitor combination (piperacillin/tazobactam or ticarcillin/clavulanate) or third- or fourth-generation cephalosporin is commonly used [2]. Vancomycin, teicoplanin, or another anti-MRSA agent can be added when risk factors for MRSA is present [23]. The anti-fungal agent should be considered in immunocompromised status (neutropenia, chemotherapy, transplant, diabetes mellitus), prolonged invasive vascular devices, total parenteral nutrition, necrotizing pancreatitis, and prolonged administration of broad-spectrum antibiotics.

Current guidelines suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) for the initial management of septic shock [2, 23]. However, it is not recommended to be routinely used for most other serious infections, including bacteremia and sepsis without shock [2].

Dose-optimization should be based on antibiotic pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties in critically ill patients with sepsis and septic shock. Variety of conditions in critically ill (unstable hemodynamic, increased cardiac output, increased extracellular volume, variable kidney, and hepatic perfusion, reduced serum albumin), alter antimicrobial PK, affecting volume of distribution, drug clearance, drug binding. In addition, assessment of optimal antimicrobial dosing is individual and very demanding. Antimicrobial stewardship programs are recommended in order to help clinicians with antibiotic management and reduction of antimicrobial resistance.

Time-dependent antibiotics require drug concentrations greater than the minimum inhibitory concentration for a certain period between doses, which usually ranges 40–50% (for piperacillin/tazobactam 100%) of the inter-dose interval for their best action [24]. Experiments showed that the PK/PD target could be achieved only with extended or continuous infusion. Several clinical trials published

in recent years have assessed the benefit on continuous infusions overextended infusions for beta-lactam antibiotics. Although the data are not entirely consistent, recent meta-analysis of RCTs demonstrated protective effect of continuous therapy [25].

For vancomycin, it is suggested loading dose of 25–30 mg/kg (actual body weight) to rapidly achieve target plasma concentration [23]. Pre-dose monitoring of trough concentration of vancomycin is recommended. For aminoglycosides, concentration-dependent antibiotics, peak drug plasma concentrations should be attained with once daily dosing (i.e. 5–7 mg/kg daily gentamicin). Comparable studies showed decrease renal toxicity with this regimen compared to multiple daily dosing [26].

Empiric antimicrobial therapy should be narrowed when the pathogen is detected, and sensitivities are determined. Criteria for early de-escalation of antimicrobial therapy can be based on clinical progress, infection resolution as indicated by biomarkers, especially procalcitonin, and a relatively fixed duration of combination therapy. Although high-quality data on clinically driven de-escalation are limited, unnecessarily prolonged antimicrobial therapy is certainly associated with adverse effects (i.e. Clostridium difficile colitis). Studies have shown that daily assessment for de-escalation of antimicrobial therapy may be associated with improved mortality rates [27].

Current guidelines recommended 7–10 days antimicrobial treatment for most serious infections; however, longer treatment is necessary for patient with slow clinical response, undrainable focus of infection, bacteremia with *S. aureus*, some fungal and viral infection, or immunologic deficiencies [2]. Serum procalcitonin levels (together with clinical response) should be used for de-escalation of antibiotic therapy [28].

SOURCE CONTROL

Rapid source control should be performed as soon as possible following initial resuscitation [29]. Intra-abdominal infection along with necrotizing soft tissue infection and implanted device infection, are the sites where a rapid source control seems more feasible (drainage of infected collection, debridement of infected solid tissue, removal of devices, catheters or foreign bodies). Surgery gives an opportunity to take the first local microbiological samples.

VASOACTIVE MEDICATIONS

Norepinephrine is recommended as the first line vasopressor in septic shock [2]. The dosage may range 5–20 μg/min, and it is not based on the weight of the patient [30]. Data from the recent literature are in favor of early initiation of vasopressors during septic shock in order to prevent deep and durable hypotension. Moreover, early administration of norepinephrine in septic shock was significantly associated with lower rate of cardiogenic pulmonary edema and new-onset arrhythmia [30].

Recent systematic review and meta-analysis do not support routine use of dopamine since norepinephrine is more potent, reduces risk of tachycardia and arrhythmia, and therefore results in lower mortality compared to dopamine [31]. SSC guidelines suggest adding low dose vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine in order to achieve target MAP and to decrease norepinephrine dosage [2].

Septic shock is a distributive shock, but it is important to think of combined cardiac dysfunction even in the early stages of disease. Inotropic agents should be considered if inadequate cardiac output is present.

CORTICOSTEROIDS AND METABOLIC RESUSCITATION PROTOCOL

The use of corticosteroids was controversial over the years. The large multicenter Adjunctive corticosteroid treatment in critically ill Patients With Septic Shock study showed shorter durations of shock and ICU stay in the glucocorticoid group compared with the placebo group [32]. Meta-analysis of 42 RCTs showed that corticosteroids result in small reduction in mortality in critically ill patients but increase the risk of neuromuscular weakness [33].

The retrospective study by Marik et al. [34] demonstrated that the administration of intravenous vitamin C, hydrocortisone, and thiamine is successful in preventing progressive organ dysfunction, especially acute kidney injury and even decreased mortality in patients with septic shock [34, 35]. However, further trials are needed to determine whether this metabolic resuscitation protocol can be recommended as a treatment for septic shock.

ACUTE RESPIRATORY DISTRESS SYNDROME / MECHANICAL VENTILATION

Acute respiratory distress syndrome (ARDS) is one of the most frequent organ disfunction due to sepsis [36]. The mortality in this patient group is assessed to be as high as 40% [37]. ARDS is defined as a loss of aerated lung tissue as a result of edema and atelectasis, with reduced respiratory system compliance and impaired gas exchange. Mechanical ventilation and concept of protective lung strategy with reduction of tidal volume (VT) is imperative in the management of ARDS [38, 39]. Low VTs (4–6 ml/kg of predicted body weight) aim to maintain end-inspiratory plateau pressure, PPLAT ≤ 30 cmH2O in order to prevent alveolar overdistension. Several meta-analyses supported Lachmann's "open lung concept" with higher levels of positive end-expiratory pressure to avoid collapse and reopening of alveolar units, combined with protective VTs [39]. Furthermore, the use of inspiratory pressure to open up atelectatic lung regions and end-expiratory pressure (so-called recruitment maneuvers), showed beneficial effect on the outcome, without increasing the risk of barotrauma [38, 39].

According to actual guidelines, prone position and extracorporeal membrane oxygenation are reserved only for

selected cases of severe ARDS (P/F ratio < 20 kPa) [36, 38]. By contrast, high frequency oscillation and inhaled nitric oxide are not recommended. Future investigations are suggested for corticosteroids and extracorporeal CO_2 removal [39]. Reported pilot study from Strategy of Ultra-Protective lung ventilation with Extracorporeal CO_2 Removal for New-Onset moderate to severe ARDS showed promising results with the strategy of ultra-protective lung ventilation (VT of 4 ml/kg predicted body weight and PPLAT≤ 25 cmH2O) and extracorporeal CO2 removal to prevent severe respiratory acidosis [40]. According to LUNG safe study, non-invasive ventilation is associated with higher mortality in ARDS with P/F ration lower than 150 mmHg [41]. A fluid-conservative strategy to minimize fluid infusion and weight gain in patients with ARDS is associated with better outcome [36].

NUTRITION

Based on expert consensus, early enteral nutrition within 24–48 hours is standard for critically ill patients [2]. Early enteral nutrition should be initiated as soon as possible, right after initial resuscitation, taking care of gastrointestinal intolerance. According to the latest European Society for Clinical Nutrition and Metabolism guidelines, trophic feeding (defined as 10–20 kcal/h or up to 500 kcal/d) is recommended for the initial phase of sepsis advancing as tolerated after 24–48 hours to > 80% of target energy goal over the first week [42]. The delivery of 1.2–2 g protein/kg/d is suggested. Parenteral nutrition is more invasive, associated with greater risks and rates of complications. Due to the bacterial translocation mechanism, parenteral nutrition is associated with more infection than enteral nutrition [42]. Parenteral nutrition is reserved only for patients where enteral route is not possible or as addition to enteral nutrition to achieve full caloric support.

OTHER SUPPORTIVE THERAPIES

The current guidelines for transfusion and blood products management, stress ulcer prophylaxis, venous thromboembolism prophylaxis, renal replacement therapy, and immunoglobulins did not change significantly between the two revisions of SSC bundle [2, 43]

CONCLUSION

Sepsis is a clinical syndrome associated with high incidence, high mortality, and high cost of treatment. In order to reduce mortality and improve patients' outcomes, early recognition of sepsis and appropriate immediate management during the initial hour is of outmost importance for clinicians. The main goal of SSC is dissemination of evidence-based guidelines worldwide. However, new large multicenter trials are needed to develop further protocols. Development of new therapeutic agents and novel extracorporeal devices for multiple organ support are likely to be essential to further improve the outcome of patients with sepsis.

Conflict of interest: None declared.

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Сепса и септични шок – рано препознај, брзо делуј, лечи исправно

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САЖЕТАК

Сепса је ургентно стање па стога захтева рано препознавање и што хитније спровођење терапијских поступака већ у првим минутима. Од прве дефиниције из 1991. године до данас сепса је остала главни изазов за клиничаре и научнике. Упркос напретку у технологији и терапији, смртност и трошкови лечења су неприхватљиво високи. Септични шок је главни узрок смрти критично оболелих болесника. После дугорочног праћења исхода преживелих запажени су когнитивно оштећење и функционална онеспособљеност. Од свог оснивања 2002. године, Кампања за преживљавање сепсе има за циљ примену стратегија и подизање свести о изазовима повезаним са сепсом широм света. Имплементација препорука и мера за хитно збрињавање болесника довела је до значајног смањења морталитета. Ипак, проблем представљају земље средњег и ниског економског развоја где не постоје ни тачни епидемиолошки подаци о сепси.

Кључне речи: сепса; септични шок; ургентно стање; препоруке

DOI: https://doi.org/10.2298/SARH180917019S
UDC: 615.212-053.2; 616-083-053.2

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Analgesia in the palliative care of children

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SUMMARY
Due to the increasing incidence of terminal illnesses in children, there is great urgency within pediatric medicine to give these patients the best palliative care possible. The main focus of palliative care is to alleviate suffering resulting from the psychophysical condition of the child, which is mostly due to physical pain. The first phase of managing pain in palliative care is quantifying and qualifying pain levels, although this is sometimes difficult to do with pediatric patients. In addition to implementing strategies that alleviate or remove pain for patients, it is also crucial to give patients and their families a feeling of full control over pain.
In practice, non-pharmacological and pharmacological methods of analgesia are present. Pharmacological methods include non-opioid and opioid analgesics, followed by co-analgesics as well as methods of regional anesthesia.
In order to give these patients the best care possible, it is necessary that the approach be individual, multimodal, multidisciplinary, and considerate of every detail.
Keywords: pain; palliative care; pediatric patients; analgesia

INTRODUCTION

Terminal illnesses that affect children are a major issue within the medical community. Pediatricians are most often faced with malignant diseases where the survival rate is increasing, and where more than 80% of children diagnosed with malignant tumors can survive for more than five years due to advances in diagnostics, therapy, and supportive care [1]. By improving palliative care methods, pediatricians are able to increase the lifespans of these terminally ill children. Palliative care is defined by the World Health Organization as an "approach to improve the quality of life of patients and families who face life-threatening illness, by providing pain and symptom relief, spiritual and psychosocial support from diagnosis to the end of life and bereavement" [2]. Because pain is the main cause of anxiety, emotional, and behavioral problems with pediatric patients, the main focus of palliative care is to prevent and stop pain, so that patients and their families can have a better quality of life [3, 4, 5].

The World Health Organization defines pain as an unpleasant sensory or emotional experience associated with actual or potential tissue damage [6]. According to this definition, it is clear that pain does not have to be linked to existing tissue damage and that emotional and cognitive components are an important component of the identification of pain. As a result, although this may be more difficult with younger children, patients should be encouraged to complain about pain in order minimize potential tissue damage [7, 8].

In order to create an effective treatment plan to stop and prevent the development of pain, pediatricians must account for the child's age, the psychophysical condition of the child, as well as the characteristic of the pain. The first step in treating pain is recognizing it, then qualifying and quantifying it. The second step is finding the best pharmacological and/or non-pharmacological method to treat the pain, and as such, pain therapy requires a multidisciplinary and multimodal approach [9–12].

TYPES OF PAIN IN CHILDREN

Using pain duration as a basis, pain can be divided into two types: acute and chronic. Acute pain begins suddenly, is associated with a painful stimulus, and is short-lived. Chronic pain can be the result of inadequately treated acute pain or may be chronic from the outset. Chronic pain significantly impairs the quality of life.

Based on the pathophysiological mechanism of pain, pain is divided into nociceptive and neuropathic [13]. Nociceptive pain includes somatic and visceral pain. Somatic nociceptive pain is localized, constant, described as dull or sharp, worsens with movement, and is caused by tissue injury or inflammation. Visceral pain is caused by injury or inflammation of internal organs and can be constant if the pain

Received • Примљено: September 17, 2018
Revised • Ревизија: March 18, 2020
Accepted • Прихваћено: March 19, 2020
Online first: April 23, 2020

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originates from a solid organ, or intermittent in the form of cramps, or colic as a result of obstructions in hollow organs. Neuropathic pain is caused by injury, inflammation, or dysfunction of the central or peripheral nervous system [14]. Patients may have mixed pain consisting of somatic, visceral, and neuropathic pain all at the same time or each separately at different times.

Breakthrough pain is a transient strengthening of a constant or controlled pain. There are three types of breakthrough pain: incidental, spontaneous, and pain at the end of a dosing interval [15, 16].

Cancer pain can also be acute and chronic. Acute pain is developed as a consequence of a tumor mass invading surrounding anatomical structures, which leads to their damage, compression, rupture, inflammation, or as a result of diagnostic and therapeutic procedures. Chronic pain is the consequence of the development of the tumor mass itself, metastases in other parts of the body, as well as a result of diagnostic and therapeutic procedures [17, 18].

Until recently, it was thought that neonates did not feel pain or felt less pain compared to older children and adults, but new research within the last decade has concluded that they do feel pain. In fact, fetuses can begin to feel pain from the 26th week of development [19].

ASSESSMENT OF THE PAIN

There are three basic methods for assessing pain: self-reporting, physiological indicators, and by observing the child's behavior. Often, there is disagreement between objective estimates of the severity of the patient's difficulty and assessment, so the standard in assessing the existence of pain is to ask the child whether he/she feels pain (self-reporting) [20, 21]. In younger children, this can be difficult due to problems in understanding. Preschoolers may verbalize the intensity of pain. School-age children may verbalize pain and use an objective measurement of pain. Adolescents should be able to locate and verbalize pain levels.

The second method of assessing pain is to measure physiological reactions to pain, which can be tracked through indicators such as pulse, blood pressure, breathing, redness, paleness, and increased sweating [22, 23].

The third method is observing the behavior of the patient, although this is not a specific pain indicator [24]. The behavior of the child must be interpreted in accordance with its age. Infants who feel pain will cry, scream, refuse food, sleep poorly, make grimaces, or exhibit hypersensitivity or irritability. Facial expression measures appear most useful and specific in neonates. Toddlers may be verbally aggressive, cry, exhibit regressive behavior or withdraw, guard painful areas of body, or be unable to sleep. Preschoolers may attempt to push a stimulus away before it is applied, be uncooperative, see the pain as a punishment, cling to a parent or nurse, or may request emotional support. School-age children experience nightmares related to pain, have muscular rigidity, exhibit body stiffness, closed eyes, wrinkled forehead, as well as engage in the same behaviors listed for preschoolers and toddlers. Adolescents may deny pain in the presence of peers, have changes in sleep patterns and appetite, or display regressive behaviors in the presence of their family.

PAIN SCALES

The most used scales for newborns are the Premature Infant Pain Profile and the CRIES Postoperative Pain Scales [25, 26]. Between the ages of two months and seven years the FLACC (Face, Legs, Activity, Cry, Consolability) scale is used for postoperative pain assessment [27]. Well established self-report pain scales for preschoolers include the Poker Chip Scale, Wong-Baker Faces Scale, and Faces Pain Scale – Revised (FPS-R) [28]. School-age children and adolescents can usually use verbal scales or visual analog pain scales [29]. As for the assessment of pain for children with cognitive impairment, the Non-communicating Child's Pain Checklist – Postoperative Version is recommended [30, 31]. The greater the degree of cognitive impairment, the greater is the likelihood that the child feels less pain.

METHODS OF ANALGESIA

Methods of analgesia include non-pharmacological and pharmacological methods that include the use of non-opioid and opioid analgesics with the use of co-analgesics or adjuvants, as well as methods of regional anesthesia. Developmental differences in response to pain and analgesic efficacy should be taken into account when planning analgesia [32].

NON-PHARMACOLOGICAL METHODS

There is evidence that supports the use of psychological intervention for a variety of pain indications that include physiological, behavioral, and cognitive techniques aimed at reducing pain and pain-related distress through the modulation of thoughts, behaviors, and sensory information [32]. Non-pharmacological methods include various ways of distracting the child's attention through cognitive methods, emotional support, presence of the parents during painful procedures, massage therapy, acupuncture, as well as physical techniques that promote muscle relaxation, transcutaneous electrical nerve stimulation, or hypnosis [33, 34]. The methods listed here are incredibly helpful and are seldom harmful.

PHARMACOLOGICAL METHODS

In order to choose the appropriate medications and their doses, it is necessary to confirm that the child's organs are anatomically developed, although their organ function will not be fully developed until later on, as it takes three months for organs to reach maturity [35]. The most

Table 1. Non-opioid analgesics for the relief of pain in neonates, infants, and children according to WHO recommendations [32]

	Dose (oral route)			
Medicine	Neonates 0–29 days	Infants from 30 days to 3 months	Infants 3–12 months or children 1–12 years	Maximum daily dose
Paracetamol	5–10 mg/kg every 6–8 hours[a]	10 mg/kg every 4–6 hours[a]	10–15 mg/kg every 4–6 hours[a,b]	Neonates, infants, and children max. 4 doses/daily
Ibuprofen	/	/	5–10 mg/kg every 6–8 hours	Child: 40 mg/kg

[a]Children who are malnourished or in a poor nutritional state are more likely to be susceptible to toxicity at standard dose regimens due to reduced natural detoxifying glutathione enzyme;
[b]maximum of 1 g at a time

important factors to consider for the metabolism of drugs are immature liver enzymes and decreased renal function (reduced glomerular filtration) [36]. Glomerular filtration rate has a range of only ½ of adult values at birth, and tubular secretion rates are only 20% of adult capacities. There are also some significant differences in the structure and function of the child's body at birth when they have a higher percentage of body water and less fat compared with older children. Age-related differences in protein binding with drugs also exist. The effects of drugs may vary with age, and dosages must be changed to anticipate and avoid side effects [37].

Before administering analgesics, guidelines must be consulted and pediatricians must strive to achieve maximum efficacy with the chosen method of analgesia. According to the two-step scale of pain from the World Health Organization, the first stage of pain is mild, and it requires the administration of non-opioid analgesics like paracetamol or ibuprofen, with or without co-analgesics. The second stage of pain is moderate to severe, and opioid analgesics should be used with or without co-analgesics [38]. Drugs should be given according to a schedule, not on demand, because in practice this means that the child will not receive the medicine. The administration of the drug should try to be non-invasive, preferably given orally. Therapy must be individually adapted to each patient [38]. It is extremely important to monitor the child and its reaction to the medication at all times, and if necessary, make changes to the therapy.

Non-opioid analgesics are used in the first stage of pain, according to the World Health Organization. Non-steroid anti-inflammatory drugs like ibuprofen and paracetamol are used. These medications work by blocking cyclooxygenase, where ibuprofen drugs work peripherally, while paracetamol leads to the central blockage of enzymes [39].

Opioid analgesics are used in the second, more severe, stage of pain. They can be administered orally, subcutaneously, intravenously, with a continuous infusion, or a PCA (patient-controlled analgesia) pump [40]. The advantage of the PCA is that it eliminates high peaks and low troughs by allowing the patient to press the demand button when they begin to feel pain [41]. Opioid analgesics bind to opioid receptors in the central nervous system, but their use requires monitoring because depression of the respiratory center can occur. Cardiorespiratory monitoring and observation is recommended when opioids are administered to infants less than 2–3 months of age.

NON-OPIOID ANALGESICS

Paracetamol and ibuprofen are used to alleviate mild pain. For children up to three months of age, the only recommended drug for mild pain is paracetamol, while ibuprofen can be used with older infants. Routes for administration are oral (tablets, syrups), rectal (suppositories), or intravenous. Paracetamol is a well-tolerated drug and produces few side effects in the gastrointestinal tract, but there is a risk of hepatotoxicity and acute overdose [42, 43]. In addition, having an analgesic effect, ibuprofen also has an anti-inflammatory and antithrombotic effect. Like the entire NSAID group of drugs, there are significant adverse effects for the mucosa of the gastrointestinal tract when ibuprofen is used [44]. There is a plateau for the analgesic effect of these drugs, but not for their side effects.

OPIOID ANALGESICS

In cases of moderate to severe pain, there is a variety of opioid analgesics that can be used. Of opioid analgesics, morphine is always the medication of choice, while others are considered and used when the side effects of morphine begin to appear [45]. Morphine is dosed gradually until pain is alleviated and there is no maximal dose because the pain acts as an antidote for respiratory depression, unlike non-opioid analgesics (Tables 1–4). Dosages should be adjusted to the patient following his/her pain level indication. The range of effective doses is very wide among children and can differ significantly for one child at different times. Opioid rotation is defined as the practice of changing between different opioids in a set schedule to prevent potential adverse effects and limit dose escalation [46]. The oral route of administration is recommended for the use of opioid analgesics, while the intramuscular route of administration is very unpleasant for children and should be avoided.

When administering opiates, the risks of tolerance, addiction, and withdrawal syndrome must be taken into consideration [47]. Tolerance to opioids occurs when the body becomes accustomed to a certain dose and an increased dose is required to obtain the same effect. Addiction is the creation of psychological and physical dependence on a drug, creating an irresistible need to take the medication again, regardless of possible consequences. Withdrawal syndrome is characterized by symptoms like agitation, insomnia, tremors, gastrointestinal symptoms like nausea,

Table 2. Starting dosages for opioid analgesics for opioid-naive neonates according to WHO recommendations [32]

Medicine	Route of administration	Starting dose
Morphine	IV injection[a]	25–50 mcg/kg every 6 hours
	SC injection	
	IV infusion	Initial IV dose 25–50 mcg/kg, then 5–10 mcg/kg/hour 100 mcg/kg every 6 or 4 hrs
Fentanyl	IV injection[b]	1–2 mcg/kg every 2–4 hours[c]
	IV infusion[b]	Initial IV dose 1–2 mcg/kg, then 0.5–1 mcg/kg/hour

[a]Administer IV morphine slowly over at least 5 minutes;
[b]intravenous doses for neonates are based on acute pain management and sedation dosing information; lower doses are required for non-ventilated neonates;
[c]administer IV fentanyl slowly over 3–5 minutes

Table 3. Starting dosages for opioid analgesics in opioid-naive infants (1 month – 1 year) according to WHO recommendations [32]

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	80–200 mcg/kg every 4 hours
	IV injection[a]	1–6 months: 100 mcg/kg every 6 hours 6–12 months: 100 mcg/kg every 4 hours (max. 2.5 mg/dose)
	SC injection	
	IV infusion[a]	1–6 months: initial IV dose: 50 mcg/kg, then: 10–30 mcg/kg/hour 6–12 months: initial IV dose: 100–200 mcg/kg, then: 20–30 mcg/kg/hour
	SC infusion	1–3 months: 10 mcg/kg/hour 3–12 months: 20 mcg/kg/hour
Fentanyl[b]	IV injection	1–2 mcg/kg every 2–4 hours[c]
	IV infusion	Initial IV dose 1–2 mcg/kg[c], then 0.5–1 mcg/kg/hour
Oxycodone	Oral (immediate release)	50–125 mcg/kg every 4 hours

[a]Administer IV morphine slowly over at least 5 minutes;
[b]intravenous doses of fentanyl for infants are based on acute pain management and sedation dosing information;
[c]administer IV fentanyl slowly over 3–5 minutes

Table 4. Starting dosages for opioid analgesics in opioid-naive children (1–12 years) according to WHO recommendations [32]

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	1–2 years: 200–400 mcg/kg every 4 hours 2–12 years: 200–500 mcg/kg every 4 hours (max. 5 mg)
	Oral (prolonged release)	200–800 mcg/kg every 12 hrs
	IV injection[a]	1–2 years: 100 mcg/kg every 4 hours 2–12 years: 100–200 mcg/kg every 4 hours (max. 2.5 mg
	SC injection	
	IV infusion	Initial IV dose: 100–200mcg/kg[a], then 20–30 mcg/kg/hour
	SC infusion	20 mcg/kg/hour
Fentanyl	IV injection	1–2 mcg/kg[b], repeated every 30–60 minutes
	IV infusion	Initial IV dose 1–2 mcg/kg[b], then 1 mcg/kg/hour
Hydromorphone[c]	Oral (immediate release)	30–80 mcg/kg every 3–4 hrs (max. 2 mg/dose)
	IV injection[d]or SC injection	15 mcg/kg every 3–6 hours
Methadone[e]	Oral (immediate release)	100–200 mcg/kg every 4 hours for the first 2–3 doses, then every 6–12 hours (max 5 mg/dose initially)[f]
	IV injection[g] or SC injection	
Oxycodone	Oral (immediate release)	125–200 mcg/kg every 4 hours (max. 5 mg/dose)
	Oral (prolonged release)	5 mg every 12 hours

[a]Administer IV morphine slowly over at least 5 minutes;
[b]administer IV fentanyl slowly over 3–5 minutes;
[c]hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing; use extreme caution when converting from one route to another; when converting from parenteral hydromorphone to oral hydromorphone, doses may need to be titrated up to 5 times the IV dose;
[d]administer IV hydromorphone slowly over 2–3 minutes;
[e]due to the complex nature and wide interindividual variation in the pharmacokinetics of methadone, it should only be used by practitioners experienced with its use;
[f]methadone should initially be titrated like other strong opioids; the dosage may need to be reduced by 50% 2–3 days after the effective dose has been found to prevent adverse effects due to methadone accumulation; from then on, dosage increases should be performed at intervals of one week or more and with a maximum increase of 50%;
[g]administer IV methadone slowly over 3–5 minutes

vomiting, poor appetite, tachycardia, tachypnea, hypertension, and fever. Children who have been on opiates for a long time and at high dosages require gradual reduction of opiate use in order to prevent the development of addiction. If opioid therapy lasted for 7–14 days, the dose can be decreased by 10–20% of the original dose every 8 hours. In the case of a long-term therapy protocol, the dose should not be reduced more than 10–20% per week [38]. When opioid overdose occurs, central respiratory depression develops, which can lead to a coma. Naloxone can be administered to a patient to stop the immediate opioid overdose, but opioid addiction and the development of withdrawal syndrome cannot be cured by Naloxone, so further treatment will be needed to treat the addiction [48].

ADJUVANT CO-ANALGESICS

Co-analgesics have a primary purpose other than pain management, but they can be used in addition to analgesics to better control pain relief. Corticosteroids, bisphosphonates, antidepressants, anticonvulsants, and ketamine can be used as co-analgesics, but there are still no recommendations for their use in pediatric patients.

METHODS OF REGIONAL ANESTHESIA

The application of regional anesthesia in childhood depends on the physiological specifications of their age, as well as on the technical capabilities of the anesthesiologist [49]. The effect of the block is short-term, and for long-term effects, catheter techniques are used. The use of catheter techniques improves the control of postoperative pain, reduces the use of analgesics and opioids, postoperative

nausea and vomiting, time spent in the hospital, as well as costs, all of which improves the satisfaction of the patients and their families with the procedure [50].

CONCLUSION

The primary goal of treating terminally ill children of all ages is giving them life without pain. It is necessary to keep in mind that a child often cannot adequately interpret the pain he/she feels, so it is necessary to monitor the child at all times and adjust the therapy accordingly. Pain therapy in palliative care should always be multimodal and multidisciplinary because this will improve efficacy and minimize side effects.

Conflict of interest: None declared

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Аналгезија у палијативном збрињавању деце

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САЖЕТАК

Услед све већег пораста броја деце оболеле од неизлечивих болести, велики значај у педијатријској медицини је палијативно збрињавање ове деце. Главни задатак палијативног збрињавања је ублажавање патње која произилази из психофизичког стања детета, а највећим делом из бола. Понекад је изузетно тешко препознати, квантификовати и квалификовати бол код педијатријских болесника, а то је управо прва фаза у проналажењу најбољег начина за ублажавање патње. Кључно је пронаћи најбољи начин за ублажавање или уклањање бола, али начин који ће како детету тако и родитељу пружити осећај потпуне контроле над болом.

У пракси су заступљене нефармаколошке и фармаколошке методе аналгезије. Фармаколошке методе укључују неопиоидне и опиоидне аналгетике, потом коаналгетике, као и методе регионалне анестезије.

Да бисмо на најбољи начин збринули ову децу, неопходно је да приступ буде индивидуалан, мултимодалан, мултидисциплинаран, и мора се посветити пажња сваком детаљу.

Кључне речи: бол; палијативно збрињавање; педијатријски болесници; аналгезија

DOI: https://doi.org/10.2298/SARH190813036V
UDC: 340.6:616.8

ARTICLE FOR PRACTITIONERS / РАД ЗА ПРАКСУ

Форензичка неурологија – улога неуролога у судскомедицинском вештачењу

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САЖЕТАК

Форензичка неурологија има задатак да на основу познавања функционалне неуроанатомије и механизама неуролошких болести процени и објасни последице различитих обољења и траума нервног система у свим ситуацијама које могу бити од значаја за правни систем. У овом раду смо, на основу сопственог искуства, покушали да истакнемо оне области форензичке медицине у којима су налази и експертско мишљење неуролога не само важни већ и кључни за доношење што је могуће праведнијих судских одлука. Намера нам је да подржимо напоре ка успостављању још ангажованије улоге неуролога у појединим областима, на првом месту у вештачењима одговорности и урачунљивости извршилаца кривичних дела и као њихове процесне способности.

Кључне речи: форензичка неурологија; судска медицина; вештачење

УВОД

Форензичка неурологија (или неурофорензика) јесте клиничка грана судске медицине која, полазећи од познавања функционалне неуроанатомије и механизама неуролошких болести, треба да процени и објасни последице различитих обољења и траума нервног система у свим ситуацијама које могу бити од значаја за правни систем [1]. Суд од неуролога очекује да пружи одговоре на многа питања која имају правне импликације и која се често срећу у свакодневној судској пракси. Како наизглед мала неуротраума може изазвати значајну и трајну онеспособљеност? Када деменција доводи до губитка пословне, тестаментне и друге способности? Да ли је особа оболела од епилепсије била неурачунљива у време извршења кривичног дела?

На овом задатку неурологу је често потребна помоћ у виду адекватне сарадње са другим сродним областима као што су неуропсихологија, неурохирургија, неуропатологија и психијатрија, као и примена различитих дијагностичких метода као што су електроенцефалографија, компјутеризована томографија мозга, магнетна резонанца мозга или функционална неурорадиологија [2].

У овом раду смо покушали да истакнемо оне области форензичке медицине у којима су налази и експертско мишљење неуролога не само важни већ и кључни за доношење што је могуће праведнијих судских пресуда [3].

ОБЛАСТИ НЕУРОФОРЕНЗИКЕ

Током последњих седам година (1. 6. 2012 – 31. 5. 2019) аутор овог рада је, као неуролог, био укључен у 97 вештачења, која су на захтев суда извршена у Институту за судску медицину „Милован Миловановић" или од стране Судскомедицинског одбора Медицинског факултета Универзитета у Београду. Од свих наведених случајева 43 (44%) случаја су се односила на неуротрауму и животну и професионалну онеспособљеност, 31 (32%) случај је био у вези са нарушеним капацитетом (способношћу) за самостално одлучивање, 5 (5%) случајева се тицало неуролошких болести и криминалитета и 18 (19%) случајева је било у вези са питањем несавесног лечења оболелих и/или умрлих од различитих неуролошких болести (Слика 1). У даљем тексту укратко ћемо се позабавити најважнијим аспектима неуролошког вештачења у свакој од наведених области.

ЖИВОТНА И ПРОФЕСИОНАЛНА ОНЕСПОСОБЉЕНОСТ ИЗАЗВАНА НЕУРОТРАУМОМ

У савременом свету повреде нервног система представљају водећи узрок инвалидитета па и смртности код особа млађих од 45 година [4]. Зато и није необично што је у скоро половини случајева за које је тражена неуролошка експертиза то било због неуротрауме. Најчешће се радило о повредама главе и мозга (28 случајева, 65%), затим следе повреде периферних нерава (10

Received • Примљено: August 13, 2019
Revised • Ревизија: May 25, 2020
Accepted • Прихваћено: June 13, 2020
Online first: June 18, 2020

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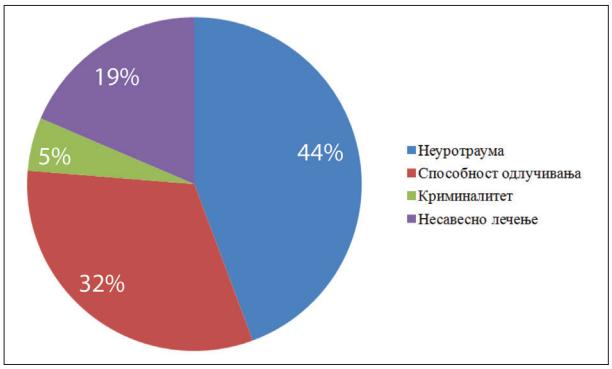
случајева, 23%) и, на крају, трзајне повреде врата (пет случајева, 12%).

Квалитетна и потпуна неуролошка експертиза у свим случајевима неуротрауме подразумева четири важна корака: 1) утврђивање недвосмислне узрочно-последичне везе између предметног догађаја и насталих повреда, 2) дефинисање свих секвела претходних повреда и посебних стања повређеног која могу допринети тежим последицама актуелних повреда, 3) проверу да ли је збрињавање и лечење актуелних повреда спроведено у складу с принципима добре клиничке праксе и да ли су све повреде процењене на основу објективних метода допунског испитивања и 4) објективну процену свих последица неуротрауме које могу бити неуролошке (хемипареза, лезије кранијалних и периферних нерава, посттрауматска епилепсија итд.), когнитивно-бихевиоралне (неуропсихолошке) и не-неуролошке (контрактуре) [5].

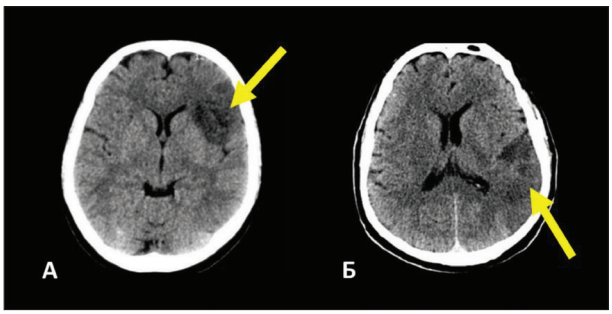
Поједине ситуације представљају посебан изазов за неуролога када је у питању вештачење неуротраума, а релативно често се срећу у пракси. Прва се односи на ретроспективну дијагнозу потреса мозга, посебно у ситуацији када је медицинска документација непотпуна или неквалитетно вођена [6]. Друга се односи на процену посткомоционог синдрома који се доминантно манифестује у виду субјективних тегоба код којих је често присутна аггравација, па чак и симулација [7]. Трећа, потенцијално проблематична ситуација је процена постојања дифузне аксоналне лезије у ситуацији када иницијални снимци мозга компјутеризованом томографијом и магнетном резонанцом не показују постојање морфолошки видљивих лезија [8]. Следећа је утврђивање корелације између механизма повреде после судара аутомобила са задње стране и симптома трзајне повреде врата [9]. На крају, у склопу вештачења саобраћајног трауматизма, неурологу се често поставља питање о тежини повреда и употреби, односно неупотреби сигурносног појаса [10]. Све ове ситуације и дилеме често захтевају додатне анализе и помоћ сродних неуронаука или допунских метода испитивања чији детаљнији приказ превазилази обим и намену овог текста.

СМАЊЕН КАПАЦИТЕТ / НЕСПОСОБНОСТ ОДЛУЧИВАЊА УСЛЕД НЕУРОЛОШКИХ ПОРЕМЕЋАЈА

Капацитет подразумева поседовање когнитивне способности за процесуирање, задржавање и разумевање релевантних информација, као и процену ризика и последица појединих одлука (способност одлучивања). Закон претпоставља да је свака особа очуваних капацитета способна да сама одлучује у специфичним околностима и да сама процени и сагледа ризик и корист од доношења или изостанка неке одлуке. Најважнија чињеница у вези са капацитетом јесте то да је он специфично везан за време, ситуацију и задатак [11].



Слика 1. Области судскомедицинског вештачења у којима је био ангажован неуролог (*n* = 97)
Figure 1. Fields of forensic expertise in which a neurologist was engaged (n = 97)

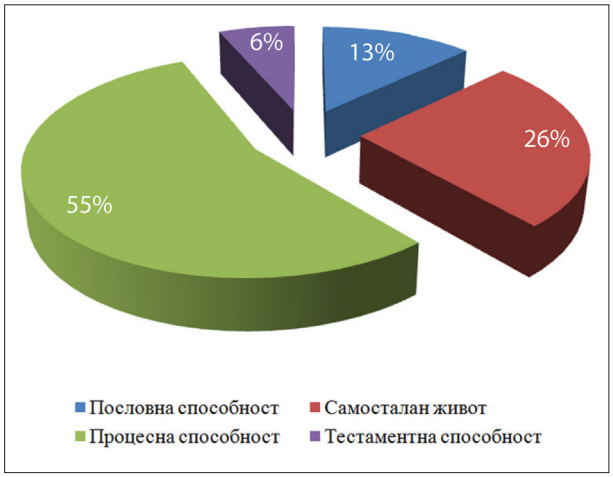


Слика 2. Фокалне исхемијске лезије мозга (стрелице) у Брокиној зони за експресивни говор (А) и Верникеовој зони за рецептивни говор (Б) које доводе до губитка процесне способности услед немогућности адекватне комуникације
Figure 2. The focal ischemic brain lesions (arrows) in the Broca's area for expressive speech (A) and the Wernicke's area for receptive speech (B) that cause loss of capacity to stand trial due to the inability of adequate communication

Питање капацитета, тј. способности одлучивања појединца, поставља се најчешће у ситуацијама у којима особа треба да донесе одлуку која њу саму, њено здравље или њену имовину може довести у опасност [12]. Постоје два аспекта способности: клиничка и правна. Као правни концепт, капацитет подразумева минималну способност за спровођење законски регулисаних процедура и може бити грађанско-правна (тестаментна способност, финансијска споособност, способност за самосталан живот) или кривично-правна (процесна способност или способност појединца да му се суди) [11].

Смањен капацитет одлучивања последица је присуства неуролошког и/или психијатријског обољења које ремети више кортикалне функције или функције језика и говора са губитком способности комуникације. Најзначајнији неуролошки узроци губитка виших кортикалних функција јесу Алцхајмерова болест и друге дегенеративне деменције, мада треба нагласити да и поједине фокалне лезије (трауме, инфаркт или тумори) у стратешки важним деловима мозга (кортикалне зоне за говор, таламус) могу довести до губитка способности одлучивања [12] (Слика 2).

У серији наших вештачења која су се односила на процену капацитета најчешће се радило о експертизи



Слика 3. Различите врсте способности које је процењивао неуролог (*n* = 31)
Figure 3. Different types of capacities assessed by a neurologist (n = 31)

процесне способности (17 случајева, 55%) (Слика 3). Вештачење процесне способности спроводи се на захтев суда и треба да пружи одговор на питање да ли је оптужени у стању да учествује у судском поступку који се против њега води. Најчешће је у питању кривична одговорност и експертизу ради лекар кога суд именује за вештака [13]. Вештачење процесне способности подразумева однос окривљеног и вештака који у неким елементима знатно одступа од уобичајеног односа болесника и лекара. Прво, лекар који већ лечи окривљеног од болести или поремећаја који би потенцијално могли да наруше процесну способност не би требало да самостално учествује у вештачењу. Друго, нема поверљивости информација на релацији лекар (вештак) – болесник (окривљени), јер ће лекар – вештак свој налаз доставити суду, а може, уколико постоји такав захтев, дати исказ на суду. На крају, окривљени има право да не сарађује са вештаком. Шта подразумева очувана процесна способност? Компетентност неке особе да учествује у судском поступку подразумева рационално и чињенично разумевање кривичног поступка и способност оптуженог да учествује и сарађује у сопственој одбрани. Дугим речима, оптужени треба да буде: 1) способан за сарадњу са браниоцем (да разуме оптужницу, разуме сопствену позицију и разуме улогу браниоца, тужиоца и судије) и 2) способан да доноси одлуке у вези са оптужницом (нпр. како се изјаснити по питању оптужнице). Болести и оштећења без јасно медицински документованих неуролошких, бихевиоралних и когнитивних испада никако не могу довести до процесне неспособности, али понекад могу захтевати посебан третман оптуженог (нпр. ограничено трајање рочишта, могућност давања исказа у седећем положају итд.) [14].

НЕУРОЛОШКЕ БОЛЕСТИ И КРИМИНАЛИТЕТ

Особе са различитим неуролошким болестима могу бити гоњене у кривичном поступку и оне по правилу одбрану базирају на свом неуролошком обољењу. Задатак неуролога је да процени да ли је и у којој мери њихова болест имала утицај на криминогено понашање и на способност да схвате значај свог дела, а задатак суда је да процени да ли они треба да буду кажњени и на који начин. Неуролошке болести и стања која се најчешће доводе у везу са криминогеним понашањем јесу епилепсија, поремећаји спавања и секвеле трауматских лезија мозга [15]. У даљем тексту биће речи о епилепсији као обољењу којим се, по правилу, баве искључиво неуролози и о њеном могућем утицају на урачунљивост приликом извршења кривичног дела.

Питања која суд најчешће упућује неурологу у случајевима у којима оптужени болује од епилепсије јесу да ли насиље може бити манифестација епилепсије, тј. самог епилептичког напада, односно да ли насиље може бити покренуто претходним епилептичким нападом. Насилно понашање међу болесницима са епилепсијом може се сврстати у периктално насиље (током или непосредно после напада) и интериктално насиље (независно од напада, тј. између напада) [16].

Како епилептички напад може довести до неурачунљивости? На првом месту услед појаве невољног облика понашања у виду епилептичних аутоматизама, као и услед поремећеног расуђивања изазваног постикталним психотичним понашањем у периоду непосредно после напада [16, 17]. Епилептични аутоматизми представљају мање-више координисане и комплексне невољне радње које често подсећају на нормалну моторну активност, али су неадекватни за тренутну ситуацију, немају сврху и стереотипно се понављају. Иако извршиоци тежих кривичних дела који болују од епилепсије своју одбрану често заснивају управо на овом облику невољног понашања, треба истаћи да је прекршај који се може јавити у таквом стању по правилу тривијалан, нпр., болесник је изашао из продавнице а да није платио робу или се укрцао на аутобус или воз а да није купио карту итд. Баналност ових прекршаја последица је саме чињенице да епилептични аутоматизми најчешће представљају наставак непосредне преикталне моторне радње или просте репетитивне секвенце коплекснијих моторних радњи [17].

Студија из Енглеске која је у периоду од 1975. до 2001. године идентификовала само 13 ослобађајућих пресуда услед смањене урачунљивости изазване епилептичким нападом показала је да се преко две трећине криминалних радњи одиграло у непосредном постикталном периоду [18]. Споменута студија је значајно допринела дефинисању форензичких критеријума за довођење у везу неког криминалног дела са епилептичким нападом. Лекар треба процену да заснива на следећих пет критеријума: 1) оптужени треба да има претходно дијагностиковану епилепсију и понашање током предметног догађаја треба да буде конзистентно понашању током ранијих напада, 2) сам чин треба да буде атипичан за карактер појединца и непримерен за околности, тј. без очигледног мотива, 3) с обзиром на то да се епилептички напад јавља изненада („попут олује“), не сме бити никаквих индиција о претходном умишљају нити постикталном прикривању доказа,

4) уколико постоје сведоци или снимци надзорних камера, они би требало да укажу на елементе измењеног стања свести у време предметног догађаја (непомично зурење, стереотипије, несврсисходне активности) и 5) зато што се чин дешава током икталних или постикталних аутоматизама, са појавом самог напада почиње и поремећај памћења у виду антероградне амнезије тако да би окривљени морао да има несећање у вези са предметним догађајем [17, 18].

Неуролошка процена урачунљивости у кривичним поступцима у нашој серији вештачења била је релативно ретка, свега 5%. Утисак аутора овог текста је да је разлог за спорадично ангажовање неуролога када је у питању процена урачунљивости извршиоца кривичних дела то што наши судови и даље у овим предметима дају предност психијатрима. Аргумент за обавезно укључивање неуролога би био то да су понашање и емоције такође израз мождане активности те да процена неурачунљивости и невољних облика понашања у већини случајева подразумева обавезно учешће неуролога [19].

НЕСАВЕСНО ПОСТУПАЊЕ ПРИЛИКОМ ДИЈАГНОСТИФИКОВАЊА И ЛЕЧЕЊА НЕУРОЛОШКИХ ОБОЉЕЊА

Основно значење појма лекарске грешке је поступање лекара супротно општепризнатим правилима властите струке (*contra legem artis*). Међутим, само она лекарска грешка која доведе до погоршања здравља или смрти болесника предмет је кривичне одговорности лекара, тј. представља кривично дело несавесног лечења [20]. Дакле, појам несавесног пружања лекарске помоћи подразумева примену очигледно погрешног или неподобног средства или начина дијагностиковања и/или лечења са штетном последицом по болесника. У јурисдикцијама обичајног права несавесно поступање са болесником се заснива на принципима немара (површност и непотпуност). Како дефинисати немар у медицини? Иако се закони знатно разликују од земље до земље, опште правило на основу кога се дефинише немар јесте ситуација у којој здравствени радник не показује разумно очекивани ниво компетентности (сходно својој едукацији) приликом пружања здравствене услуге [21].

Међу радњама или пропустима који се могу сматрати несавесним поступањем јесу: 1) неуспех у правилном и благовременом дијагностиковању болести, при чему су потребне дијагностичке методе лако доступне; 2) пропуст у обезбеђивању одговарајућег третмана за медицинско стање или болест, и 3) неразумно кашњење у лечењу већ дијагностикованог обољења. Под немаром, нарочито у болничким условима лечења, може се сматрати још и: 4) неадекватно вођење медицинске документације, 5) непримењивање адекватних превентивних поступака (нпр. аникоагулантна терапија) и 6) непримењивање одговарајућих хигијенских мера (нпр. приликом лумбалне пункције). Последњих година многи правни системи признају као несавесно поступање и кршење принципа информисаног пристанка, тј. необавештавање болесника о могућим последицама дијагностичког и/или терапијског поступка који би, по сопственој тврдњи, болесник одбио да је унапред имао одговарајуће информације [22]. Одговорност за лекарску грешку различито се третира у кривичним и грађанскоправним (парничним) поступцима. Уопштено се може рећи да кривична одговорност лекара постоји за грубе (драстичне) грешке, са тешким последицама по болесника. Насупрот кривичним, у парничним поступцима у којима се разматра могућност накнаде штете настале услед евентуалних пропуста током лечења, у обзир се узимају и мање (суптилније) грешке лекара [20].

Табела 1. Десет најчешћих пропуста неуролога који могу имати медиколегалне последице
Table 1. Ten most common omissions by neurologists that can have medicolegal consequences

1.	Није уочио акутни фокални неуролошки дефицит Missed acute focal neurological deficit
2.	Није препознао ране знаке повишеног интракранијалног притиска Missed early signs of increased intracranial pressure
3.	Није на време започео лечење дефицита витамина Б$_1$ и/или Б$_{12}$ Did not start treatment of vitamin B_1 and/or B_{12} deficiency on time
4.	Пропустио је дијагнозу субарахноидалне хеморагије Missed subarachnoid hemorrhage
5.	Није урадио лумбалну пункцију код неуроинфекције Failure to perform cerebrospinal fluid exam in neuroinfection
6.	Није препознао неконвулзивни епилептички статус Failure to recognize nonconvulsive status epilepticus
7.	Пропустио је акутну/субакутну компресију кичмене мождине Missed acute/subacute spinal cord compression
8.	Није узео у разматрање неуроинтервентне терапијске опције Not recognized neurointerventional therapeutic options
9.	Пропустио је кратак период за примену терапије Missed narrow windows of therapeutic opportunity
10.	Није дијагностиковао мождану смрт и пропустио је могућност кадаверичне донације органа* Failure to recognize brain death and the possibility of organ donation

*У земљама са развијеним програмом донације органа / *In countries with an advanced organ donation program*

У нашој серији неуролошких вештачења 1/5 (19%) била је у вези са питањем несавесног дијагностиковања и лечења неуролошких обољења. Разлози за покретање тужбе против неуролога били су прогресија болести и смртни исход (61%), кашњење у дијагнози и лечењу неуролошких болести (22%) и трајне функционалне последице услед (не)адекватног третмана (17%). При томе, у преко ¾ случајева (78%) радило се о болесницима који су иницијално збрињавани у ургентним пријемима или одељењима интензивне неге. Зато сваки неуролог који ради на ургентном пријему треба посебну пажњу да обрати на болеснике са акутно насталим фокалним неуролошким дефицитом, затим на оне са епизодичним поремећајем свести и епилептичким нападима, изненадном и јаком главобољом, вртоглавицом и акутним и/или субакутним развојем слабости екстремитета.

Такође, сваког болесника са већ дијагностикованим хроничним неуролошким обољењем треба примити у болницу уколико постоји нагла прогресија симптома болести или уколико дође до појаве нестабилних виталних параметара [23]. За крај, табеларно је приказано 10 најчешћих грешака неуролога са могућим медико-легалним последицама (Табела 1).

ЗАКЉУЧАК

У овом чланку смо покушали да кроз сопствено искуство истакнемо место и улогу неуролога у тиму судскомедицинских вештака и да идентификујемо оне области у форензичкој медицини где је његова екпертиза од прворазредног значаја. Сматрамо да постоји простор за још ангажованијим приступом и да је неопходно проширити улогу неуролога на првом месту у областима вештачења одговорности и урачунљивости извршиоца кривичних дела и њихове процесне способности. Искрено се надамо да ћемо овим радом допринети унапређењу даље сарадње и још бољој међусобној комуникацији како лекара форензичара тако и медицинске и правне струке.

ЗАХВАЛНОСТ

Аутори рада желе да се захвале др Ради Стијовић за безрезервну помоћ у вези са језичком и стилском обрадом текста.

Сукоб интереса: Аутори изјављују да нема сукоба интереса у вези са овим радом.

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Forensic neurology – the role of a neurologist in a forensic medical assessment

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SUMMARY

Forensic neurology is tasked with assessing the consequences of injuries as applied to different situations that interface with the law based on the understanding of nervous system functioning and the mechanisms of neurological diseases. In this article, based on our own experiences, we have tried to highlight the areas of forensic medicine in which the findings and the expert opinion of a neurologist were not only important, but also crucial for making fair judicial decisions. Our intention was to encourage more efforts to establish and expand the role of neurologists in certain areas, foremostly the expertise of responsibility and accountability of a crime perpetrators, as well as determining their processing ability.

Keywords: forensic neurology; forensic medicine; expert testimony

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh).*

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

АДРЕСА:
Српско лекарско друштво
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ISSN 0370-8179
ISSN Online 2406-0895
OPEN ACCESS

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The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

ETHICAL APPROVAL. Manuscripts with human medical research should contain a statement that the subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee, and conforms to the legal standards. Experimental studies with human material and animal studies should contain statement of the institutional ethics committee and meet legal standards.

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The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

PLAGIARISM. Since January 1, 2019 all manuscripts have been submitted via SCIndeks Assistant to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control. The manuscripts with approved plagiarism/auto-plagiarism will be rejected and authors will not be welcome to publish in Serbian Achieves of Medicine.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institution in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

SUMMARY. Along with the original article, preliminary and short communication, review article, case report, article on history of medicine, current topic article, article for language of medicine and article for practitioners, the summary not exceeding 100–250 words should be typed on the second page of the manuscript. In original articles, the summary should have the following structure: Introduction/Objective, Methods, Results, Conclusion. Each segment should be typed in a separate paragraph using boldface. The most significant results (numerical values), statistical analysis and level of significance are to be included. The conclusion must not be generalized, it needs to point directly to the results of the study. In case reports, the summary should consist of the following: Introduction (final sentence is to state the objective), Case Outline (Outline of Cases), Conclusion. Each segment should be typed in a separate paragraph using boldface. In other types of papers, the summary has no special outline.

KEYWORDS. Below the summary, 3 to 6 keywords or phrases should be typed. The keywords need not repeat words in the title and should be relevant or descriptive. *Medical Subject Headings – MeSH* (*http://www.nlm.nih.gov/mesh*) are to be used for selection of the keywords.

TRANSLATION INTO SERBIAN. The third page of the manuscript should include: title of the paper in the Serbian language; each author's full name and family name (no titles), indexed by numbers; official name, place and country of the institution in which authors work. On the fourth page of the manuscript the summary (100–250 words) and keywords (3–6) should be typed, but this refers only to papers in which a summary and keywords are compulsory. The terms taken from foreign literature should be translated into comprehensible Serbian. All foreign words or syntagms that have a corresponding term in Serbian should be replaced by that term.

If an article is entirely in Serbian (e.g. article on history of medicine, article for "Language of medicine," etc.), captions and legends of all enclosures (tables, graphs, photographs, schemes) – if any – should be translated into English as well.

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

61(497.11)

СРПСКИ архив за целокупно лекарство : званичан часопис Српског лекарског друштва = Serbian Archives of Medicine : official journal of the Serbian Medical Society / главни и одговорни уредник Гордана Теофиловски-Парапид. - Књ. 1 (1874)-књ. 2 (1875) ; књ. 3 (1879)- књ. 8 (1881) ; књ. 9 (1887)-књ. 10 (1888) ; књ. 11 (1894)-књ. 12 (1895) ; год. 1, бр. 1/2 (1895)- . - Београд : Српско лекарско друштво, 1874-1875; 1879-1881; 1887-1888; 1894-1895; 1895-(Београд : Службени гласник). - 29 cm

Двомесечно. - Текст на енгл. језику. - Има суплемент или прилог: Српски архив за целокупно лекарство. Суплемент = ISSN 0354-2793. - Друго издање на другом медијуму: Српски архив за целокупно лекарство (Online) = ISSN 2406-0895
ISSN 0370-8179 = Српски архив за целокупно лекарство
COBISS.SR-ID 3378434

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

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