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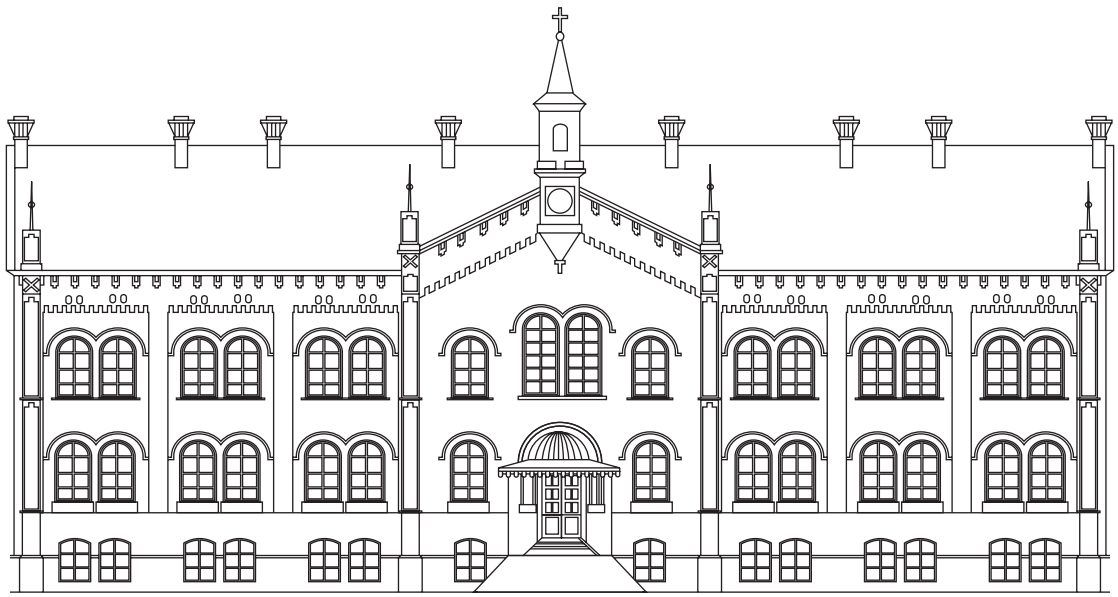

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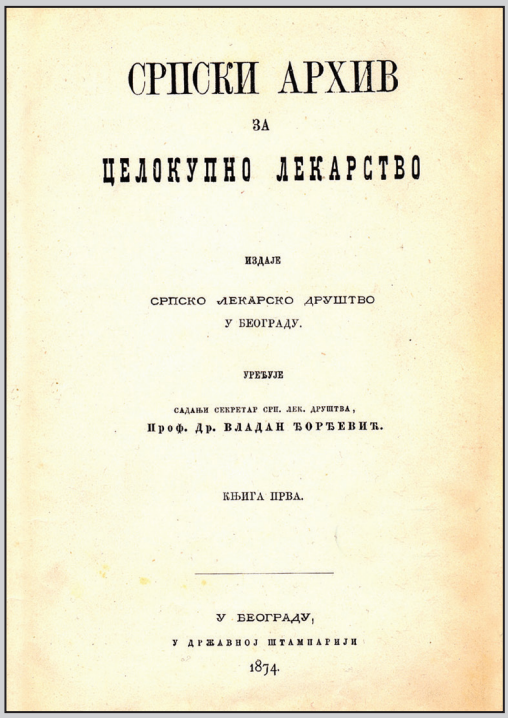

СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

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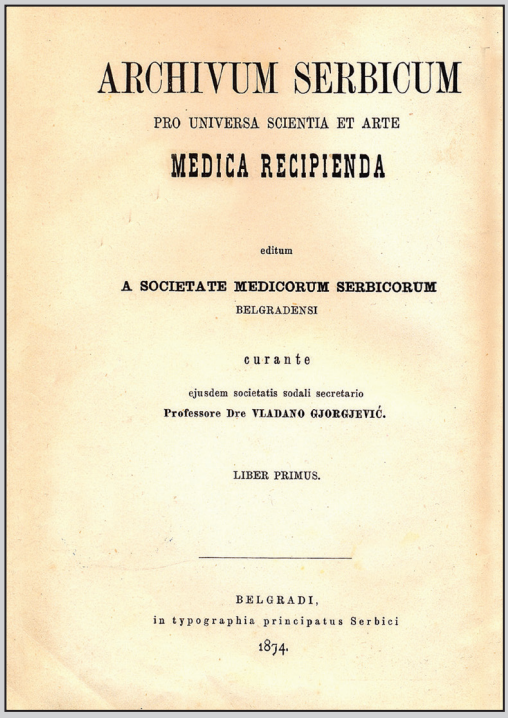

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1874.

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Efficiency of calcium hydroxide removal techniques from simulated internal root resorptions – *in vitro* study

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SUMMARY
Introduction/Objective Calcium hydroxide (CH) is the medicament of choice in endodontic treatment of internal root resorptions.
The aim of the study was to compare the effectiveness of three different techniques for CH removal from simulated internal root resorptions.
Methods Twenty-nine extracted single-root teeth were prepared using NiTi rotary files of BioRaCe system (40/.04) following irrigation. A round diamond drill was used in the making of a symmetrical standardized internal resorptions 6 mm from the apex. Three techniques for CH removal from internal resorptions were tested: modified conventional syringe irrigation (CSI), passive ultrasonic irrigation (PUI), XP-endo Finisher (XP). Resorptive cavities and apical thirds were observed under a stereomicroscope (×45) and scored (from 1 to 5), while representative samples were analysed by a scanning electron microscope. Obtained results were statistically processed by Kruskal–Wallis and Mann–Whitney U-test ($p < 0.05$).
Results The most efficient system was PUI, with 66.7% of samples rated 1 and 33.3% rated 2. The next one was XP, and the least efficient was CSI, with 33.3% of samples rated 1 (resorptive defect without medicament). There was a statistically significant difference between the PUI and CSI systems ($p < 0.05$), while there was no difference between the PUI and XP systems.
Conclusion No system completely removed the CH from the simulated internal root resorption cavities. PUI was the most effective system for removing CH. The combination of techniques provides better performance in removing CH paste residues from the canal walls.
Keywords: internal root resorption; irrigation; ultrasound; XP-endo Finisher

INTRODUCTION

Internal root resorption is a pathological process originating from pulp tissue that, as it spreads peripherally, causes the loss of hard dental tissues [1]. This process was described for the first time in 1830 [2]. It is most often caused by a trauma or an inflammatory process [2, 3]. In most cases, this is an asymptomatic process and is accidentally detected by a radiograph on which it is presented as a sharply limited and symmetrical round radiopacity corresponding to the widening of the root canal. If there is no perforation and communication with the periodontium, endodontic therapy (biopulpectomy) is indicated [4]. The application of a medicament is mandatory, as canal instrumentation and irrigation are not enough to remove granulation tissue and resorptive cells on its periphery [5]. Also, if necrotization and infection of the pulp tissue occur, mechanical instrumentation alone is insufficient for bacteria elimination from irregular spaces of the root canal.

Calcium hydroxide is the medication of choice in endodontic treatment of internal root resorption due to its antibacterial, therapeutic, regenerative and biocompatible properties and has a beneficial effect on mineralization processes [6]. Dissociated hydroxyl ions interfere with the integrity of the bacterial membrane, disrupting the flow of nutrients and destroying phospholipids from unsaturated fatty acids [7].

The CH must be completely removed from the root canal walls prior to the obturation in order not to compromise the penetration of the sealer into the dentinal tubules and to affect the binding and physical properties of the sealer, e.g., eugenol based or mineral trioxide aggregate [7, 8, 9].

One of the most described techniques for calcium hydroxide removal is conventional syringe irrigation (CSI) [10]. Many authors point out the inefficiency of this technique [7, 9, 11, 12]. Due to the perceived shortcomings, like the lack of medication on the walls, numerous other techniques and instruments have been developed to clean root canals more efficiently. Some of these are as follows: passive ultrasonic irrigation, XP-endo Finisher (XP), Canal Brush, Rins Endo system, laser-activated irrigation (PIPS), sonic and ultrasonic irrigation activation, Endo Vac system, Self-Adjusting-Files [4, 5, 9, 13, 14, 15].

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Passive ultrasonic irrigation (PUI) is based on the transfer of sound energy to the irrigant. The 25–30 kHz frequency activates the irrigant and creates cavitation bubbles. Sound waves and/or energy-released cavitation increase the penetration of irrigants into irregular spaces [12]. The XP (FKG Dentaire, La-Chaux-de Fonds, Switzerland) is a NiTi nontapered instrument (size 25). At room temperature it is straight (martensite phase), and at body temperature it changes its shape into a unique spoon shape (austenite phase) with a length of 10 mm from the top and a depth of 1.5 mm, due to its molecular memory [15]. It is designed for final cleaning and irrigation, especially for ampoule dilated and irregular canals [9].

The aim of the study was to test the effectiveness of three different techniques for calcium hydroxide removal from simulated internal root resorptions.

The null hypothesis is that there is no statistically significant difference in the efficiency of calcium hydroxide removal from simulated internal resorption between the CSI, PUI, and XP systems.

METHODS

This study used 29 single-rooted, single-canal, extracted teeth. Research was approved by the institutional ethics committee (No. 36/2, 25.02.2020). Round diamond burr with water cooling was used to prepare access cavities and instrument K# 15 was used for checking canal patency. Working length, 1 mm shorter than the apex of the root, was defined. All canals were prepared with BioRaCe (FKG Dentaire) system with apical preparation of 40/.04, with obligatory irrigation of 2% NaOCl after each instrument. Final irrigation consisted of 5 ml of 2% NaOCl and 5 ml of 10% citric acid for a period of 1 minute and 5 ml of saline. Samples were imprinted into a silicone impression material (Elite HD + putti, Zhermack, Badia Polesine, Italy) in an Eppendorf tube (Eppendorf AG, Hamburg, Germany). On the approximate root surfaces longitudinal grooves were made using a diamond disc with water cooling. The roots were cut in half with a chisel and a hammer and a round drill (0.08 mm deep and 0.16 mm in diameter) was used in the making of standardized internal resorptions 6 mm coronary from the root apex. Root halves were reassembled with a dental adhesive (OptiBond Solo Plus, Kerr, USA) and returned to silicone molds, after which all the canals were filled with an aqueous suspension of calcium hydroxide (except negative controls) and closed with temporary filling Citodur hard (DoriDent – Dr. Hirschberg GmbH, Wien, Austria). Samples were incubated in a humid environment at 37°C for seven days. After seven days, the teeth were randomly divided into three groups (n = 9), and a single tooth was used for positive and negative controls. The positive control tooth was filled with calcium hydroxide, which was not removed, and the negative control sample was not filled with medication.

Group I: **CSI (modified)** – medicament was removed from the canal with hand instruments K # 15 to # 40 (master apical file – MAF) with a syringe and an open tip needle irrigation 27G (Sinomedic, China). Total irrigation consisted of 5 ml 2% NaOCl for a period of 1 minute.

Group II: **PUI** – ultrasound apparatus was used (PB-323, W&H Dentalwerk Bürmoos GmbH, Bürmoos, Austria) – ultrasonic endodontic instrument was placed in a canal, 1 mm shorter from the working length, without contact with the canal walls. The irrigation was performed in three series of 20 seconds each. Fresh irrigant was added after each cycle. Total irrigant amount consisted of 5 ml 2% NaOCl for a period of 1 minute.

Group III: **XP** – the instrument is placed in a canal, 1 mm shorter from the working length, using X-smart endo motor (Dentsply Sirona, Ballaigues, Switzerland) with a rotation of 800 rpm and a torque of 1 Ncm. Gentle brush strokes (up and down) were performed with the instrument for 1 minute with constant irrigation, for a total of 5 ml of 2% NaOCl for a period of 1 minute.

Finally, all groups were irrigated with 5 ml of 10% citric acid for 1 minute. Irrigation of all samples was completed with 5 ml of saline.

The teeth were halved again, and internal root resorptions and apical thirds were observed on a stereomicroscope (Boeco BSZ-405, Boeckel + Co (GmbH + Co); Hamburg, Germany) with an integrated digital camera, at 45× magnification. ScopeImage 9.0 computer software (Telescope, Linz, Austria) was used to display the images. Representative samples of each group were analysed by scanning electron microscope (SEM) (Tescan FE-SEM Mira 3 XMU, Tescan a.s., Brno, Czech Republic) operated at 20 keV. The samples were coated with atomic gold layer using a sputter coater (Polaron SC503, Fisons Instruments, Ipswich, UK).

Medication removal efficacy was evaluated according to the methodology of Faria et al. [16] and Topçuoğlu et al. [13] with five grades:

1 = clean internal resorption with only a few drug particles;

2 = several small agglomerates of medication;

3 = multiple medication agglomerates covering less than 50% of the internal resorption area;

4 = more than 50% of internal resorption is covered with medication;

5 = internal resorption is completelly filled with medication.

Evaluation was performed by 3 objective observers. Obtained values were statistically processed in Kruskal–Wallis and Mann–Whitney tests. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Results are shown in Table 1 and Figures 1–3.

Results of this study indicate that after passive ultrasonic irrigation, 66.7% of the samples were graded 1 and 33.3% of the samples were graded 2. After the conventional drug removal technique with MAF with permanent irrigation, 33.3% of the samples were graded 4, and 22.2% of the samples were graded 5; 11.1% of the samples were graded

Table 1. Sample ratings, depending on irrigation technique

Group	n	1	2	3	4	5
Negative c.	1	1	0	0	0	0
Positive c.	1	0	0	0	0	1
PUI	9	6	3	0	0	0
CSI	9	3	1	0	3	2
XP	9	3	2	2	2	0

PUI – passive ultrasonic irrigation; CSI – conventional syringe irrigation; XP – XP-endo Finisher

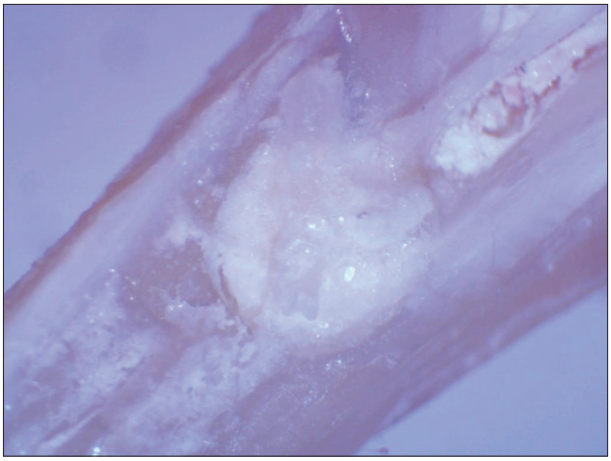

Figure 1a. Stereomicroscope image of filling of internal resorption cavity with $Ca(OH)_2$ after conventional syringe irrigation; grade 5; magnification 45×

2, and 33.3% of the samples were graded 1. For XP, 33.3% of samples had a grade of 1, while other grades had 22.2% each. A statistically significant difference was observed between the conventional drug removal technique and other irrigation techniques ($p < 0.05$). There was no statistically significant difference between PUI and XP ($p > 0.05$).

DISCUSSION

No technique has completely removed the CH paste from artificial internal root resorption, which is in agreement with the findings of numerous researchers [4, 5, 9, 13]. Also, the null hypothesis was rejected because PUI was the most effective system for removing CH from resorptive cavities as well as apical thirds. PUI and XP removed the medication much more efficiently than CSI, with no statistical difference between them.

Many studies have been published on the topic of CH removal from the root canal system after inter-session medication. Some of them have tested different irrigants [8, 12, 17, 18], while others tested different irrigation systems [9, 10, 11, 13, 14, 19]. All highlight the great problem of completely removing the medication from the walls, especially from the apical third. Some authors point out that 27% of the canal surface remains covered with CH, while our earlier studies indicate that in some cases only 48% of the root canal surface is cleared of CH [11, 20].

Internal root resorption therapy is a real challenge and one of the least successful endodontic procedures. Problems occur in almost every stage of endodontic treatment:

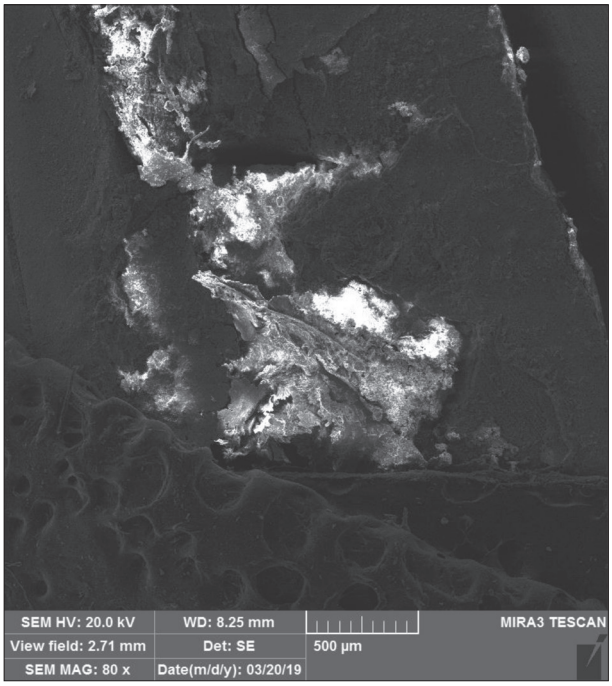

Figure 1b. Scanning electron micrograph of resorptive lacuna completely filled with $Ca(OH)_2$

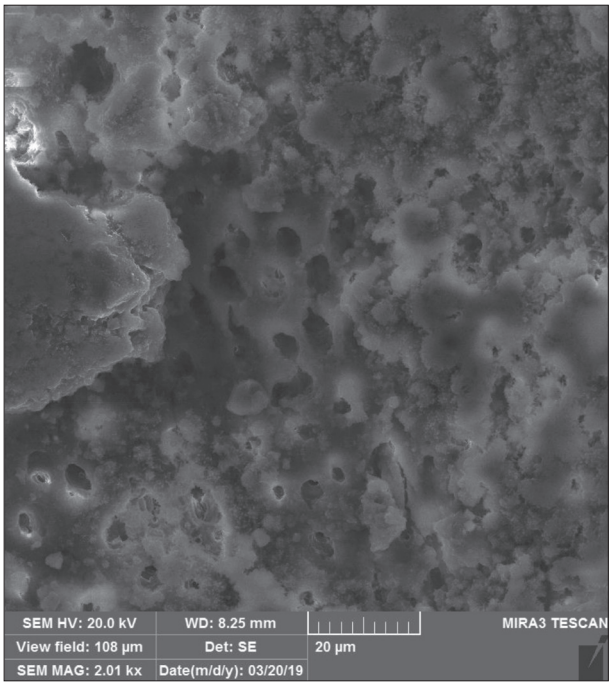

Figure 1c. Scanning electron micrograph of dentin in the apical third mainly covered with $Ca(OH)_2$ crystals

during diagnosis, removal of the entire pulp content, profuse bleeding of the granulation tissue, possible root perforation, and preparation and obturation is difficult of the canal due to irregular canal anatomy [9, 21].

The use of calcium hydroxide is essential in the endodontic treatment of internal root resorptions, as it promotes control and elimination of infection. It affects the processes of repair, remineralization and has antibacterial effects on the remaining microorganisms. Numerous studies indicate a failure to completely remove the drug from

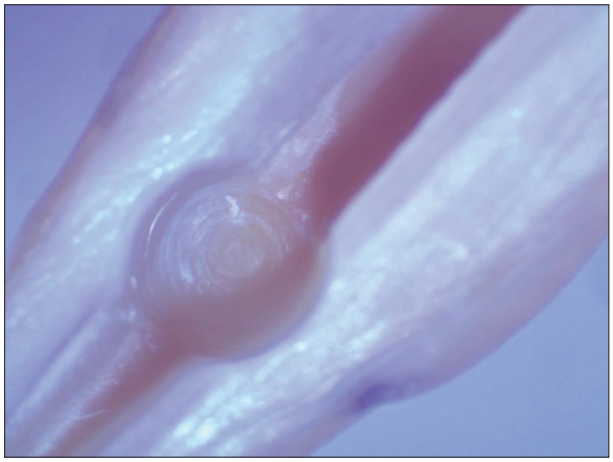

Figure 2a. Stereomicroscope image of an empty internal resorption cavity after passive ultrasonic irrigation; grade 1; magnification 45×

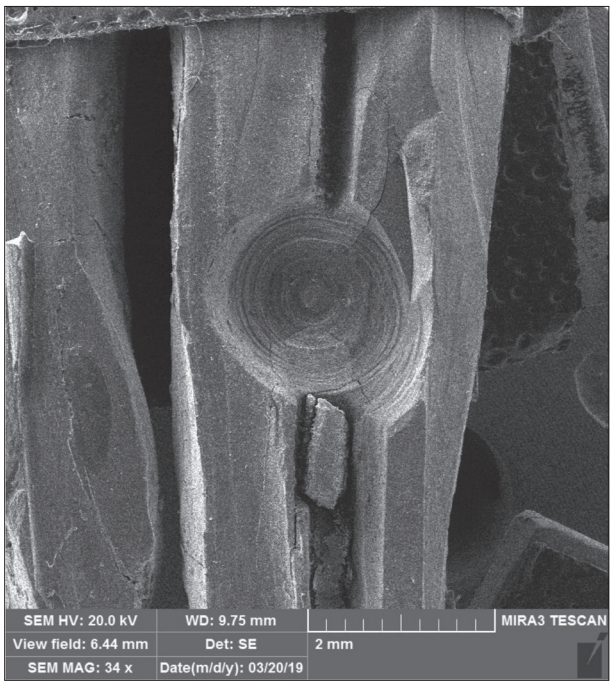

Figure 2b. Scanning electron micrograph of empty resorptive lacuna

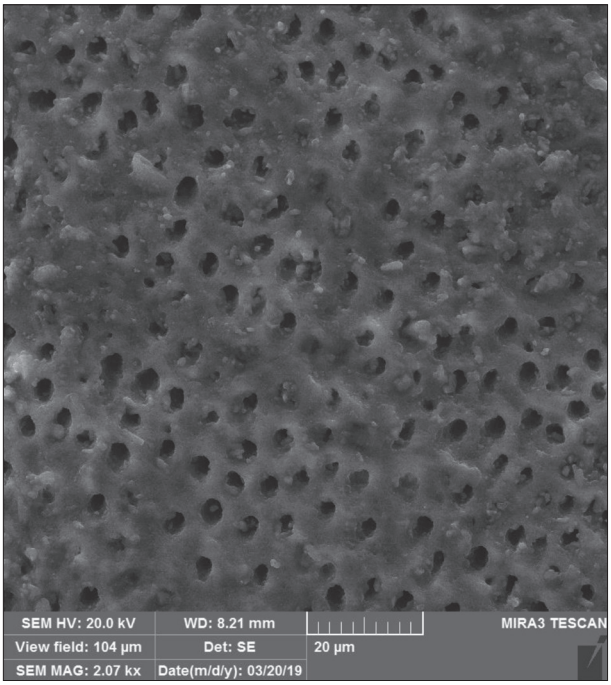

Figure 2c. Scanning electron micrograph of open dentinal tubules in the apical third

the dilated portions of the root canal or resorptive lacunae. [4, 5, 9, 13]. Today, it is known that residual CH interferes with hermetic, three-dimensional obturation and weakens it. The residual CH disturbs the binding mechanisms of different types of sealers and in the long run increases the apical leakage between the canal walls and the sealer [8]. This is especially represented with zinc-oxide eugenol-based sealers, where the newly formed calcium eugenolate alters its physical properties [8, 9]. Residual CH also affects the penetration of epoxy resin-based sealer, more so than calcium silicate-based sealer [8]. Also, there is no agreement as to whether the cleansing effect is affected by the type of vehicle in CH paste (distilled water, propylene glycol, oil etc.) [6, 14, 22]. Chou et al. [11] point out as a problem the viscosity of CH pastes with cellulose carriers with respect to the aqueous suspension, as well as the possibility that partial conversion of calcium hydroxide to calcium carbonate has occurred over time due to the reaction with carbon dioxide.

In this study, a round diamond burr was used to form simulated internal resorptions that were thus round, standardized, with the same amount of medication. In addition to the drill bit, artificial resorptions or grooves in the canal are often prepared with ultrasonic instruments or diamond discs [9, 13, 14, 15, 18]. However, internal resorption has an irregular and usually oval shape, so Da Silveira et al. [23] find it more similar to clinical conditions that the root canal interior is treated with 5% nitric acid in order to create simulated internal resorptions. Given that the efficacy of different methods of calcium hydroxide removal was investigated, artificial internal root resorption of the standardized form could not influence the evaluation of irrigation techniques, although they did not represent the complex physiological anatomy of the root canal. This is confirmed by other authors [4, 9, 18].

Different methods of quantifying calcium hydroxide residues have been described. Digital canal/resorption image analysis is most used, using non-parametric rating systems [5, 9, 18]. However, Phillips et al. [7] point out that there are concerns regarding two-dimensional quantification on uneven surfaces, so they propose chemical microtitration techniques that use high-pH calcium hydroxide. SEM analysis, helical computed tomography (CT) and micro-CT are also commonly used, but the problem of accurate detection of residual CH with respect to root canal tissue has arisen [4, 7]. The scoring system used in this study has been used in many other studies [9, 13, 14, 16, 18]. Most of them used a 3- or 4-grade system. In this study, a 5-rating system was used to describe in more detail the amount of the residual medicament on canal walls/resorption [16].

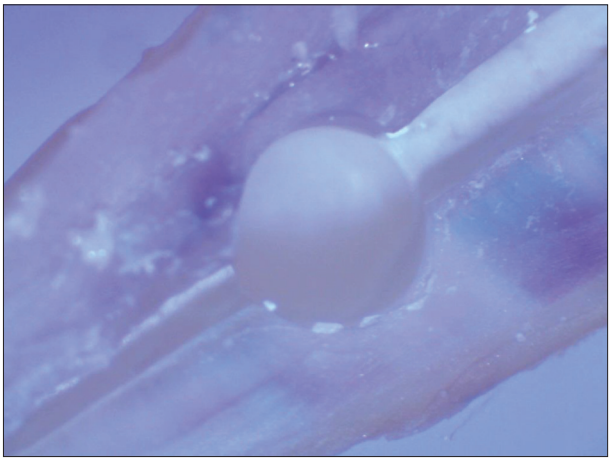

Figure 3a. Stereomicroscope image of residual medication after irrigation with XP-endo Finisher; grade 2; magnification 45×

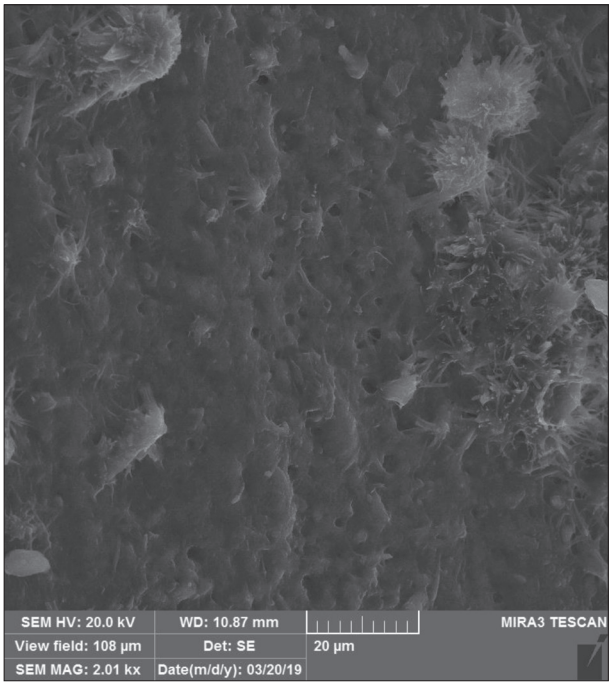

Figure 3b. Scanning electron micrograph of open dentinal tubules in the apical third, in places covered with $Ca(OH)_2$

For this research, teeth with a simple canal system were used to examine the effectiveness of irrigation no matter how complicated and complex the canal system was. The crowns of the teeth were not completely removed to provide room for irrigant storage. Despite all these extenuating circumstances for experimental purposes, no technique completely removed the medicament from the canal walls, which is also in agreement with other researchers [7, 24].

Passive ultrasonic irrigation has shown a high efficiency in removing the CH paste from internal root resorption, which is confirmed by the SEM findings where open dentinal tubules are observed. This is an effective way of removing CH from canal walls, other researchers point out [13, 14, 16, 18, 25]. Its effectiveness is reflected in the penetration of irrigants into all spaces, which is achieved by agitation of irrigants (acoustic waves and cavitation) [26]. With this technique it is important to constantly add new amounts of fresh irrigant (intermittent protocol), because the amount of residual CH is inversely proportional to the volume of used irrigant [24]. In our study, along with NaOCl, citric acid was also used, as it was found that only one irrigant was not sufficiently effective in removing the smear layer and/or calcium hydroxide [13]. This has been confirmed by previous research where PUI with both irrigants was very effective, with an average of 88% of the cleaned root canal walls [20]. Newer research underlines activating chelating irrigants (ultrasonically agitated) with PUI as very efficient [27, 28]. The combination of these two irrigants produces optimal results with the appropriate duration of irrigation, as well as the amount of irrigants themselves [8, 13, 18, 29]. Irrigation lasted 60 seconds per canal (3 × 20 seconds), as agreed by Gokturk et al. [14], although Phillips et al. [7] point out that even 30 seconds per canal is completely adequate time to remove CH.

The XP is presented as a very flexible instrument that has a large amplitude of motion in the A-phase, which is 100 times larger than a "regular" instrument of the same size, so it is recommended for inaccessible canals (FKG Dentaire). Research indicates that it is very effective in removing smear layers and dentin debris [13]. However, it did not fully meet expectations in this research. The results varied. In some samples, the drug was completely removed from internal root resorption, which is confirmed by the SEM findings, and this is in agreement with the finding of Keskin et al. [5], who state that XP is superior to other techniques but not to PUI. Its efficiency is the result of a change in shape with respect to body temperature, thus extending the cleaning effect by up to 6 mm in diameter. However, there are samples (22.2%) where internal resorption is filled with medication, even more than 50% of the resorptive lacuna. This finding is in agreement with the findings of Wigler et al. [9], who obtained similar results, and the efficiency of XP did not meet their expectations either. The aforementioned finding can be explained by the inappropriate amplitude of movement of the instrument, which does not allow the penetration of the instrument into all areas of internal resorption, or the time of 1 minute, recommended by the manufacturer, is insufficient in CH removal. Also, Bao et al. [15] point out that XP is much more efficient when used with intermittent irrigation protocol, thereby cumulatively increasing the effect of NaOCl. Continuous irrigation was used in this study. However, there is no statistically significant difference between XP and PUI systems, as found by other authors [5, 9, 14]. CSI has shown the worst results, which is in line with the findings of numerous researchers [11, 14, 15, 16]. The tip of the irrigation needle is positioned at least 1 mm shorter than the working length, to prevent extrusion of the irrigation via the foramen apical. In this way, large amounts of CH remain on the canal walls in the apical third. Despite the modification of the CSI, by introducing successive files to the MAF, our results clearly showed the limitations of mechanical instruments in irregular canal spaces.

Additional research is needed to test these and other techniques in a complex root canal system.

CONCLUSION

The null hypothesis was not confirmed. No irrigation system completely removed calcium hydroxide from artificial internal root resorption. Passive ultrasound irrigation has shown the highest efficiency in cleaning medication from internal root resorption.

For complete clinical success, multiple medicament removal systems need to be combined.

Conflict of interest: None declared.

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Ефикасност техника уклањања калцијум-хидроксида из симулираних интерних ресорпција корена – *in vitro* студија

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САЖЕТАК

Увод/Циљ Калцијум-хидроксид (КХ) јесте медикамент избора у ендодонтском лечењу интерних ресорпција.

Циљ овог рада је био да се провери ефикасност три различите технике уклањања КХ из симулираних интерних ресорпција корена.

Методе Двадесет девет једнокорених зуба је обрађено применом *NiTi* ротирајућих инструмената *BioRaCe* (40/0,04), уз иригацију. Коренови су потом засечени дијамантским диском на латералним странама и длетом подељени на две половине. Округлим дијамантским сврдлом су симетрично направљене стандардизоване интерне ресорпције на 6 *mm* од апекса. Коренске половине су затим састављене, а лентулом је унет медикамент КХ. Тестиране су три технике за уклањање КХ из интерних ресорпција: модификована конвенционална иригација шприцем (КИШ), пасивна ултразвучна иригација (ПУИ), *XP-endo Finisher* (*XP*). Ресорптивни кавитети и апексне трећине су посматрани под стереомикроскопом (×45) и бодовани системом од 1 до 5, а репрезентативни узорци су анализирани коришћењем *SEM*. Добијени резултати су статистички обрађени Краскал–Волисовим и Ман–Витнијевим *U*-тестом ($p < 0,05$).

Резултати Најефикаснији систем био је ПУИ, са 66,7% узорака оцењених оценом 1, а 33,3% оценом 2. Следећи је био *XP-endo Finisher*, а најмање ефикасан је био КИШ са 33,3% узорака са оценом 1 (ресорптивни дефект без медикамента). Статистички значајна разлика постоји између система ПУИ и КИШ ($p < 0,05$), док не постоји између система ПУИ и *XP*.

Закључак Ниједан систем није у потпуности уклонио медикамент из симулираних интерних ресорпција. Комбинацијом техника обезбеђује се бољи учинак у уклањању заосталог медикамента са зидова канала.

Кључне речи: интерна ресорпција корена; иригација; ултразвук; *XP-endo Finisher*

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Psychometric properties of North Macedonian version of the Oral Health Impact Profile for Edentulous Subjects

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SUMMARY

Introduction/Objective Dental patient-reported outcome measures are very important in a disease-specific population such as edentulous subjects.

The aim of the study was to adapt the Oral Health Impact Profile for Edentulous Subjects (OHIP-EDENT) in the cultural environment of North Macedonia.

Methods This study adapted the original 19-item version of the OHIP-EDENT. After the forward–backward translation according to international standards, the OHIP-EDENT-MAC was psychometrically tested in 109 complete denture wearers.

Results The Cronbach's α coefficient of 0.892 confirmed good internal consistency. Test–retest reliability was confirmed by high intraclass correlation coefficient of the summary scores (0.986; 95% confidence interval 0.968–0.993). The concurrent validity was confirmed by the Spearman's rank correlation coefficient (r = -0.654) between the OHIP-EDENT-MAC summary scores and a single question which rated satisfaction with the existing removable dentures using a five-point scale (1 = unsatisfied, 5 = completely satisfied). Construct validity was confirmed by exploratory factor analysis. All item loadings were above 0.4. Items grouped in four factors (dimensions), which explained 66.25% of the variance, in both non-rotated and rotated matrices. Good responsiveness was confirmed in 33 participants after complete denture relining. Their OHIP Summary score (33.09 ± 11.61) decreased significantly (t = 7.68; df = 32; p < 0.001) after treatment (24.39 ± 8). The standardized effect size was 0.75, representing moderate to large effect.

Conclusion The OHIP-EDENT-MAC showed satisfactory psychometric properties providing evidence for its use in edentulous population of North Macedonia.

Keywords: OHIP-EDENT questionnaire; psychometrics; reliability; validity responsiveness; North Macedonia

INTRODUCTION

Edentulism is generally associated with ageing, although one can keep one's own teeth throughout whole life. The rate of edentulousness differs between cultures and countries with a trend to decline in rich countries due to investments and efforts in education on oral hygiene maintenance and other preventive measures. However, the prevalence of edentulousness is still large, mostly in less developed countries [1]. Moreover, the edentulism is not likely to be greatly reduced in the near future as the average lifespan is increasing and the population is generally growing older.

Oral health-related quality of life (OHRQoL) has become an important part of patients' well-being and an important issue in dentistry as it provides insight into a patient's view of dental problems or the provided therapy. Dental patient-reported outcome measures can be assessed by several psychometrically validated questionnaires, the Oral Health Impact Profile (OHIP) being one of the most frequently used. The original 49-item OHIP was developed by Slade and Spencer in 1994, and the items were grouped (based on expert opinion) into seven domains: functional limitation, physical pain, physical limitation, psychological discomfort, social limitation, and disabilities (handicap) [2]. To reduce time consumption and incomplete answers of the 49-item OHIP questionnaire, a shorter version consisting of 14 items was developed from the original version. However, a disease-specific questionnaires are sometimes more appropriate. Therefore, many questionnaires for disease-specific patients have been developed in medicine and dentistry [3–7]. The OHIP-EDENT with 19 items has been developed for a disease-specific population suffering from tooth loss to enable measurement of the impact of edentulousness and interventions by conventional or implant-supported dentures in the edentulous population [7].

Each questionnaire has to be adapted before it can be used in other cultures and populations. The translation has to be performed according to accepted forward–backward process and the

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Table 1. North Macedonian version of the Oral Health Impact Profile for Edentulous Subjects (OHIP-EDENT) questionnaire
Ве молиме заокружете го соодветниот број на скала од 0 до 4 за секое прашање кое се однесува на проблеми со вашата протетска работа (вашата протеза)0 – никогаш; 1 – скоро никогаш; 2 – повремено; 3 – често; 4 – многу често

No.	OHIP-EDENT-MAC (NORTH MACEDONIA)
1.	Дали сте имале или имате *потешкотии при џвакање на било која храна*?
2.	Дали сте забележале *дека храната се лепи или останува* на протетичката изработка (протезата)?
3.	Дали сте забележале дека вашите *протези не налегнуваат* добро?
4.	Дали сте имале *болки во устата*?
5.	Дали Ви било или Ви е *неудобно (непријатно) да јадете некој вид на храна*?
6.	Дали сте имале или имате *болки во некој дел во устата*?
7.	Дали *протезите ви се неудобни*?
8.	Дали сте *загрижени* заради проблемите со протетичката изработка (протезата)?
9.	Дали сте *свесни* за Вашата протетичка изработка (протеза)? (Дали ви е постојано во потсвеста?)
10.	Дали сте морале да *избегнувате да јадете одреден вид на храна*?
11.	Дали сте забележале дека *не можете да јадете* некоја храна?
12.	Дали сте *прекинале оброк* заради проблеми со вашата протетичка изработка (протеза)?
13.	Дали сте *вознемирени* заради проблемите со протетичката изработка (протезата)?
14.	Дали сте се *чувствувале непријатно* заради проблемите со протетичката изработка (протезата)?
15.	Дали сте *избегнувале излегување или дружење*?
16.	Дали сте *биле помалку толерантни спрема брачниот другар или некој член од семејството*?
17.	Дали сте биле *раздразливи спрема другите (околината)*?
18.	Дали Ви се случило *помалку да уживате во друштво на други луѓе*?
19.	Мислите ли дека *животот ви нуди помалку задоволства*?

translated questionnaire must be psychometrically tested [8]. In North Macedonia, the long version of the OHIP Instrument has already been validated, but not the OHIP-EDENT [9]. Therefore, the aim of the study was to adapt the OHIP-EDENT in the cultural environment of North Macedonia.

METHODS

Subjects

A total of 109 fully edentulous subjects wearing complete dentures (CD) were included in the study. They were contacted by a telephone call and were asked to come for a control examination of their dentures. Of 182 patients, 109 responded. All dentures were previously made by undergraduate dental students under supervision of their teachers, specialists of prosthodontics at the School of Dentistry, Skopje, North Macedonia. The dentures were between nine month and six years old. The participants gave 19 answers using the OHIP-EDENT-MAC questionnaire and rated frequency of experienced difficulty in the previous week. The responses of the OHIP-EDENT-MAC questionnaire were rated using a five-point Likert's scale with the following answers: 0 – never, 1 – hardly ever, 2 – occasionally, 3 – fairly often, 4 – very often. Higher scores represented higher frequency of problems (more difficulties) and lower scores represented less problems and better OHRQoL. Zero represented absence of problems. All participants had to sign a written informed consent before being included in the study. The study was approved by the Ethics Committee of the Faculty of Dentistry, University of Skopje, and is in accordance with the ethical standards of the Declaration of Helsinki.

Translation

The forward–backward translation process of the OHIP-EDENT questionnaire was performed from the English language into the Macedonian language by two experienced dentists with an excellent knowledge of the both languages [8]. The backward translation was made by one professional of the English language who was Macedonian language native speaker. A native English language speaker compared the original and the back-translated version and agreed on the same meaning of the items. The Macedonian version was further tested to check understanding of the questions in 17 patients undergoing treatment with CD. The OHIP-EDENT-MAC version is presented in Table 1.

Reliability

The internal consistency of the OHIP-EDENT-MAC was tested by calculating Cronbach's α coefficient (value > 0.7 was considered acceptable).

The test–retest reliability was assessed by calculating intraclass correlation coefficients (ICC) based on the one-way repeated-measures analysis of variance (ANOVA) for the 27 CD wearers who filled in the OHIP-EDENT-MAC Questionnaire twice with 14–18 days between the tasks. The participants did not receive any dental treatment between the sessions.

Validity

Concurrent validity

The concurrent validity was assessed by calculating the Spearman's rank correlation coefficient between the

OHIP-EDENT-MAC summary score and a single question, which was given to participants at the same time with the OHIP-EDENT questionnaire. In a single question participants rated their satisfaction with the existing dentures on a scale from 1 (completely unsatisfied) to 5 (completely satisfied).

Construct validity

The construct validity was assessed by exploratory factor analysis (EFA). The eigenvalue of one was used for factor extraction. The item loading higher than 0.4 was considered successful.

Responsiveness

Responsiveness is the ability of a questionnaire to detect clinical changes elicited by a therapy. For that purpose, 33 participants complaining of loose dentures participated. A specialist of prosthodontics checked flanges and trimmed off excess material if it was present. After that, the dentures were relined chairside using the self-curing resin (GC Hard Reline, GC Corporation, Tokyo, Japan). During the procedure, the patients had to move lips, cheeks, and tongue, and tap the teeth of the maxillary and the mandibular CD together. That was repeated until the material set. After that, the excess material was removed and the CDs were polished in the dental laboratory. The patients were appointed for check-ups for the adjustment of the relined dentures. Seven to 15 days after completing all adjustments, the participants filled out the OHIP-EDENT-MAC questionnaire again. Paired t-test was made to analyze the significance of the differences. The standardized effect size was calculated with the following formula: mean (baseline OHIP-EDENT score – follow up OHIP-EDENT) / standard deviation of the baseline OHIP-EDENT score. According to Cohen, values < 0.2 were considered a trivial effect, 0.2–0.5 a small effect, 0.5–0.8 a moderate effect, and > 0.8 a large effect [10].

RESULTS

Participants in this study were CD wearers whose mean age was 67.27 ± 10.88 years, and 53.1% were females. The description of the participants is shown in Table 2.

Reliability

The Cronbach's α coefficient of the OHIP-EDENT-MAC summary scores showed good reliability (α = 0.892), which exceeded the minimum reliability standard of 0.7. The corrected item-total correlations ranged from 0.309 (item 19) to 0.716 (item 10). All items reached the recommended minimum correlation of 0.2. Test–retest reliability was confirmed by ICC calculation for the OHIP-EDENT-MAC summary score, which was 0.986 (95% confidence intervals ranged 0.968–0.993).

Table 2. Description of the participants

Variable	Frequency
Sex	
Male	45%
Female	55%
Smoking habits	
Yes	46%
No	54%
Ability to live alone	
Yes	96%
No	4%
Employment	
Employed	11%
Retired or unemployed	89%
Education	
Primary school	18%
Vocational school	42%
Secondary school	29%
University degree	11%

Validity

Concurrent validity

The concurrent validity was confirmed by the Spearman's rank correlation coefficient (r = -0.654) between a single question about participants' satisfaction with the existing dentures (dentures were rated 1–5, higher scores represented higher level of satisfaction) and the OHIP-EDENT-MAC summary score.

Construct validity

The Kaiser–Meyer–Olkin measure of sampling adequacy, which was 0.85, and the significance of the Bartlett's test of sphericity (approx. $\chi^2 = 1120.76$; $p < 0.0001$) demonstrated sufficient values to perform the EFA. Factor loadings of the Macedonian version of the OHIP-EDENT questionnaire are shown in Table 3, together with mean values, standard deviations, corrected item-total correlations and Cronbach's α if item deleted. All items had factor loadings above 0.4. The smallest factor loading was 0.47 for item 2 (food catching), while the highest factor loading was 0.75 for item 7 (uncomfortable dentures). The EFA revealed four factors (domains), which accounted for 66.25% of the variance, in both unrotated and rotated matrices. Table 4 shows item distribution after the varimax rotation. Loadings with less than 0.1 are omitted from Table 4.

Responsiveness

In 33 participants who complained on loose dentures, the dentures were relined chairside. Their OHIP Summary score before treatment was 33.09 ± 11.61, and dropped down significantly after the treatment to 24.39 ± 8 ($t = 7.68$; $df = 32$; $p < 0.001$). The standardized effect size was 0.75.

Table 3. Item mean values and standard deviations, corrected item-total correlation, Cronbach's α if item is deleted, and factor loadings of the North Macedonian Oral Health Impact Profile for Edentulous Subjects (OHIP-EDENT) questionnaire

Item	OHIP-EDENT-MAC				
	Mean	SD	Corrected Item-Total Correlation	Cronbach's α if item deleted	Factor loadings
1. Difficulty chewing	2.12	1.24	0.61	0.88	0.65
2. Food catching	1.61	1.11	0.41	0.89	0.47
3. Dentures not fitting	1.83	1.46	0.46	0.89	0.68
4. Painful aching	0.88	1.03	0.51	0.89	0.68
5. Uncomfortable to eat	1.99	1.24	0.64	0.88	0.61
6. Sore spots	1.28	1.16	0.54	0.88	0.74
7. Uncomfortable dentures	1.68	1.39	0.65	0.88	0.75
8. Worried	1.88	1.29	0.64	0.88	0.57
9. Self-conscious	2.13	1.38	0.32	0.89	0.81
10. Avoid eating	1.83	1.24	0.72	0.88	0.65
11. Unable to eat	1.5	1.16	0.54	0.88	0.5
12. Interrupt meals	0.93	1.25	0.61	0.88	0.7
13. Upset	1.83	1.27	0.67	0.88	0.71
14. Embarrassed	1.51	1.21	0.58	0.88	0.69
15. Avoid going out	1.02	1.16	0.45	0.89	0.74
16. Less tolerant	0.31	0.68	0.55	0.89	0.68
17. Irritable with others	0.68	0.9	0.35	0.89	0.64
18. Unable to enjoy company	0.83	1.07	0.33	0.89	0.67
19. Life less satisfying	1.25	1.12	0.31	0.89	0.64

Table 4. Item loadings in the Oral Health Impact Profile for Edentulous Subjects questionnaire after varimax rotation

Rotated Component Matrix				
Item	Component			
	1	2	3	4
1. Difficulty chewing	0.751		0.278	
2. Food catching	0.642	-0.102		0.208
3. Dentures not fitting	0.794		0.146	-0.148
4. Painful aching	0.204		0.775	0.174
5. Uncomfortable to eat	0.696		0.287	0.190
6. Sore spots	0.262		0.809	0.127
7. Uncomfortable dentures	0.805		0.308	
8. Worried	0.519	0.283	0.191	0.430
9. Self-conscious			0.193	0.874
10. Avoid eating	0.686	0.268	0.287	0.156
11. Unable to eat all kinds of food	0.495		0.487	0.121
12. Interrupt meals	0.379	0.144	0.730	
13. Upset	0.432	0.514	0.107	0.502
14. Embarrassed	0.335	0.677		0.347
15. Avoid going out		0.847		0.151
16. Less tolerant	0.259	0.601	0.428	-0.266
17. Irritable with others		0.785	0.112	-0.103
18. Unable to enjoy company		0.818		
19. Life less satisfying	-0.127	0.767		0.162

DISCUSSION

The need to culturally adapt a questionnaire when translated into another language has become very important, especially in international multicenter studies focusing on patient-reported outcome measures assessing self-perceived OHRQoL. Although the adaptation of the OHIP49 (questionnaire with 49 items) has already been provided in the North Macedonia (the OHIP49-MAC Questionnaire), the OHIP questionnaire aimed specifically for edentulous subjects has not been translated and validated yet [9]. A high prevalence of edentulousness among adults over 65 years old was found in North Macedonia, and, therefore, there was a need for cultural adaptation of the OHIP-EDENT questionnaire [11]. It was translated first into the Macedonian language (forward translation) and then back translated, according to the accepted standards. After one native English language speaker confirmed there were no significant differences in the meaning of the back-translated questions, the clarity of the items was discussed with edentulous patients who were prescribed new CDs. They stated that it was easy to understand the questions and to give answers. Therefore, it was possible to continue with further procedures of psychometric validation of the OHIP-EDENT-MAC questionnaire. In fact, the OHIP-DENT-MAC questionnaire showed good internal consistency, indicating that the Macedonian version can measure the desired theoretical construct. Even when one of the items was deleted, Cronbach's α coefficient remained satisfactory far above the value of 0.7. Moreover, the corrected item-total correlations were well above the recommended level of 0.2. Reliability was also confirmed by high ICC of the OHIP-EDENT-MAC summary scores, pointing out a high degree of agreement when filling in the same questionnaire on two separate occasions, without any treatment provided between them. A period of 14 days was considered long enough for the participants to forget the questions from the first completion of the questionnaire, similar to the strategy of other studies [9, 12–15].

Concurrent validity of the Macedonian version of the OHIP-EDENT questionnaire was confirmed by significant negative Spearman's rank correlation coefficient between the OHIP-EDENT summary scores and a degree of satisfaction with dentures (the higher the degree of satisfaction with the dentures, the lower the OHIP-EDENT-MAC summary score was registered). Construct validity was confirmed by high item loadings. The EFA analysis was used to assess the latent structure of the data. It identified only four domains, explaining 66.25% of the variability. None of the studies performing EFA could not find the originally proposed seven domains of the OHIP-EDENT, and concluded that the proposed seven domains had actually been based on the expert's opinion [16]. However, Japanese version did not provide EFA [17]. The items of the Macedonian OHIP-EDENT questionnaire actually clustered around the domains describing masticatory function (factor 1, Table 4), pain

(factor 3, Table 4), social impact (factor 2, Table 4), and psychological impact (factor 4, Table 4). However, more research will be necessary, even introduction of some additional items focused on orofacial esthetics into the OHIP-EDENT questionnaire to construct a new tool for edentulous population which would fit into the recently developed four-dimensional model of the oral health quality of life, together with the CFA [18, 19, 20].

Responsiveness of a questionnaire actually measures its sensitivity in a changed environment (e.g., changes elicited by a therapy). For that purpose, the dentures were relined in patients complaining of loose CDs after thorough examination of the respective dentures by a specialist of prosthodontics, who proposed and performed the therapy. Seven days after the denture adjustments due to sore spots had been completed, participants again filled out the questionnaire. The summary scores, as expected, dropped significantly, pointing out good responsiveness of the Macedonian OHIP-EDENT version. The effect size was 0.75, which represented a moderate effect. However, even when the dentures fit better, the patients still have difficulties inherent to complete denture wearing [21, 22, 23]. It is well known that dental implant placement improves denture support and elicits much larger effect size than a therapy which includes only a relining procedure [24–30]. The limitation of the present study may be in the fact that only summary scores of the OHIP-EDENT-MAC questionnaire were analyzed. Each of the proposed seven domains was not analyzed separately. However, the EFA of the OHIP-EDENT-MAC found only four domains of the questionnaire, and therefore it was decided to use only summary scores. Another limitation may be a diversity in patients' age and educational level, which also might have influenced the self-reported outcome measures.

CONCLUSION

The evaluation of the psychometric properties of the Macedonian language version of the OHIP-EDENT showed satisfactory cultural adaptation which provides evidence that the OHIP-EDENT-MAC can be used for the assessment of OHRQoL in edentulous population in North Macedonia.

Conflict of interest: None declared.

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Психометријске карактеристике северномакедонске верзије упитника *Oral Health Impact Profile* за безубе пацијенте

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САЖЕТАК

Увод/Циљ Мерења исхода лечења у области квалитета живота повезана са оралним здрављем су веома важна, нарочито у специфичним популацијама као што су безуби пацијенти.

Циљ студије био је да се прилагоди инструмент Профил утицаја оралног здравља (*Oral Health Impact Profile – OHIP-EDENT*) у културном окружењу Северне Македоније.

Методе У студији је адаптирана оригинална верзија упитника *OHIP-EDENT* за безубе пацијенте од 19 питања. У складу са међународним стандардима, након превода *напред-назад*, упитник је психометријски тестиран код 109 носилаца тоталних протеза.

Резултати Коефицијент Кронбахове алфе од 0,892 показао је добру унутрашњу конзистенцију. Тест–ретест поузданост је потврђена високом унутрашњом корелацијом укупног скора (0,986; уз 95% интервал поузданости 0,968–0,993). Конкурентна валидност је потврђена Спирмановим корелационим коефицијентом (r = -0,654) између укупног скора тестираног упитника и једног питања којим је оцењено задовољство постојећим протезама на скали 1–5 (1 = незадовољавајуће, 5 = потпуно задовољавајуће). Конструкциона валидност је потврђена помоћу експлораторне анализе фактора. Оптерећење свих питања је било изнад 0,4. Питања су се груписала у четири фактора (димензије), што је објаснило 66,25% варијансе како у неротираним тако и у ротираним матрицама. Добра респонзивност је потврђена код 33 пацијента након подлагања тоталне протезе. Њихов укупни скор упитника *OHIP*-19 (33,09 ± 11,61) био је значајно смањен (t = 7,68; df = 32; p < 0,001) после третмана (24,39 ± 8,0). Стандардизован ефекат величине је био 0,75, што представља умерени до велики ефекат.

Закључак Упитник *OHIP-EDENT-MAC* показао је задовољавајуће психометријске карактеристике и показао могућност за његову употребу код безубе популације Северне Македоније.

Кључне речи: упитник *OHIP-EDENT*; психометрија; поузданост; респонзивност валидности; Северна Македонија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparative analysis of International Prognostic Index for Chronic Lymphocytic Leukemia, progression-risk score, and MD Anderson Cancer Center 2011 score – a single center experience

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SUMMARY

Introduction/Objective Prognostication of chronic lymphocytic leukemia (CLL) has been substantially improved in recent times. Among several prognostic models (PMs) focused on the prediction of time to first treatment (TTFT), progression-risk score (PRS), and MD Anderson Cancer Center score 2011 (MDACC 2011) are the most relevant, while CLL-International Prognostic Index (CLL-IPI), although originally developed to predict overall survival (OS), is also being used to estimate TTFT. The aim of this study was to investigate CLL-IPI, PRS, and MDACC 2011 prognostic values regarding TTFT and OS.

Methods The analyzed cohort included 57 unselected Serbian CLL patients from a single institution, with the basic characteristics reflecting more aggressive disease than in the general *de novo* CLL population. The eligible patients were assigned investigated PMs, and TTFT and OS analyses were performed.

Results Patients with higher risk scores according to CLL-IPI, PRS, and MDACC 2011 underwent treatment significantly earlier than patients with lower risk scores ($p = 0.002$, $p = 0.019$, and $p < 0.001$, respectively). In multivariate analysis, MDACC 2011 and CLL-IPI retained their significance regarding TTFT ($p = 0.001$ and $p = 0.018$, respectively), while PRS did not. CLL-IPI was the only significant predictor of OS both at the univariate ($p = 0.005$) and multivariate ($p = 0.013$) levels.

Conclusion CLL-IPI, PRS, and particularly MDACC 2011 are able to predict TTFT even in cohorts with more advanced-disease patients, while for prediction of OS, CLL-IPI is the only applicable among the three PMs. These results imply that PMs should be investigated in more diverse CLL populations, as it is in real-life setting.

Keywords: chronic lymphocytic leukemia; CLL-IPI score; progression risk score; MDACC 2011 score; overall survival; time to first treatment

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia of adults in Western countries, affecting predominantly elderly individuals with the median age of 72 years at diagnosis [1]. Up to 80% of patients are asymptomatic at the time of diagnosis, without indication for treatment [2, 3]. However, most of them will require therapy sooner or later during their disease course, with various outcomes, from refractoriness to long-lasting remissions. Heterogeneity of the clinical course of CLL stems from variability of clinical and biological features of both leukemic clones and hosts, which consequently imposes the need of personalized treatment approach [4].

In an attempt to refine the prognosis for individual patients, different prognostic models (PMs) have been developed. Forty years ago, Rai and Binet staging systems were established for risk stratification of CLL patients by estimating tumor burden using only physical examination and complete blood count [5, 6]. Although they are easily applicable and widely used, these staging systems do not reflect biological diversity of the disease, which limits their accuracy in predicting the disease course and outcome.

During the last two decades, a number of biological and genetic markers with major prognostic significance in CLL have been discovered, such as chromosomal aberrations (del13q, del17p, del11q, trisomy 12) mutational status of *TP53* and immunoglobulin heavy variable (*IGHV*) genes [7, 8]. Some of them have been, in combination with clinical variables, incorporated into different PMs aiming to predict time

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to first treatment (TTFT), response to particular therapies, and overall survival (OS) [4, 9, 10].

Wierda et al. [11] and Gentile et al. [12] proposed PMs that are able to identify patients with increased risk for treatment commencement among early-stage CLL patients. The former authors introduced MD Anderson Cancer Center 2011 score (MDACC 2011), a nomogram involving unfavorable cytogenetics (del11q and del17p), *IGHV* mutational status, level of lactate dehydrogenase (LDH), size of the largest cervical lymph node (LN) and the number of enlarged LNs. These markers were combined in a complex formula used to calculate the score value for each patient [11]. The latter authors proposed the progression-risk score (PRS), a simple multivariate model which stratifies patients into three risk categories based on stage, absolute lymphocyte count (ALC), serum β_2-microglobulin (β_2m), and *IGHV* mutational status [12, 13].

Recently, the International CLL-IPI Working Group introduced the International Prognostic Index for CLL (CLL-IPI), which resulted from a comprehensive meta-analysis of individual patient data, with the aim to predict the overall survival [14]. Patients were stratified into four risk groups (low, intermediate, high, very high) depending on the status of five variables: age, stage, β_2m, *IGHV* mutational status, and *TP53* status (mutation of *TP53* and/or del17p) [14].

All the mentioned PMs exert good discriminative power between risk-groups regarding either TTFT, OS, or both [14–22]. Even though CLL-IPI emerged as the most relevant one, each of these PMs can be taken into consideration depending on individual center's best practice and possibilities.

It is noteworthy that, for the purpose of TTFT prediction, these PMs have been developed within the cohorts of mostly early-stage patients [11, 12, 14]. Having in mind that, at most centers, genetic analyses necessary for all three scores are not being routinely performed at diagnosis but prior to first therapy, it is of great importance to test PMs in real-life settings [3, 23].

The objective of this study was to compare the prognostic strength of CLL-IPI, PRS, and MDACC 2011 in a cohort of CLL patients treated at a single institution.

METHODS

Study group

A total of 57 CLL patients diagnosed, treated, and followed at the Clinic of Hematology, University Clinical Center of Serbia, (Belgrade, Serbia) 2005–2018 were retrospectively analyzed for parameters within CLL-IPI, PRS, and MDACC 2011. All standard demographic, clinical, and laboratory characteristics were determined at diagnosis, while molecular and genetic markers were determined during the period from diagnosis to first treatment.

The number of patients enrolled in this study was limited by the availability of clinical and molecular data, mainly due to the following reasons: 1) analyses of *IGHV* mutational status, cytogenetic abnormalities and *TP53* mutational status are being performed after setting the indications for treatment, noting that *IGHV* and *TP53* mutational analyses are still not being routinely done at our institution; 2) some of the methods, such as determination of *IGHV* and *TP53* mutational status, were introduced in our institution in 2012 so, for the purpose of this study, we performed these analyses retroactively in patients for whom we had stored pretreatment blood samples.

Common cytogenetic abnormalities associated with CLL (del13q, del17p, del11q, trisomy 12) were detected by fluorescence *in situ* hybridization (FISH). The *TP53* mutational status was determined as recommended in Pospisilova et al. [24]. The *IGHV* mutational status was analyzed as recommended in Ghia et al. [25].

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the University of Belgrade Faculty of Medicine, Belgrade, Serbia (reference number: 29/XII-6) and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Scoring

In order to stratify patients according to CLL-IPI, 1 point was assigned for age > 65 years and stage Binet B–C or Rai I–IV, 2 points for β_2m concentration > 3.5 mg/L and unmutated *IGHV*, and 4 points for the presence of *TP53* mutation and/or del17p. Patients with score ≤ 1 were defined to be low-risk, score 2–3 intermediate-risk, score 4–6 high-risk, and score 7–10 very high-risk [14]. Thirty-eight patients with complete data were assigned CLL-IPI.

PRS was determined in 28/57 patients by scoring four variables: 1 point for Rai stage I–II and 2 points for ALC $\geq 10 \times 10^9$/L, elevated β_2m, and unmutated *IGHV* [12]. Patients with Rai stage III and IV, and those with incomplete data could not be assigned PRS. Low (score 0–2), intermediate (score 3–5), and high-risk (score 6–7) patients were defined by this PM.

MDACC 2011 score was determined in 42/57 patients using the original formula from Wierda et al. [11].

Statistical analysis

Quantitative variables are expressed as medians with 25th–75th percentiles. Categorical data are presented by absolute numbers with percentages. Kolmogorov–Smirnov test was used to assess the data distribution. TTFT was defined as the time from the diagnosis to the first therapy line. Overall survival was defined as time from diagnosis to death from any cause or the last follow-up. The estimates and graphical presentation of TTFT differences were performed via Kaplan–Meier approach. Univariate and multivariate Cox regression analysis was used to identify predictors of TTFT and OS. Variables significant in univariate analysis were entered to multivariate analysis. Hazard ratio (HR) with corresponding 95% confidence interval (CI) is presented for all evaluated predictors. All statistical tests were two

sided. Statistical analysis was performed using the SPSS 21.0 software (IBM Corp., Armonk, NY, USA). In all tests, p value < 0.05 was considered statistically significant.

RESULTS

Description of the cohort

Median age at diagnosis was 56.5 years (range 38–75 years). The cohort consisted of 41 male and 16 female patients (M:F = 2.6:1) and all of them underwent treatment after the median TTFT of 5.5 months (range 0–71 months). All patients received fludarabine-based therapy, 47 of them (82%) in the first treatment line. The remaining 10 patients (18%) were treated in the first line as follows: chlorambucil monotherapy (four patients), cyclophosphamide, vincristine, and prednisone (CVP) (four patients), alemtuzumab (one patient), and splenectomy (one patient). Overall response rate to the first treatment line was 79% (41% achieved complete response and 38% partial response), and 21% were unresponsive (12% stable disease and 9% progressive disease). After the first therapeutic line, 48 patients (84%) experienced disease progression, seven patients (12%) remained in the first remission until the last check-up or disease-unrelated death, and two patients (4%) were lost after completion of the first therapy. During the median follow up of 71.5 months (range 4–142 months), 14 patients (25%) were still alive, while 38 patients (67%) died (five patients were lost to follow-up). Median OS was 77 months (95% CI 69–85 months). Cohort characteristics are given in Table 1.

Assessment of risk

Patients were scored by CLL-IPI, PRS, and MDACC 2011 as described in the Methods section. Considering the fact that there were no patients in the low-risk group according to CLL-IPI and only two low-risk patients according to PRS, for the purpose of TTFT and OS analysis, patients were divided into two risk groups regarding these two PMs: intermediate risk and high / very high risk by CLL-IPI, and low/intermediate and high risk by PRS. In regard to the MDACC 2011, the cohort was dichotomized by the median score value of 53.6 (range 14.2–75). Proportions of patients in each risk group are given in Table 2.

Prediction of TTFT by CLL-IPI, PRS, and MDACC 2011

Higher score values of CLL-IPI and PRS, as well as MDACC 2011 > 53.6, were significant predictors of shorter TTFT in the univariate analysis. Namely, an increase of CLL-IPI and PRS by 1 score point increased the risk of treatment commencement by approximately 1.4 times (HR 1.385; 95% CI 1.121–1.710; p = 0.002 for CLL-IPI and HR 1.414; 95% CI 1.060–1.888; p = 0.019 for PRS). Cox regression analysis identified MDACC 2011 as the strongest predictor of TTFT (HR 1.046; 95% CI 1.020–1.073; p < 0.001) (Table 3).

Table 1. Clinical and biological characteristics of chronic lymphocytic leukemia patients

Characteristics	Patients (%)	Median (Q1, Q3)
Age		56.5 (52.2–65.7)
< 50	9 (16.1)	
50–65	33 (58.9)	
> 65	14 (24.6)	
Sex		
male	41 (71.9)	
female	16 (28.1)	
ALC (x10^9/L)		38.9 (16.1–83.9)
< 10	5 (10.4)	
≥ 10	43 (89.6)	
Hemoglobin (g/L)		128 (114.5–144.5)
≤ 100	7 (14.0)	
> 100	43 (86.0)	
Platelet count (× 10^9/L)		174.5 (112–226.3)
≤ 100	10 (20)	
> 100	40 (80)	
β_2-microglobulin (mg/L)	39 (68.4)	3.98 (2.78–4.86)
LDH (IU/L)	47 (82.5)	383 (315–592)
Lymph node of maximal size (cm)		
< 5	41 (77.4)	
≥ 5	12 (22.6)	
Rai		
0	5 (9.1)	
1–2	38 (69.1)	
3–4	12 (21.8)	
Binet		
A	18 (32.7)	
B/C	37 (67.3)	
CLL score[#]		
3	1 (2)	
4	10 (20.4)	
5	38 (77.6)	
CD38		
Positive (≥ 30%)	19 (36.5)	
Negative (< 30%)	33 (63.5)	
Type of infiltration		
nodular/interstitial	16 (32)	40 (40–58)
diffuse	34 (68)	80 (80–90)
IGHV		
mutated	11 (19.6)	
unmutated	45 (80.4)	
FISH		
del13q/trisomy12/ normal	44 (77.2)	
del11q	10 (17.5)	
del17p	3 (5.3)	
TP53		
wild-type	48 (84.2)	
mutated	9 (15.8)	

Q1 – quartile 1; Q3 – quartile 3; ALC – absolute lymphocyte count; LDH – lactate dehydrogenase; *IGHV* – immunoglobulin heavy variable gene; FISH – fluorescent *in situ* hybridization; CLL – chronic lymphocytic leukemia; [#]Matutes score

Table 2. Scoring of patients according to the CLL-IPI, PRS, and MDACC 2011

Risk assessment	Patients (%)	GfA*
CLL-IPI		
Low	/	
Intermediate	15 (39.5)	15 (39.5)
High	20 (52.6)	23 (60.5)
Very high	3 (7.9)	
PRS		
Low	2 (7.1)	11 (39.3)
Intermediate	9 (32.1)	
High	17 (60.7)	17 (60.7)
MDACC 2011		
≤ median#	21 (50)	
> median	21 (50)	

CLL-IPI – International Prognostic Index for Chronic Lymphocytic Leukemia; PRS – progression-risk score; MDACC 2011 – MD Anderson Cancer Center 2011 score;
*grouping for Kaplan–Meier analysis of time to first treatment and overall survival;
#median score value of MDACC 2011 was 53.6

The ability of these three PMs to predict TTFT was also tested by the Kaplan–Meier method. The patients were firstly dichotomized regarding calculated risk across all three examined PMs (Table 2). It was demonstrated that median TTFTs in groups of higher risk of CLL-IPI, PRS, and MDACC 2011 were three, six, and one month, respectively, as opposed to median TTFTs in groups of lower risk being 21, 38, and 20 months, respectively. The analysis confirmed a strong association between both PRS and MDACC 2011 and treatment-free period (p = 0.007 for PRS and p = 0.001 for MDACC 2011), while CLL-IPI exhibited a trend toward statistical significance (p = 0.074) (Figure1).

At the multivariate level, MDACC 2011 and CLL-IPI emerged as the significant predictors of TTFT (HR 1.051; 95% CI 1.019–1.083; p = 0.001 and HR 1.493; 95% CI 1.071–2.083; p = 0.018, respectively), while PRS did not show statistical significance (Table 3).

Prediction of OS by CLL-IPI, PRS, and MDACC 2011

CLL-IPI appeared to be a significant predictor of OS at the univariate level (HR 1.405; 95% CI 1.110–1.778; p = 0.005), PRS exhibited borderline significance (HR 1.473; 95% CI 0.997–2.177; p = 0.052), while MDACC 2011 was not significant. Multivariate analysis emphasized CLL-IPI as the only significant predictor of OS among three examined PMs (HR 1.657; 95% CI 1.113–2.468; p = 0.013) (Table 3).

DISCUSSION

The anticipation of the disease course has emerged as one of the main goals in the management of CLL and foundation of personalized treatment approach. Baseline clinical, biological and molecular characteristics of individual patients are being used in different patterns in order to predict the disease progression. With this aim, several prognostic models (PMs) have been developed recently, primarily for predicting TTFT and OS [9–12, 14, 26].

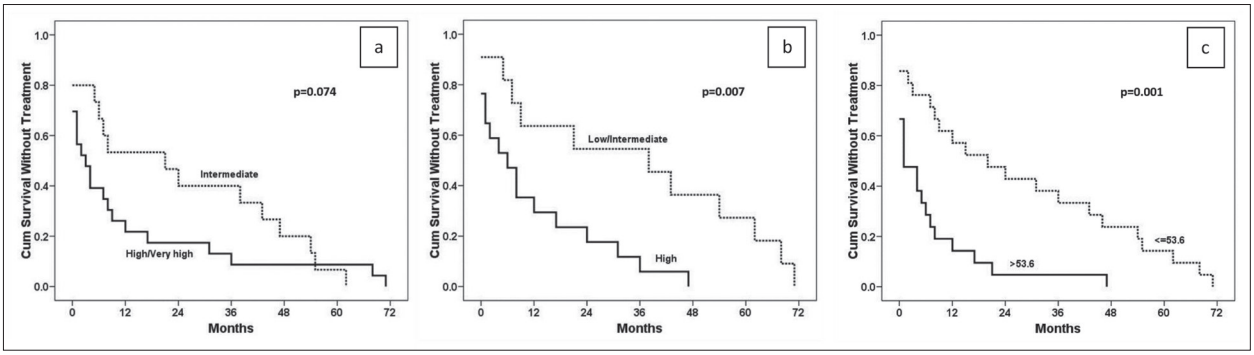

Figure 1. Analysis of time to first treatment for patients stratified according to CLL-IPI (a), PRS (b), and MDACC 2011 (c); for the purpose of Kaplan–Meier analysis, the patients were grouped into two risk categories according to each prognostic model: CLL-IPI – intermediate vs. high / very high (no patients in the low-risk group); PRS – low/intermediate vs. high; MDACC 2011 – the patients were dichotomized by the median score value of 53.6;
(a) CLL-IPI: median TTFT for patients with intermediate risk was 21 months and for high / very high risk three months.
(b) PRS: median TTFT for patients with low/intermediate risk was 38 months and for high risk six months.
(c) MDACC 2011: median TTFT for patients with MDACC 2011 ≤ 53.6 was 20 months and for patients with MDACC 2011 > 53.6 it was one month;
CLL-IPI – International Prognostic Index for Chronic Lymphocytic Leukemia; PRS – progression-risk score; MDACC 2011 – MD Anderson Cancer Center 2011 score

Table 3. Cox regression analysis of the time to first treatment and the overall survival

Score types	Time to first treatment						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI
CLL-IPI	**0.002**	1.385	1.121–1.710	**0.018**	1.493	1.071–2.083	**0.005**	1.405	1.110–1.778	**0.013**	1.657	1.113–2.468
PRS	**0.019**	1.414	1.060–1.888	/	/	/	0.052	1.473	0.997–2.177	/	/	/
MDACC 2011	**< 0.001**	1.046	1.020–1.073	**0.001**	1.051	1.019–1.083	0.167	1.019	0.992–1.047	/	/	/

HR – hazard ratio; CI – confidence interval; CLL-IPI – International Prognostic Index for Chronic Lymphocytic Leukemia; PRS – progression-risk score; MDACC 2011 – MD Anderson Cancer Center 2011 score

In this study, we analyzed a cohort of CLL patients from a single institution for variables that constitute CLL-IPI, PRS, and MDACC 2011 PMs.

Regarding TTFT, our results confirmed high predictive value of all three PMs, underscoring MDACC 2011 as the most significant one. Patients from the analyzed cohort with MDACC 2011 > 53.6 were treated one month after diagnosis, while those with ≤ 53.6 remained asymptomatic for almost two years. It should be noted that the patients included in our cohort exhibited more aggressive clinical course than patients from the cohorts analyzed to date regarding this issue. This aggressiveness is reflected in the fact that our patients were predominantly of intermediate and high risk according to the CLL-IPI and PRS. Also, a median of MDACC 2011 in our cohort was 53.6, which is considerably higher than that in the original MDACC or other validating cohorts [11, 15, 27]. Moreover, the proportion of patients with unmutated *IGHV* was 80%, higher than in the general CLL population (45–65%) [11, 14, 28, 29, 30]. Hence, it is not surprising that all our patients fulfilled criteria for treatment initiation after a median of 5.5 months, and most of them died during the median follow-up of around six years. Along with considerably younger median age at diagnosis in comparison with the general CLL population, the cohort's characteristics are the consequence of the following issues: 1) the majority of the patients were sampled for molecular and cytogenetic analysis and/or for biobanking shortly before the first treatment line, which made only patients with active disease eligible for this study. Knowing that approximately 40% of CLL patients never fulfill the criteria for treatment commencement, we may speculate that these patients carry favorable biological profile, while among those with active disease, unfavorable molecular characteristics are to be expected [31]; 2) as our institution represents the largest tertiary hematology center in Serbia, to which patients from the inner parts of the country are being referred as they develop active disease, this consequently concentrated patients with high tumor burden and more adverse biological features. High proportion of patients younger than in a typical CLL population is consistent with the data showing that younger CLL patients carry more unfavorable biological profile and experience shorter time to treatment [32]. Nevertheless, all three PMs analyzed in this study (CLL-IPI, PRS, and MDACC 2011) predicted shorter TTFT in higher *vs*. lower risk groups (three *vs*. 21 months, six *vs*. 38, and one *vs*. 20, respectively). Multivariate analysis pointed out MDACC 2011 as the strongest predictor of TTFT.

To the best of our knowledge, this is the second study that made comparison between CLL-IPI and MDACC 2011 concerning TTFT prediction, after a comparative study of five PMs by Molica et al [19]. In this research, the authors demonstrated a slight superiority of PRS over four other PMs, among which were MDACC 2011 and CLL-IPI. When focusing on the comparison between MDACC 2011 and CLL-IPI, the result was in favor of MDACC 2011, which is consistent with our findings [19]. In addition, this study clearly showed that PMs defined by both clinical and genetic parameters are more precise in predicting TTFT than those incorporating only variables that indicate tumor burden [17, 21]. When comparing these PMs with regard to TTFT, it should be noted that CLL-IPI was primarily designed to predict OS in contrast to MDACC 2011 and PRS, which were developed to estimate therapy-free period [11, 12, 14]. Although MDACC 2011 and PRS have been developed and validated within the cohorts of mostly early-stage, asymptomatic CLL patients, our results suggest that their use among patients with more advanced disease is equally valuable. Of note, a novel PM named International Prognostic Score for Early CLL (IPS-E) has been developed and externally validated recently [33]. It successfully discriminates patients in early-stage CLL considering TTFT using only three variables: *IGHV* mutational status, ALC > 15×10^9/L, and palpable lymph nodes. Smolej et al. [34] even proposed modified IPS-E called AIPS-E containing *IGHV* mutational status, FISH, and ALC. These newest PMs strongly support the use of combined biological and clinical features in CLL prognostication.

Regarding overall survival, in our cohort CLL-IPI was demonstrated to be a significant predictor of OS at both univariate and multivariate levels, PRS showed borderline significance only in the univariate analysis, while MDACC 2011 was not significant. As mentioned previously, PRS and MDACC 2011 have not been originally designed for prediction of OS and were developed within the cohorts of patients not requiring treatment at the time of study recruitment, while CLL-IPI was built upon participants of prospective treatment trials, which included predominantly symptomatic patients [11, 12, 14]. However, bearing in mind that similar clinical and genetic variables are used for construction of all three PMs, the question arises whether PRS and MDACC 2011 could also be used in estimating OS. Looking into variables of PRS and MDACC 2011, one can notice that three out of four variables of PRS (stage, ALC, and β_2m), and five out of six variables of MDACC 2011 (del11q, del17p, LDH, number of enlarged LNs, and size of the largest cervical LN) may evolve from the time of asymptomatic disease to the moment of the first therapy. Taken that into account, and based on our results, we speculate that MDACC 2011 is probably inapplicable in terms of OS prediction. On the other hand, PRS showed borderline significance with regard to OS, which implies that in a modified manner (i.e., inclusion of patients with advanced stage, higher threshold for ALC) PRS could be investigated also in terms of OS prediction.

The main limitation of our study is the small number of patients in the cohort, which challenges the reliability of the results. Atypical age and prognostic data distribution in comparison with general CLL population represent one center experience which we used to show that even in the circumstances of more aggressive features of the disease, examined PMs may separate the patients in need for immediate or very soon treatment from those who will be stable and free of therapy for some period of time. Nevertheless, studies on larger cohorts of patients with a more aggressive disease profile need to confirm these findings.

CONCLUSION

What is the purpose of anticipating TTFT in patients with CLL? Earlier attempts to treat asymptomatic CLL patients resulted only in extended event-free survival, without impact on OS. However, the development of new targeted therapies and their proven efficacy in high-risk patients, along with the advances in risk stratification, reopened the door for early interventional trials.

PMs consisting of both clinical and genetic variables seem to be efficient enough to predict TTFT. In our cohort, high CLL-IPI, PRS and particularly MDACC 2011 values clearly designated patients who would experience short TTFT, implying that they could be good candidates for interventional treatment. Predicting TTFT will be crucial if research on the early interventional trials in the era of novel targeted drugs demonstrates survival benefit for intermediate and high-risk patients. Until then, improvement of PMs by incorporation of new genetic markers remains an achievable and realistic goal.

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Authors Biljana Mihaljević and Vojin Vuković contributed equally to this article.

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Упоредна анализа интернационалног прогностичког индекса за хроничну лимфоцитну леукемију, скора ризика од прогресије и скора Центра за рак *MD Anderson* – искуство једног центра

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САЖЕТАК

Увод/Циљ Прогноза хроничне лимфоцитне леукемије (ХЛЛ) значајно је унапређена у последње време. Међу неколико прогностичких модела чији је циљ предвиђање времена до прве терапије (енг. *TTFT*) издвајају се скор ризика од прогресије (енг. *PRS*) и скор Центра за рак *MD Anderson* из 2011. год. (енг. *MDACC* 2011), док се интернационални прогностички индекс за ХЛЛ (енг. *CLL-IPI*), иако примарно установљен за предикцију укупног преживљавања (енг. *OS*), добро показао и у предикцији *TTFT*. Циљ овог рада је да се испита значај поменутих прогностичких модела у погледу предвиђања *TTFT* и *OS*.

Методе Анализирана кохорта је обухватила 57 неселектованих болесника са ХЛЛ Универзитетског клиничког центра Србије са просечно агресивнијим профилом болести у односу на општу популацију *de novo* болесника са ХЛЛ. Болесници су оцењивани према наведеним скоровима уз анализу *TTFT* и *OS*.

Резултати Болесници са вишим вредностима *CLL-IPI*, *PRS* и *MDACC* 2011 примили су прву терапију значајно раније у поређењу са болесницима са нижим вредностима ових скорова ($p = 0,002$, $p = 0,019$ и $p < 0,001$, редом). У мултиваријантној анализи, *MDACC* 2011 и *CLL-IPI* су задржали прогностички значај у предикцији *TTFT* ($p = 0,001$, односно $p = 0,018$), док је *PRS* овај значај изгубио. *CLL-IPI* је био једини значајан предиктор *OS* у униваријантној ($p = 0,005$) и у мултиваријантној анализи ($p = 0,013$).

Закључак *CLL-IPI*, *PRS* и нарочито *MDACC* 2011 су добри предиктори *TTFT* чак и у кохортама болесника са агресивнијом болешћу, док је за предикцију *OS* од ова три прогностичка модела *CLL-IPI* једини применљив. Ови резултати показују да би прогностичке моделе требало испитати на болесницима са ХЛЛ у различитим фазама болести, какви се срећу у реалној клиничкој пракси.

Кључне речи: хронична лимфоцитна леукемија; скор *CLL-IPI*; скор *PRS*; скор *MDACC* 2011; укупно преживљавање; време до прве терапије

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Beta-2 microglobulin removal with postdilution online hemodiafiltration – comparison of three different dialysis membranes

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SUMMARY

Introduction Accumulation of middle molecular weight uremic toxins causes various complications in chronic hemodialysis (HD) patients. Postdilution online hemodiafiltration (OL-HDF) efficiently removes these molecules.

This study aimed to assess the effectiveness of three different dialysis membranes in removing β_2-microglobulin (β_2m) within a single session of postdilution OL-HDF.

Method A prospective single-center study was carried out in 30 patients (23 males and seven females, average age 54.87 ± 11.66 years, time on dialysis 4.95 ± 5.4 years) on maintenance HD. Each patient was followed for three consecutive weeks on OL-HDF with three different dialyzers: DiacapPro 19H, FX CorDiax 800, and Elisio 21H, randomly switched weekly. The reduction ratios (RR) of β_2m and albumin were compared individually. The results were analyzed with the Kolmogorov–Smirnov test, ANOVA, and the Kruskal–Wallis test.

Results The average convective volume for all patients was 21.38 ± 2.97 L/session. β_2-m RR was 70.86 ± 6.87%, 74.69 ± 6.51%, and 70.04 ± 9.37% with Diacap Pro 19H, FX CorDiax 800 and Elisio 21H membrane, respectively (p = 0.054). Albumin RR was 6.20 ± 2.12% with Diacap Pro 19H membrane, 6.01 ± 2.97% with FX CorDiax 800 membrane, and 6.46 ± 2.91% with Elisio 21H membrane (p = 0.812). Albumin loss was < 4 g/dialysis treatment for all membranes.

Conclusion All investigated membranes effectively remove β_2-m in postdilution OL-HDF with a tolerable albumin loss. The highest β_2-m RR was determined for FX CorDiax 800 membrane, but with no statistically significant difference.

Keywords: uremic toxins; middle molecules; albumin; β_2-microglobulin; dialyzer; hemodiafiltration

INTRODUCTION

End-stage renal failure patients requiring maintenance hemodialysis (HD) exhibit significant retention of uremic toxins. Small, water-soluble molecules, weighing up to 500 Da and not bound to protein carriers are readily cleared with HD. However, larger and/or protein-bound uremic toxins are much more difficult to remove [1]. The "middle molecules," having a molecular weight 500–60,000 Da, include several cytokines, adipokines, growth factors, and signaling proteins, such as interleukin-1β, interleukin-6, interleukin-18, tumor necrosis factor α, β_2-microglobulin (β_2m), pentraxin-3, YKL-40, and leptin. They have diverse biological roles and are associated with chronic inflammation, cardiovascular disease, and other complications in HD patients [1]. Microinflammation, malnutrition, and oxidative stress are important non-traditional risk factors for the development of atherosclerosis and resistance to erythropoietin [1–5].

Conventional HD with high-flux membranes has very limited efficiency in removing larger middle molecules [1]. Modalities employing convective transport, such as online hemodiafiltration (OL-HDF), enable enhanced removal of large uremic toxins, thus achieving cardioprotective effect and improving outcomes for HD patients [6, 7, 8]. The efficiency of HDF in middle molecules removal depends on the overall convective volume (Vconv), which is related to vascular access blood flow (Qavf), effective blood flow (Qb), and membrane properties [6, 7, 8]. Contemporary HDF membranes have a high ultrafiltration coefficient (Kuf > 40 ml/h × mmHg), sieving coefficient for β_2m > 0.6, sieving coefficient for albumin < 0.01 to prevent albumin loss over 4 g / 4 hour session, internal capillary diameter > 200 μm and capillary density per surface area > 11,000 allowing for dialysate flow (Qd) of 400–500 mL/minute [6, 7, 8]. Vconv represents the sum of the substitution volume and the net ultrafiltration volume achieved to correct extracellular fluid overload. Vconv target should be ≥ 22L per dialysis session to achieve a convection dose target [6, 7, 8].

In clinical practice, the efficiency of HDF treatment in clearing middle molecules is assessed by determining serum β_2m levels before

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and after the procedure. β_2m is a water-soluble polypeptide, made of 99 amino-acid residues, with a molecular weight of 11,815 Da. Its plasma levels increase with age in healthy individuals related to the physiological decrease in glomerular filtration rate over 50 years of age. The substance was first discovered some 50 years ago after being isolated from the urine of patients with tubular proteinuria due to chronic cadmium poisoning [9]. Nevertheless, its significance in dialysis patients was only acknowledged 15 years later, when it was isolated as a major component of the amyloid substance in dialyzed individuals, predominantly targeting the cartilage of osteoarticular tissue [10]. The incidence of dialysis-related amyloidosis increases with patients' age and longer dialysis vintage. The Japanese Society for Dialysis Therapy recommends achieving maximum predialysis serum β_2m concentration < 30 mg/L, but preferably < 25 mg/L to attenuate the development of this condition [11]. Also, β_2m seems to be significantly associated with mortality in maintaining HD patients [12].

This study aimed to assess the effectiveness of three different dialysis membranes in removing the middle molecule uremic toxin, β_2m, with postdilution OL-HDF.

METHODS

This prospective, single-center study was carried out among 30 patients treated with maintenance postdilution OL-HDF at the Center for Nephrology and Dialysis, Kragujevac University Clinical Center. The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Kragujevac University Clinical Center (Decision No 01-20-765). All the patients gave their informed consent for participation.

All the patients were receiving regular maintenance HDF program on Fresenius 5008S (Fresenius Medical Care, Bad Homburg, Germany), Gambro Artis (Baxter Gambro Dasco S.p.a., Medolla, Italy) and B. Braun Dialog+ (B. Braun Avitum AG, Melsungen, Germany) machines with controlled ultrafiltration, thrice weekly, with routine dialysis parameters: dialysis time four hours, dialysis buffer with bicarbonate, Qb range 257 ± 18.65 mL/minute and Qd of 500 mL/minute. Blood flow and Qd were not changed for any patient throughout the follow-up. The standard ultrapure dialysis fluid (bacterial count < 0.1 CFU/L and endotoxin content < 0.03 EU/mL) was used with dialysate temperature set at 37°C and sodium level of 140 mmol/L, potassium 2 mmol/L, magnesium 0.5 mmol/L, and calcium 1.25 mmol/L, 1.5 mmol/L or 1.75 mmol/L. The average Vconv was 21.38 ± 2.97 L per dialysis session (Table 1). All the patients were dialyzed through an arteriovenous fistula. The anticoagulation used was heparin sodium at an average dose of 4508.32 ± 541.92 IU per HDF session. Orders for anticoagulation type, dosage, and administration regimen (bolus injection and continuous infusion) remained unchanged. The patients received treatment with different erythropoiesis-stimulating agents (epoetin-α, epoetin-β, darbepoetin-α). All the patients were anuric with a diuresis of < 50 mL/day. Patients with an active infection, current bleeding issue, or on immunosuppressive therapy were not included in this investigation.

Table 1. Dialysis-related parameters in the investigated population

Variable	Mean ± SD
Qnuf (mL/min)	11.74 ± 3.9
Qsubs (mL/min)	80.64 ± 14.2
Qconv (mL/min)	92.37 ± 13.39
Vsubs (L)	18.58 ± 3.2
Vconv (L)	21.38 ± 2.97
FF (%)	36 ± 5
Qb (mL/min)	257 ± 18.65

Qnuf – net ultrafiltration rate; Qsubs – substitution flow rate; Qconv – convective flow rate; Vsubs – substitution volume; Vconv – overall convective volume; FF – filtration fraction; Qb – effective blood flow

Each patient was followed for three consecutive weeks during which three different dialyzers – DiacapPro 19H (B. Braun Avitum), FX CorDiax 800 (Fresenius Medical Care) and Elisio 21H (Nipro Corporation, Osaka, Japan) – were switched on a weekly basis. The technical characteristics of each membrane are presented in Table 2 [13, 14, 15]. Thus, each patient underwent three consecutive treatments with each dialyzer in a randomly assigned sequence. Dialyzer setup and preparation involving a pre-rinsing were done per the clinic's standard operating procedure. All the dialyzers were pre-rinsed in the same manner.

Blood was collected on mid-week dialysis before and after the treatment. Serum β_2m and albumin concentrations were determined by the turbidimetric method on the Beckman Coulter AU680 chemistry analyzer. The reference range for β_2m in healthy adults with this method is 0.97–1.84 mg/L and the optimum target predialysis β_2m

Table 2. Characteristics of investigated membranes

Characteristic	Diacap Pro 19H	FX CorDiax 800	Elisio 21H
Composition	a	Helixone plus	Polyethersulfone
Surface (m^2)	1.9	2	2.1
Kuf (mL/h/mmHg)	97	62	76
Capillary wall thickness (μm)	37	35	40
Internal capillary diameter (μm)	200	210	200
β_2-microglobulin SC	0.7	0.900	0.8
Albumin SC	<	0.001	0.002
Sterilization method	Gamma rays	Steam	Gamma rays
Manufacturer	B. Braun Avitum AG, Germany	Fresenius Medical Care, Germany	Nipro Corporation, Japan

Kuf – ultrafiltration coefficient, SC – sieving coefficient

serum level in dialyzed patients is < 25 mg/L. The serum albumin reference range is 35–57 g/L. β_2m reduction ratio (RR) was calculated from the following equation: $RR_{\beta 2m}$ (%) = [1 - (C_{post}/C_{pre})] × 100; where C_{pre} stands for β_2m level before and C_{post} for β_2m level after the predilution OL- HDF session [16]. Serum albumin concentration after OL-HDF session was calculated from the following formula: $Albumin_{post} = C_{alb}$ post/{1 + [(UF)/0.2 × (BW_{pre} – UF)]}, where C_{alb} is measured serum albumin concentration (g/L), UF is net ultrafiltration achieved during the particular dialysis session (L / 4 hours), and BW_{pre} is measured body weight before dialysis (kg) [16]. Albumin RR was determined from the equation: RR_{Alb} = [1 - (C_{post}/C_{pre})] × 100, where C_{pre} is serum albumin concentration before dialysis (g/L) and C_{post} is serum albumin concentration after dialysis (g(L) [16].

Ferritin and C-reactive protein (CRP) serum levels were determined on the Beckman Coulter AU680 apparatus. The reference range for ferritin in maintenance HD patients is 100–500 ng/mL. CRP was expressed as an average from two consecutive monthly measurements with a normal value being ≤ 5 mg/L and level > 5 mg/L signified the presence of microinflammation. Intact parathyroid hormone (iPTH) in serum was determined using the immunoradiometric assay on WALLAC WIZARD 1470 Gamma Counter (GMI, Ramsey, MN, USA). The normal range for iPTH is 11.8–64.5 pg/mL, and the upper limit for maintenance HD patients is 675 pg/mL [17]. Prealbumin and transferrin levels were determined with an immunoturbidimetric method on the Abbott Architect machine. The normal results for a prealbumin blood test in hemodialyzed adults are ≥ 0.3 g/L.

Normalized protein catabolic rate (nPCR) was calculated from the formula: nPCR = (PCR × 0.58)/Vd, where PCR is protein catabolic rate, Vd is body fluid volume. PCR was determined from the equation: PCR = [(9.35 × G) + (0.29 × Vd)], where G stands for an interdialytic rise in urea, which is established from the formula G = [(C1 - C2)/Id] × Vd, where C1 and C2 denote pre- and post-dialysis urea concentrations (mmol/L) and Id – the time between the two dialyzes (h). Body fluid volume is calculated as Vd = 0.58 × DW, where DW is dry body mass, i.e., patients' body mass after stable dialysis (kg) [18].

Interdialytic weight gain (IDWG) was calculated as the patients' weight at the beginning of each HD session minus the weight after the previous HD session, divided by the nephrologists' determined dry weight (%).

Dialysis adequacy was assessed based on the single pool Kt/V index calculated according to the Daugirdas' second-generation formula: Kt/Vsp = -ln(C_2/C_1 - 0.008 × T) + (4 - 3.5 × C_2/C_1) × UF/W, where C_1 and C_2 are pre-post dialysis urea levels (mmol/L), T is dialysis duration (h), UF – ultrafiltrate removed (L), and W body weight after HD (kg). According to the K/DOQI guidelines, the target Kt/Vsp is ≥ 1.2 [18].

The urea reduction ratio (URR) was calculated from the formula: URR = (1 - R) × 100%, where R is the difference between pre- and post-dialysis urea serum concentration. URR target range for adequate dialysis is 65–70% [18].

Arteriovenous fistula blood flow (Qavf) was measured with color Doppler ultrasound examination on a LOGIQ P5 machine (GE Healthcare, Chicago, IL, USA), with a 7.5 MHz probe. The reference range for adequate blood flow is 500–1000 mL/minute.

The data were analyzed by the Kolmogorov–Smirnov test, ANOVA, and Kruskal–Wallis test, using the SPSS Statistic for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) for statistical analysis.

RESULTS

The study population consisted of 23 males and seven females with an average age of 54.87 ± 11.66 years, an average time on dialysis of 4.95 ± 5.4 years, average body mass index of 23.49 ± 3.75 kg/m^2, and average dialysis adequacy index (spKt/V) of 1.41 ± 0.25 (Table 3). The etiology of end-stage renal disease was nephroangiosclerosis in 11 patients (36.66%), chronic glomerulonephritis in seven patients (23.32%), polycystic kidney disease in four patients (13.34%), and diabetic kidney disease, obstructive nephropathy, and unknown chronic nephropathy in one patient each. The comorbidities included hypertension (21 patients; 70%), hypertensive cardiomyopathy (seven patients; 23.32%), dilatative cardiomyopathy (one patient; 3.34%), and complications of diabetes mellitus (one patient; 3.34%). Mean serum indicators of anemia, iron status, microinflammation, malnutrition, and secondary hyperparathyroidism are presented in Table 4. The patients had well-controlled blood pressure and did not exceed the recommended values of IDWG.

Table 3. General patients' data

General patients' data	Mean ± SD
Number	30
Sex (M/F, %)	23/7 (76.66/23.34)
Age (years)	54.87 ± 11.66
Time on dialysis (years)	4.95 ± 5.4
Body mass index (kg/m^2)	23.49 ± 3.75
Systolic arterial blood pressure (mmHg)	128 ± 8.72
Diastolic arterial blood pressure (mmHg)	77.32 ± 5.12
Mean arterial blood pressure (mmHg)	94.22 ± 5.3
Dry body weight (kg)	71.82 ± 12.54
Interdialytic weight gain (kg)	2.35 ± 0.94
IDWG as a percentage of dry body weight (%)	3.44 ± 1.58
Ultrafiltration rate (mL/h)	587.5 ± 235.2
Ultrafiltration rate per body mass (mL/kg/h)	8.57 ± 3.92
Vascular access blood flow rate (ml/min)	936 ± 460.9
Single pool Kt/V	1.41 ± 0.25
Urea reduction ratio (%)	69.41 ± 7.06

IDWG – interdialytic weight gain

Twenty-one patients (70%) had predialysis serum β_2m level < 30 mg/L. Among them, 11 patients (36.67%) had predialysis serum β_2m level < 25 mg/L. The average RR of β_2m was 70.86 ± 6.87% with Diacap Pro 19H membrane, 74.69 ± 6.51%, with FX CorDiax 800 membrane, and 70.04 ± 9.37% with Elisio 21H membrane. No statistically

significant difference ($p > 0.05$) was observed between these values (Table 5).

Table 4. Laboratory parameters in the investigated population

Laboratory parameters	Mean ± SD
Hemoglobin (g/L)	101.2 ± 7.06
Hematocrit (%)	30.45 ± 1.78
Iron (m	11.2 ± 5.5
TSAT (%)	33.52 ± 15.2
Ferritin (ng/mL)	568.42 ± 267.85
Transferrin (g/L)	1.6 ± 0.4
iPTH (pg/mL)	220.22 ± 189.45
Total protein (g/L)	66.57 ± 3.02
Albumin (g/L)	39.77 ± 2.64
Prealbumin (g/L)	0.34 ± 0.09
Uric acid (m	368 ± 68.72
C-reactive protein (mg/L)	4.57 ± 5.48
nPCR (g/kg/24 hours)	2 ± 0.6

TSAT – transferrin saturation; nPCR – normalized protein catabolic rate; iPTH – intact parathyroid hormone

Table 5. β_2-microglobulin reduction rate, serum albumin decrease, and albumin reduction rate within a single post-dilution OL-HDF session

Variable	Membrane type			p
	Diacap Pro 19H	FX CorDiax 800	Elisio 21H	
RR-β_2M (%)	70.86 ± 6.87	74.69 ± 6.51	70.04 ± 9.37	0.054
Δ salbumin (g/L)	2.5 ± 0.92	2.4 ± 1.28	2.6 ± 1.2	0.746
RR-albumin (%)	6.2 ± 2.12	6.01 ± 2.97	6.46 ± 2.91	0.812

RR – reduction rate; Δ – difference between pre-and post-dialysis levels; s – serum

All the patients had post-dialysis serum albumin concentration > 35 g/L. The average decrease in serum albumin level after OL-HDF with Diacap Pro 19H, FX CorDiax 800, and Elisio 21H membranes was 2.5 ± 0.92 g/L, 2.4 ± 1.28 g/L, and 2.6 ± 1.2 g/L respectively. RR of albumin with the same membranes was 6.2 ± 2.12%, 6.01 ± 2.97%, and 6.46 ± 2.91%, respectively. No statistically significant difference ($p > 0.05$) was observed in neither of these parameters between different dialyzers (Table 5).

DISCUSSION

Cardiovascular diseases are the leading cause of death in patients on maintenance HD. Uremic toxins, altered endothelial function, chronic microinflammation, malnutrition, oxidative stress, resistance to erythropoietin, and anemia are the major non-traditional risk factors for the development of cardiovascular complications in this population [19, 20]. Early detection and optimal control of these issues seem to play a key role in preventing cardiovascular co-morbidity in HD patients [21]. In recent years, direct cardiotoxicity of uremic toxins has been increasingly demonstrated, while a reduction in middle molecule retention appears to be independently associated with decreased risk of mortality [22].

β_2m is a prototype of middle molecules, commonly used as a representative marker of this group of molecules retention and removal. Its concentration notably increases in end-stage renal failure and may cause the development of dialysis-related amyloidosis [23, 24]. The target β_2m predialysis level of < 30 mg/L was met in 70% of our study population, while 36.67% even had predialysis β^2m level < 25 ml/L [11, 23–26]. The highest β_2m removal rate in our study population was achieved with FX CorDiax 800 dialyzer, even though the difference was not statistically significant. This advantageous performance can be explained by the FX CorDiax membrane characteristics which have a higher sieving coefficient compared to the other investigated membranes.

Previous studies have demonstrated that the average β_2m removal rate ranges 50–60% with regular high-flux HD, to 70% with medium cut-off membranes, to 80–85% with high volume (Vconv > 22 L / dialysis session) post-dilution OL-HDF [23–26]. Somewhat lower β_2m RR achieved with post-dilution OL-HDF in our study population, ranging 70.04–74.69%, can be explained by lower than average Vconv and Qb in our study population (Table 1). High Vconv is the key factor for efficient removal of middle molecules with high volume online post-dilution and patients with Vconv < 22 L per dialysis session have significantly lower Qb and higher filtration fraction compared to patients with higher Vconv. Nevertheless, in clinical practice, Vconv ≥ 22 L per session is attainable in only around 75% of patients. In our study population, 50% of the patients achieved Vconv ≥ 22 L, while an overall of 66.67% had Vconv ≥ 20 L per dialysis session. Optimization of overall Vconv depends on patient-related factors, such as hematocrit and serum total protein level, as well as on dialysis-related determinants, including Qb, type of dialysis machine, and dialysis session length [27, 28]. The target Qb should be ≥ 350 mL/minute and it depends on Qavf and the diameter of dialysis needles. A mature fistula should have a blood flow rate greater than 600 mL/minute and some of the patients in our study group failed to fulfill this criterion due to poorly functioning fistulas, thus affecting the possibility to achieve target Qb [28]. High hematocrit and high total serum protein may increase filtration fraction and decrease the overall Vconv; however, this was not the case in our study population. In addition to these factors, achieving and maintaining target Vconv also requires continuous education and training of medical staff [28].

The lowest albumin loss during the HDF session in our study group was demonstrated with FX CorDiax 80 dialyzer. The advertised membrane characteristics for this dialyzer present a lower sieving coefficient for albumin compared to Elisio 21 dialyzer (Table 2). Nevertheless, all the patients in this study had albumin RR < 11%, accounting for a tolerable albumin loss of < 3.5 g per four-hour dialysis session. Furthermore, all the patients had post-dialysis serum albumin level > 35 g/L. Even though HDF provides better clearance of middle molecules than conventional dialysis, thus possibly improving survival, OL-HDF can lead to an increase in albumin loss across the dialyzer, especially with high permeability membrane and high Vconv, which can eventually lead to

malnutrition [29, 30]. It is therefore important to note that none of the patients in our study developed hypoalbuminemia.

CONCLUSION

All investigated membranes effectively remove middle-molecular-weight uremic toxins with acceptable albumin loss. The highest removal rate of β_2m and the lowest albumin loss was achieved with FX CorDiax 800 dialyzer.

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Уклањање бета-2 микроглобулина постдилуционом онлајн хемодијафилтрацијом – процена ефикасности три различите дијализне мембране

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САЖЕТАК

Увод/Циљ Накупљање уремијских токсина средње молекулске масе може узроковати бројне компликације код болесника лечених хроничним хемодијализама. Постдилуциона онлајн хемодијафилтрација (*OL-HDF*) успешно уклања ове молекуле.

Рад је имао за циљ да испита ефикасност три различите дијализне мембране у уклањању β_2-микроглобулина (β_2m) током појединачне сесије постдилуционе *OL-HDF*.

Методе Проспективном студијом је обухваћено 30 болесника (23 мушкараца и седам жена, просечне старости 54,87 ± 11,6 година, са дужином дијализног лечења 4,95 ± 5,4 године) који се лече постдилуционом *OL-HDF*-ом. Код свих испитаника је одређен индекс редукције β_2m и албумина током једног третмана постдилуционом *OL-HDF*-ом сукцесивном применом три дијализне мембране: *DiacapPro* 19*H*, *FX CorDiax* 800 и *Elisio* 21*H*. За статистичку анализу коришћени су Колмогоров–Смирновљев тест, *ANOVA* и Краскал–Волисов тест.

Резултати Просечан укупни конвективни волумен износио је 21,38 ± 2,97 литара по сесији. Индекс редукције β_2m износио је 70,86 ± 6,87% за мембрану *DiacapPro* 19*H*, 74,69 ± 6,51% за мембрану *FX CorDiax* 800, и 70,04 ± 9,37% за мембрану *Elisio* 21*H* (p = 0,054). Индекс редукције албумина је био 6,20 ± 2,12% за мембрану *DiacapPro* 19*H*, 6,01 ± 2,97% за мембрану *FX CorDiax* 800, и 6,46 ± 2,91% за мембрану *Elisio* 21*H* (p = 0,812). Губитак албумина у току појединачне дијализне сесије за све три дијализне мембране био је мањи од 4 *g* / 4 *h*.

Закључак Све испитане мембране ефикасно уклањају β_2m применом постдилуционе *OL-HDF* уз безбедан губитак протеина. Највећи индекс редукције β_2m уз најмањи губитак албумина остварен је применом мембране *FX CorDiax* 800.

Кључне речи: уремијски токсини; средњи молекули; албумин; β_2-микроглобулин; дијализатор; хемодијафилтрација

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical analysis of internal fixation femoral neck fractures with two or three canulated screws

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SUMMARY

Introduction/Objective Angular stability and dynamic fixation are key factors to successful healing of femoral neck fractures.

The objective was to evaluate the efficacy of internal fixation of femoral neck fractures with two parallel self-tapping antirotation screws (SAF) compared to standard, three cannulated cancellous screws (CCS) fixation.

Methods In total 100 fractures were retrospectively analyzed, divided in two groups in which two SAF screws were used in parallel (n = 50) or three standard screws in an inverted triangle configuration (n = 50). The groups were compared with operation time, time of consolidation, femoral neck shortening, Harris hip score and reoperation rates.

Results SAF parallel fixation group of patients achieved consolidation rate of 86% compared to 74% in CCS fixation group, without statistically significant difference between the examined groups ($p > 0,05$). Dynamization of implants was significantly positively correlated with the fracture healing time in both examined groups (SAF: $r = 0.324$, $p = 0.025$; CCS: $r = 0.572$, $p = 0.001$), with significantly shorter healing time in SAF patients – on average 15 weeks (15.02 ± 1.44) in relation to the CCS group of patients – 19 weeks (19.81 ± 2.94) ($\chi^2/z = 7.048$, $p < 0.001$). There was no statistically significant difference in the Harris hip score and reoperation rate among the study groups ($\chi^2 = 2.44$, $p = 0.487$; $\chi^2 = 0.500$, $p = 0.696$).

Conclusion Our results suggested that dual parallel fixation is simpler, less invasive and it demands less performance time. It is not inferior to fixation with three screws, from the point of biomechanics, possible complications, healing and functional recovery.

Keywords: femoral neck fractures; bone union; internal fixation

INTRODUCTION

Femoral neck fractures include injuries involving the area between the head of the femur and the intertrochanteric line and account for nearly half of all hip fractures, increasing exponentially with age [1]. The specific intracapsular environment with vulnerable vascular supply, and burden some biomechanics of the hip, contribute to the high complication rates seen after osteosynthesis of these fractures [2].

Internal fixation is frequently used for undisplaced fractures and for displaced intracapsular fractures in which preservation of the femoral head is preferred or the patient with poor premorbid conditions for arthroplasty [3, 4]. Traditionally intracapsular femoral neck fractures are operatively treated with three cannulated cancellous screw, but controversy remains over what the ideal number and correct position of screws should be for treating these fractures [5, 6].

However, the outcomes after conventionally inverted cancellous three screw fixation of femoral neck fractures have not been uniformly positive and the rates of revision surgery ranging 8–27% [7]. One of the main reasons for such poor outcomes is reflected in a more technically demanding procedure in terms of fracture reduction and correct placement of screws. A simpler technique of placing only two parallel screws, one higher and the other lower in the femoral neck, may be a suitable alternative to improve complication rates of surgical treatment of femoral neck fracture in properly selected patients.

Objective

The primary objective of our trial was to evaluate the clinical outcome of internal fixation of femoral neck fractures by double screws versus three cancellous screws fixation in skeletally mature patients.

METHODS

After Institutional Review Board approval (ref. no. 12-2466-12, approval date March 9, 2015) we retrospectively reviewed data from January 2014 to January 2017 from the University Clinic of Orthopedics and Traumatology, at the Clinical Center in Niš. The study included a series of 100 patients with femoral neck fractures treated by the same group of surgeons.

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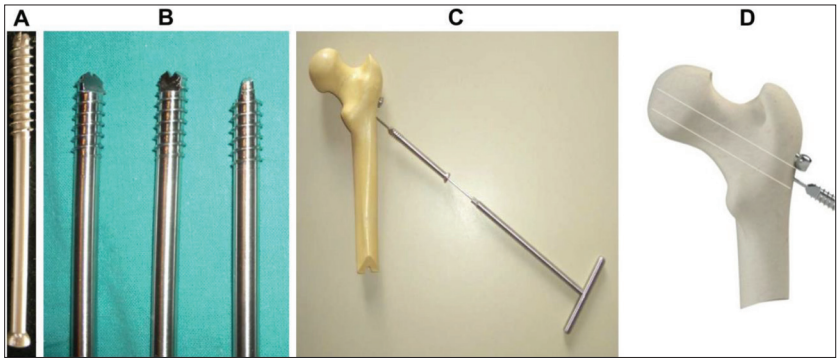

Figure 1. Standard AO 6,5 mm cannulated cancellous screw (A); self-tapping cannulated screws and position of the implant in femoral neck (B, C, D)

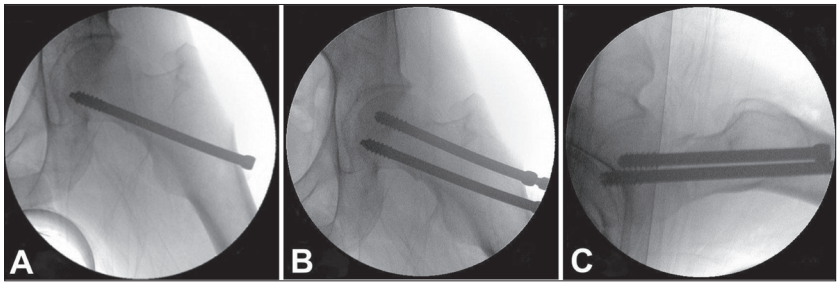

Figure 2. Plain radiographs to verify correct placement of self-tapping cannulated screws femoral neck fixation (A – distal screw placement; B – proximal screw placement; C – profile parallel placement)

A group of 50 patients with femoral neck fractures were treated surgically with two parallel inserted self-tapping anti-rotational screw fixation (SAF) group, while the other group of 50 patients were surgically treated using the multiple cancellous screw fixation method with three cannulated cancellous screws (CCS) group. Data were collected and compared retrospectively in both groups. Patients were selected using random allocation software [8]. The patients were not blinded to their treatments. All patients were followed up until fracture union or a revision surgery was performed. No patient was lost by the end of the first-year follow-up.

The inclusion criteria were for all patients who had either an undisplaced fracture, or a displaced femoral neck fracture with American Society of Anesthesiologists score range 1–3, who walked independently prior to the fracture, in the absence of hip osteoarthritis. We excluded from the study patients with pathological femoral neck fractures, open femoral neck fractures, femoral neck fractures in skeletal immaturity patients, polytrauma patients (ISS > 16) with ipsilateral fractures of femoral neck and shaft fractures and patients older than 65 years who had a severe concomitant medical condition (Grade 4, 5 American Society of Anesthesiologist Score).

Fracture management

In all selected cases the surgery was performed either in spinal or general anesthesia, with patients positioned supine on a traction table using the technique of closed reduction under C-arm control with manual traction and internal rotation of the injured extremity (Whitman's maneuver). If closed reduction was not satisfied after two attempts, open reduction through Watson-Jones approach was carried out. In our clinical practice, for the last 15 years, we predominantly used for osteosynthesis of femoral neck fractures, double SAF from a domestic supplier (D.O.O. Traffix, Niš, Serbia). Anti-rotational self-tapping cannulated screw is made by medical steel 316LVM, body diameter screw of 7.2 mm, with threads thickness of 9 mm with a thread's length of 16 mm and self-tapping tip (Figure 1B, Figure 1).

The first group of 50 patients, in our study, underwent surgery with dual SAF cannulated implant from a domestic supplier (D.O.O. Traffix). Anti-rotational self-tapping cannulated screw is made by medical steel 316LVM, body diameter screw of 7.2 mm, with threads thickness of 9 mm with a threads length of 16 mm and self-tapping tip The second group (CCS) of patients consists of other 50 patients with femoral neck fractures surgically treated by using standard 6.5 or 7.3 mm three CCS (Figure 1). The SAF screws are designed to adjust to the load to which they are exposed and, on the other hand, to minimally injure bone tissue. Derotation compression of the fragment is achieved by parallel position of the SAF screws. These characteristics make the concept distinctive by itself. The tip of each screws was driven into head of femur to within 5 mm, approximately, from the subchondral bone plate (Figure 2).

On the other hand, three cancellous screws, in most cases, were placed in the configuration of an inverted triangle, respecting the principles of three-point fixation (Three-Point Principle) [9].

Assessment methods

Radiographic parameters

Before internal fixation, based on radiographs, the fracture classification according to Pauwel and Garden classification was performed. Pauwel's type II and III fractures (≥ 50°) were considered unstable and Garden III or IV fractures were considered displaced. Acceptable reduction parameters have been defined as a neck shaft angle 130–150°, less than 15 degrees of valgus with no varus angulation, and 0–15° of lateral angulation [10]. Intraoperative reduction assessments were graded as anatomical, acceptable or poor in both groups of patients. Preoperative and postoperative data were recorded, including age, type of fracture, degree of posterior comminution, surgical timing, duration of surgery, and final outcomes.

Functional outcome assessments and complications

Postoperatively, all patients received antibiotic prophylaxis for 48 hours and deep vein thrombosis prophylaxis for three weeks. Postoperatively, sitting was encouraged at the first day, non-weight-bearing ambulation with the aid of a walker frame was allowed after one or two weeks as long as the pain was tolerated. Patients were encouraged to partial weight bearing six weeks after the operation. After hip X ray confirmation that fracture healed, full weight bearing was allowed. Postoperative radiographs were assessed until the end-point was reached, defined as fracture consolidation, collapse of the femoral neck, loss of reduction that necessitated reintervention, necrosis of the head or pseudarthrosis of the neck, with a minimum period of six months elapsed from the time of the fracture. As a predictor of poor outcome, the influence of posterolateral comminution on healing time and stability of fixation was tested. The sliding length of the lag screws after fracture consolidation was measured by comparing the immediate postoperative and final anteroposterior radiographs.

The complete functional recovery of the patient after the minimum of one-year follow-up was verified in our study. The values obtained by filling in the questionnaires of Harris hip score scaled 1–100. After the 12-month-follow-up, all patients in both groups were studied for the functional outcome, as well as the effect of femoral neck shortening on gait pattern and muscle strength and reoperation rate was recorded.

Data analysis

Statistical analysis was performed with SPSS® Version 16.0 for Windows® (SPSS Inc, Chicago, IL, USA). Baseline and outcome variables were compared between the investigated groups. Proportions and means among groups were compared using either the χ^2 or Fisher's exact test and Student's t test, respectively. Statistical significance was set at $p < 0.05$.

The study was approved by the local Medical Research Ethics Committee (ref. no. 12-2466-12, approval date March 9, 2015) and carried out according to the declaration of Helsinki

RESULTS

A total of 100 patients with undisplaced and displaced femoral neck fractures were included in this retrospective study. Their baseline socio-demographics data and significance in prevalence, in relation to the treatment groups (SAF *vs*. CCS), are shown in the Table 1.

The mean operative time for the fixation with two cannulated screws was significantly shorter by approximately 14 minutes (52.89 *vs.* 39.17 minutes, $p < 0.0001$, unpaired t-test) (Figure 3). Intraoperative blood loss and average fluoroscopy time were similar in both groups, with no significant difference ($p = 0.75$; $p = 0.62$).

Statistical analysis of the data founded that the majority of patients in the overall population achieved anatomical type of fracture reduction or acceptable one, without statistical significance ($p = 0.490$), as shown in Table 2.

Table 1. Patient data among the study groups

Parameters		SAF (n = 50)	CCS (n = 50)	p
Age (years) mean ± SD (min–max)		58.06 ± 10.35 (27–79)	51.86 ± 16.52 (16–80)	0.027
Sex (%F, %M)		40%F, 60%M	46%F, 54%M	> 0.05
Garden class	I	14	10	> 0.05
	II	22	27	> 0.05
	III	11	10	> 0.05
	IV	3	3	> 0.05
Pauwels class	I	31	29	> 0.05
	II	17	18	> 0.05
	III	2	3	> 0.05
CRIF n (%)		45 (90%)	37 (74%)	0.038

SAF – self-tapping antirotational fixation; CCS – cannulated cancellous screws; CRIF – closed reduction and internal fixation

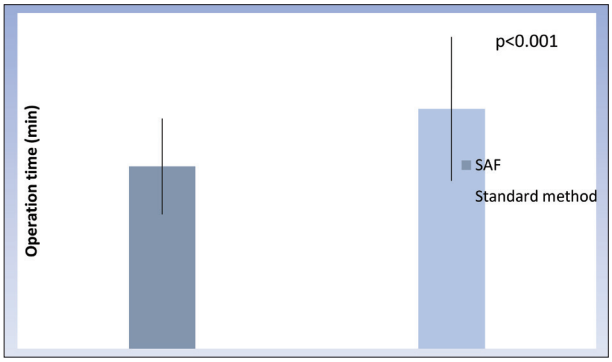

Figure 3. Operating time among studies groups; SAF – self-tapping cannulated screws

Table 2. Reduction quality assessment among the study groups

Assessment of reduction	Total n (%)	SAF n (%)	CCS n (%)	χ^2	p
acceptable	39 (39%)	20 (40%)	19 (38%)	1.428	0.490
anatomical	54 (54%)	28 (56%)	26 (52%)		
poor	7 (7%)	2 (4%)	5 (10%)		

SAF – self-tapping antirotational fixation; CCS – cannulated cancellous screws

The SAF group of patients had union rate of 86%, consolidation was observed in 43 of the 50 fractures. In the group which was made standard methods of treatment, consolidation was observed in 37 out of 50 fractures (74%). There was no statistically significant difference among the examined groups ($p > 0.05$).

In relation to posterolateral comminution, implant dynamics, meaning a migration of the lag screw(s) in the femoral neck or lateralization of the lag screw(s) due to fracture collapse, were observed more frequent in patients treated by surgical technique with multiple cancellous screws thickness of 6.3/7.5 mm and was greater than or equal to 10 mm which was statistically significantly ($\chi^2 = 6.474$, $p < 0.001$). Also, the union time was significantly shorter in SAF group (15.02 ± 1.44) compared to patients in CCS group (19.81 ± 2.94) with posterolateral fracture comminution ($\chi^2 = 7.048$, $p < 0.001$) (Table 3).

Table 3. Posterolateral comminution, union time and dynamization of implant

Characteristics	SAF	CCS	χ^2/z*	p
Posterolateral comminution n (%)	43 (86%)	43 (86%)		1.000
Union time (weeks) mean ± SD (min–max)	15.02 ± 1.44 (10–22)	19.81 ± 2.94 (12–26)	7.048*	< 0.001
Implant dynamization (mm) mean ± SD (min–max)	3.33 ± 1.96 (0–10)	13.18 ± 6.21 (2–24)	6.474*	< 0.001

SAF – self-tapping antirotational fixation; CCS – cannulated cancellous screws

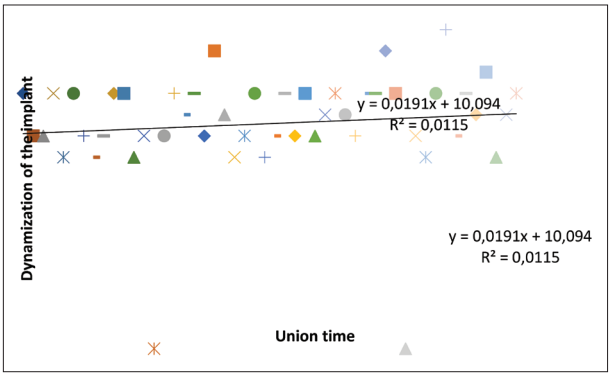

Figure 4. Relationship between implant dynamics and fracture healing time in patients undergoing cannulated cancellous screws fixation

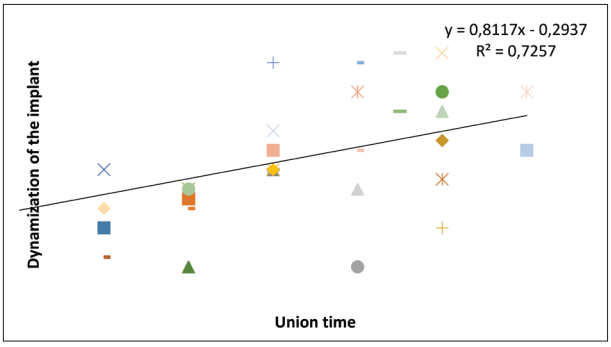

Figure 5. Relationship between implant dynamics and fracture healing time in patients undergoing self-tapping cannulated screws fixation

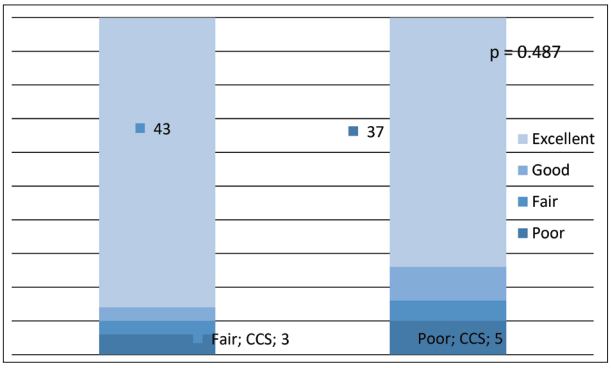

Figure 6. Assessments of complete functional recovery obtained by Harris hip score; SAF – self-tapping antirotational fixation; CCS – cannulated cancellous screws

Comparing the fracture healing rate time with the degree of dynamization of implants in both groups of patients with posterolateral comminution, we came to the result that dynamization of implants significantly positively correlated with the fracture healing time in both examined groups, respectively (SAF: r = 0.324, p = 0.025; CCS: r = 0.572, p = 0.001) (Figure 4 and 5).

After one-year follow-up, Harris hip score values (SAF: 89.7 ± 8.4; CCS: 82.2 ± 14.3) were similar, with no statistically significant difference (χ^2 = 2.44, p = 0.487) (Figure 6).

Reoperation was performed in five patients (10%) of SAF group and eight patients (16%) in CCS group of patients. It was found that there was no statistically significant difference in the incidence of reoperation rate between the tested method (χ^2 = 0.500, p = 0.696).

Of the total number of patients operated by dual SAF implants, in five patients were performed reoperation procedures (two nonunions, one varus collapse and two healed fractures with advanced stage of femoral head necrosis - III and IV grade by Ficat and Arlet classification). Because of the developing of the osteoarthritis of injured hip, total hip replacement was carried out in all cases.

DISCUSSION

So far, there have not been many studies investigating double screw femoral neck fixations [11]. Mostly, the authors compared the rates of treatment complications between fixed angular plate and three screw fixation methods, emphasizing significantly higher prevalence in blood loss and duration of operation in the group of patients treated with fixed angular plates [12, 13]. Our data suggest that the use of the CCS was associated with approximately 14 minutes longer surgery which was significantly shorter in the SAF group of patients (52.89 *vs.* 39.17 minutes, p < 0.0001, p = 0.62, unpaired t-test).

Screw loosening, fracture displacement and some other complications may often occur with regards to the internal fixation of femoral neck fractures, which in turn increases the rates of nonunion and femoral head necrosis [14]. Furthermore, it is generally known that the compressive forces have a positive impact on fracture healing, but it is unclear what the degree of dynamic compression is needed to promote healing the fracture, in order to prevent the prevalence of the shear forces which are the main cause of mechanical failure of fixation [15, 16]. During healing of femoral neck fracture, both bone resorption and shear forces of the fracture site can result in secondary sliding and displacement, even though the fracture was reduced in anatomic reduction quality, which tend to cause femoral neck shortening resulted in poorer functional outcome scores compared to patients who healed in an anatomic position [17]. Our study shows that dynamization of implants significantly positively correlated with the fracture healing time in both examined groups, respectively (SAF: r = 0.324, p = 0.025; CCS: r = 0.572, p = 0.001) indicating that fracture union rate was significantly shorter in group of patients treated with SAF method of fixation, average time 15 weeks (15.02 ± 1.44) on related to CCS group of patients which was average 19

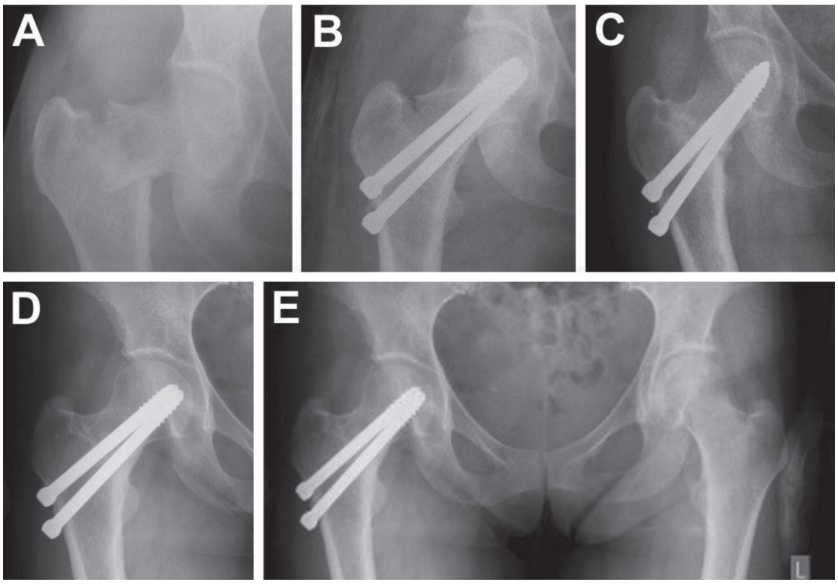

Figure 7. A 43-year-old female patient with unstable vertical (Pauwel III) intra-capsular femoral neck fractures, when Adam's arch is missing and lateral cortex suffers the greatest load, in our series of patients treated with two self-tapping antirotational fixations screws – serial follow up X-ray (A – initial; B – 12 weeks postoperative; C – six months; D – 12 months; E – 24 months postoperative)

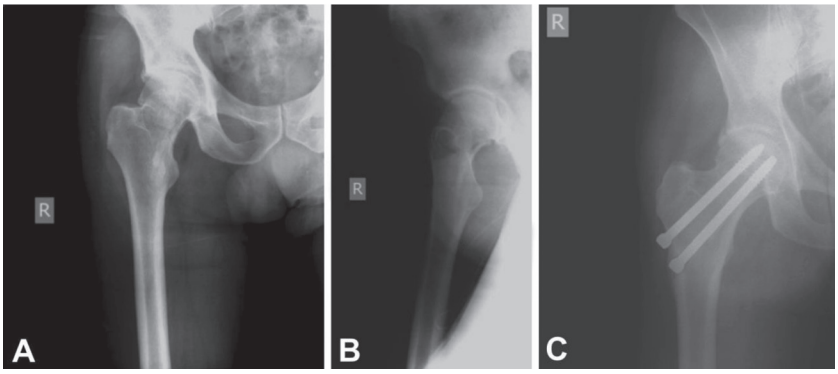

Figure 8. A – effect of "biological plate": anteroposterior view of femoral neck fractures with posterior wall comminution in a 63-year-old male patient; B – profile view indicated disrupted posterior wall of femoral neck fractures; C – six months postoperative X-ray show significant thickening of the lateral cortex around the distal screw with fracture healing

weeks (19.81 ± 2.94) ($\chi^2/z = 7.048$, $p < 0.001$). It follows that SAF fixation improves rotational control of fracture fixation represents a technically less demanding procedure.

Secondary sliding of implants (dynamization), which leads to resorption of fragments and shortening of the femoral neck, lasts until the end of the third month postoperatively, as part of normal bone consolidation. In cases of poor-quality fracture reduction and severe osteoporosis this event can cause uncontrolled excessive shortening of the femoral neck, which further leads to higher possibilities of nonunion and fixation failure after femoral neck fractures [18]. Literature data suggest that there is a high incidence of the unacceptable collapse of the femoral neck (≥ 10 mm), approximately 30%, after fixation displaced and undisplaced femoral neck fracture with posterolateral comminution with three cancellous screws, the thickness of 6.5 or 7.3 mm [19]. In our study, the average dynamization of the implant in SAF group was 5 mm, while in a CCS group it was 17 mm, which was a statistically significant difference ($p < 0.001$). Despite the overall better value of Harris hip score for patients who had undergone SAF surgery (SAF: 89.7 ± 8.4; CCS: 82.2 ± 14.3), we found no statistically significant difference in functional recovery after one follow-up among the tested groups ($\chi^2 = 2.44$, $p = 0.487$). Considering the study's average revision rate among the studied groups (SAF = 6% *vs*. CCS = 8%) no significant difference between the two groups could be observed.

According to previous findings, it has been well known that the disruption of posterior wall of the femoral neck fractures is a major cause of excessive shortening of the femoral neck during the healing phase, and that adversely affects fracture healing, functional outcome and the occurrence of reoperation rate [20]. To ensure stable fixation and healing of the femoral neck fractures, it is necessary to secure three point of support which need to be adjusted to the biomechanical characteristics of the implant: the subchondral bone head of the femur for rotational stability (the first point of fixation), Adam's arch and femoral calcar of the neck of the femur (the second point of fixation) and support of lateral femoral cortex (the third point of fixation) [21, 22].

If Adam's arch of the caudal fragments remains intact (as it happens in the majority of femoral neck fractures) use of thick, rigid plate, such as dynamic compression plate, is not required, and placement of free cannulated screws are enough for secure fracture fixation. Placed in parallel position, free cancellous screws give enough support to the femoral calcar and Adam's arch [23, 24]. This approach also causes less trauma to the soft tissues and requires shorter surgery duration. In our series intraoperative blood loss and average fluoroscopy time were similar in both groups, with no significant difference ($p = 0.75$; $p = 0.62$) which supports this claim.

But, in the cases when Adam's arch as the support of the second point of fixation is missing and cannot support the implant (Pauwels type III of femoral neck fractures, basicervical femoral neck fractures, comminuted femoral neck fractures), double lever becomes a single, and large load suffers lateral cortex of the femur as a third point of support of internal fixation [25]. In these situations, additional reinforcement with an appropriate implant is required, in order to achieve resistance to the shear force inherent in these vertical fractures. Recently, the use of a medial

buttress plate on the medial side of the femoral neck has been proposed by some authors, with satisfactory initial results. However, it requires a more extensive surgical dissection and care must be taken not to damage the femoral head blood supply [26, 27]. SAF in most cases in our study was performed after closed reduction (90%) as a less surgically demanding procedure, where even after open fracture reduction (10%) adequate dynamic compression of the fracture site was provided without additional damaging the blood supply to the femoral head (LFCA and MFCA) (Figure 7). In order to achieve better angular stability and dynamic compression of the unstable Pauwels III fracture, recently, AO foundation authors introduced a new implant called Femoral Neck System (DePuy Synthes, Zuchwil, Switzerland), to improve the biomechanical performance of fracture fixation. They have biomechanically proven that implant is superior versus fixations with three parallel cannulated screws and comparable to both dynamic hip screw with antirotation screw and dynamic hip screw with blade in terms of sustainability of the restored neck length for unstable Pauwels III fractures [28].

One of the proofs overloading the third point of internal fixation of the femoral neck fractures is a thickening of the lateral cortex at the site around the distal screw, which was clearly visible on X-rays several weeks after dual SAF screw fixation. The pain was present until the "biological plate" did not finish its formation and provide solid support to the screw (Figure 8).

This phenomenon can be explained by the presence of micro-movements of the screw due to the load, causing osteogenesis followed by formation at first irritative callus, and then supportive periosteal callus around the distal screw on the lateral femoral cortex. This example shows that the lateral cortex could not always respond to the high demands that are placed in front of the third fixation point and that even in the cases of perfect fracture reduction and stabilization, micro-movements occurred. To avoid reduction loss or excessive femoral neck shortening after internal fixation with free cannulated screws, it is necessary to strengthen the lateral cortex, especially in the case of osteoporotic patients [29].

The present retrospective study has certain limitations, that must be acknowledged. Firstly, it is a preliminary report with a small number of cases. Secondly, we found a small number of avascular necrosis cases in SAF group, which may be due to the short follow-up period. But it has certain character, which is reflected in the fact that the data analyzed here cover particular type of injury, where a large number of patients suffered unstable femoral neck fractures, almost equally distributed (SAF = 28% *vs*. CCS = 26% according to Garden type, SAF = 38% *vs*. CCS = 42% according to Pauwels type) in both studied groups.

CONCLUSION

Our data shows that the double screw SAF prevents the excessive collapse of the femoral neck fracture, respecting the principles of three-point fixation, acting as a load sharing device. Likewise, with significantly shorter duration of surgery, SAF provides optimal conditions for the healing of the comminuted fracture without further shortening the length of the femoral neck and functional damage to the hip abductor lever in properly selected patients. There is also a trend supporting the preferential use of the SAF over the CCS in terms of complication rates but lacks statistical significance. Nevertheless, more clinical prospective randomized trials should be done to evaluate the effectiveness of this implant.

Conflict of interest: The author Milorad B. Mitković at the moment of writing of this paper has an agreement on temporary assignment to patent use. Other authors declare no conflict of interest.

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Клиничка анализа унутрашње фиксације прелома врата бутне кости применом два или три канулирана завртња

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САЖЕТАК

Увод/Циљ Ангуларна стабилност и динамичка фиксација су кључни фактори за успешно зарастање прелома врата бутне кости.

Циљ ове студије је процена ефикасности унутрашње фиксације прелома врата бутне кости са два паралелна самонарезујућа антиротациона завртња (CA3) у односу на три канулирана спољашња завртња.

Методе Ретроспективно је анализирано 100 прелома врата бутне кости, који су хируршки збрињавани са два CA3 завртња ($n = 50$) или три стандардна AO завртња у конфигурацији обрнутог троугла ($n = 50$). Упоређивани су дужина операције, време зарастања прелома, степен скраћивања врата бутне кости током консолидације прелома, крајњи функционални резултат мерен Харисовим скором и стопа реоперације.

Резултати У групи у којој се користила дуална (CA3) паралелна фиксација, консолидација прелома је остварена у 86% случајева у односу на 74% у групи са три канулирана завртња, без статистички значајне разлике међу испитаним групама ($p > 0,05$). Динамизација имплантата значајно позитивно је корелирала са временом зарастања прелома у обе испитиване групе (CA3: $p = 0,324$, $p = 0,025$; AO: $r = 0,572$, $p = 0,001$), са значајно краћим временом зарастања у групи CA3 пацијената – просечно 15 недеља (15,02 ± 1,44) у односу на AO групу пацијената – 19 недеља (19,81 ± 2,94) ($\chi^2 / z = 7,048$, $p < 0,001$). Према Харисовом скору кука и стопи реоперација, није примећена значајна разлика између група ($\chi^2 = 2,44$, $p = 0,487$; $\chi^2 = 0,500$, $p = 0,696$).

Закључак Резултати указују да је дуална паралелна фиксација (CA3) једноставнија, мање инвазивна и захтева мање времена за извођење. Није инфериорна у односу на фиксирање са три завртња, са становишта биомеханике, могућих компликација, зарастања и функционалног опоравка.

Кључне речи: унутрашња фиксација; прелом врата бутне кости; зарастање

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Analysis of risk factors for cement leakage in percutaneous kyphoplasty – does sedoanalgesia increase the risk?

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SUMMARY
Introduction/Objective Several studies have evaluated anesthesia type as a possible risk factor for cement leakage in percutaneous vertebral augmentation procedures. This study has the largest series in the literature revealing data on the incidence of cement leakage in percutaneous kyphoplasty under sedoanalgesia. The aim of the study was evaluating the possible association between sedoanalgesia and cement leakage in percutaneous kyphoplasty procedures.
Methods In this study, 195 vertebral compression fractures treated with percutaneous kyphoplasty under sedoanalgesia in 165 patients were retrospectively reviewed. The association between sedoanalgesia and cement leakage in percutaneous kyphoplasty procedures was evaluated.
Results The mean age (years) of study population was 64.37 years (range 24–108 years), and the male–female ratio was 71/94. No significant difference in the proportion of males (n = 71, 43.03%) and females (n = 94, 56.96%) was observed between groups. Among the 195 fractured segments, most frequent fractures were observed at the T12 (n = 41, 21.02%) and L1 (n = 65, 33.33%) levels.
Conclusion Sedoanalgesia is not a risk factor for cement leakage in percutaneous kyphoplasty and offers a safe anesthesia option to avoid possible complications.
Keywords: vertebral compression fracture; percutaneous kyphoplasty; cement leakage; sedoanalgesia

INTRODUCTION

Spinal fractures secondary to trauma, osteoporosis and osteolytic metastasis are a common cause of severe pain, neurological deficit, morbidity, and profoundly impaired quality of life [1].

Proponents of surgery believe that decompression, fracture reduction and instrumentation are essential for stabilising the spine and reducing pain [2].

Surgical management of thoracolumbar fractures is preferred for patients with progressive neurological loss, unstable fractures or polytrauma, who require fixation for earlier and easier rehabilitation.

For neurologically intact patients, surgical management of thoracolumbar fractures remains controversial. Several authors have reported good clinical results after nonoperative management without fracture reduction and using conservative treatments, including analgesics, bed rest, spinal (thoracolumbosacral or lumbosacral) orthoses and calcium, magnesium, and vitamin D supplements [3].

For those who are intolerant to the side effects of conservative approaches or those who have failed to achieve pain control, percutaneous cement augmentation procedures represent a minimally invasive adjunct [4]. Percutaneous vertebroplasty (PV) and percutaneous kyphoplasty (PK) have gained widespread recognition as successful techniques for reducing pain and improving functional measures and quality of life [4]. The indications for PV and PK include painful osteoporotic vertebral fractures, vertebral fractures caused by neoplasms and various types of traumatic fractures, such as vertebral compression fractures in the absence of neurological symptoms. These minimally invasive techniques reduce blood loss and avoid damage to the paraspinal muscles [5].

Cement leakage is a serious complication of PV and PK, which may cause severe chemical or thermal injury to neurovascular structures and pulmonary embolism [6]. Cement may leak into the spinal canal or epidural, paravertebral, and intradiscal spaces. Although rare, venous leakage can occur mostly in neoplastic or osteoporotic fractures [7].

Various factors can influence the incidence of cement leakage, such as cement viscosity, injected cement volume and intravertebral clefts [8]. Leakage during PK occurs in 25% of cases, which is significantly lower than the rate in PV (70%) [9]. The differences in leakage rates between PK and PV were attributed to the cavity-creation approach by balloon filling in PK, which helps contain the cement within the vertebral body [1]. The height of the fractured vertebral body is reconstructed by balloon filling during PK. This procedure may also affect the shape and size of an intervertebral cleft, which has been proven to be a risk factor for cement leakage in PK in previous studies [10].

Several studies have evaluated anaesthesia type as a possible risk factor for cement leakage

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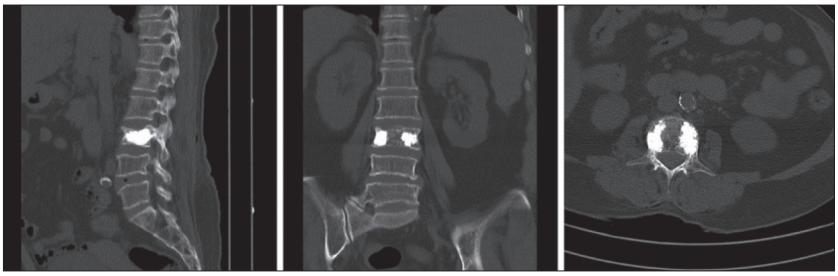

Figure 1. Computed tomography images presenting the ideal cement distribution to fractured vertebral body after bipedicular approach; a – sagittal; b – coronal; c – axial

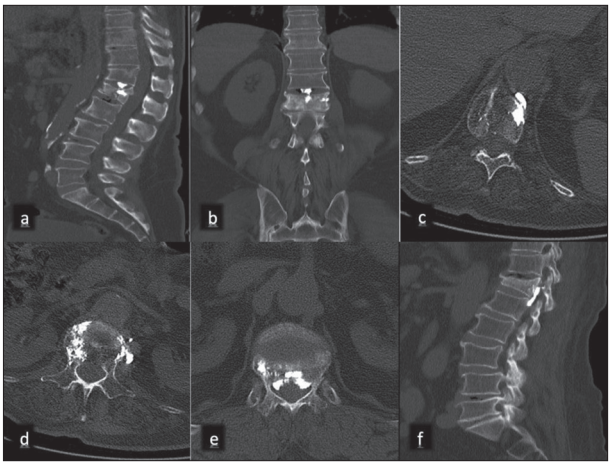

Figure 2. Cement leakage types, computed tomography images; a – intradiscal (sagittal); b – mixed – intradiscal and left paravertebral (coronal); c – paravertebral – anterior (axial); d – paravertebral – left (axial); e – epidural (axial); f – epidural (sagittal)

in PV and/or PK procedures; however, most studies have involved a small sample size or they did not interpret the data independently for each procedure type [3, 9, 11, 12]. Therefore, a procedure-specific incidence rate of cement leakage in large series could not be revealed in recent studies. To recent knowledge, this study has the largest series in the literature revealing data on the incidence of cement leakage in PK under sedoanalgesia. This study was conducted to evaluate the association between sedoanalgesia and cement leakage in PK procedures.

METHODS

Study design

This study was approved by the Ethical Committee of our institution, and written informed consent was obtained from all patients. In this study, 195 vertebral compression fractures treated with PK under sedoanalgesia at our hospital in 165 patients from January 2015 to January 2018 were retrospectively reviewed.

The inclusion criteria were as follows: 1) severe back pain; 2) failure of conservative treatment; 3) more than 50% loss of vertebral body height presented on sagittal X-ray film and/or computed tomography (CT), and 4) high signal intensity on short tau inversion recovery (fat-suppressed) sequence on magnetic resonance imaging (MRI) confirming recent vertebral body fractures of the thoracolumbar region (Figure 1). The exclusion criteria were as follows: 1) fracture accompanied by neurological deficit; 2) radicular pain; 3) intolerance to bone cement material, and 4) contraindication to MRI.

Data regarding age, sex, number of treated vertebrae, location, fracture morphology, surgical approach, duration of surgery, amount of injected cement, and the presence and distribution of cement leakage were collected. Cement leakage was assessed on postoperative axial, coronal, and sagittal CT scans of the spine and classified into four locations, as defined by previous studies: epidural, intradiscal, paravertebral, and mixed [3, 13, 14].

In the literature provided by Scopus and PubMed databases for the last 10 years, medical documents published in English on cement leakage in PK under any type of anesthesia were reviewed (keywords: 'cement leakage,' 'kyphoplasty,' 'general anesthesia,' 'local anesthesia,' and 'sedoanalgesia'). The results of this study were compared with the literature data.

Patient characteristics

In this study, 165 patients with 195 fractured segments of T5–L4 were enrolled. Among the patients enrolled in this study, 94 were women (56.9%) and 71 were men (43.1%), and their age ranged 24–108 years, with a mean of 64.3 ± 10.1 years.

Surgical procedure

All PK procedures were performed with the patients under sedoanalgesia in a prone position by the same right-handed, senior surgeon.

For conscious sedoanalgesia, 1-μg/kg intravenous fentanyl, 20-μg/kg intravenous midazolam, and 25-mg intravenous ketamine were administered. If needed, 20-μg/kg additional doses of intravenous midazolam were repeated during the procedure. For local anesthesia, 5-mL 1% lidocaine was injected intradermally. A guidewire was inserted after the appropriate entry point was identified under fluoroscopy. As soon as the fractured vertebra was confirmed, a working tunnel was inserted into the vertebral body until it passed the pedicle border. The core drill and balloon were inserted through the working tunnel to the anterior two-thirds of the vertebral body. The balloon was expanded with a contrast agent under fluoroscopy until a satisfactory restoration of vertebral body height was achieved. Following the withdrawal of the contrast agent and balloon, in this order, preprepared bone cement at a semisolid state was injected into the cavity created in the vertebral body. At that stage of the procedure, multiple fluoroscopic images were obtained at both axial and coronal planes, and the patients were instructed to move their lower extremities to confirm that the neurovascular structures were not injured. Lastly, the working tunnel

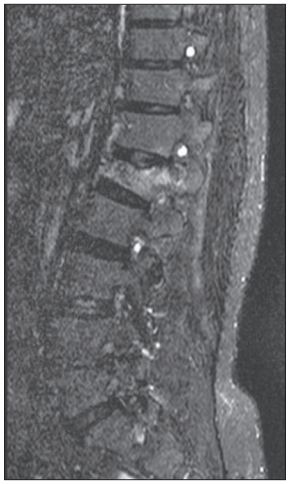

Figure 3. High signal intensity on short tau inversion recovery (fat-suppressed) sequence on sagittal magnetic resonance imaging confirming recent L1 vertebral compression fractures

was removed, and the entry point was closed with a single simple suture (Figure 2).

Assessment indices

Postoperative CT images were obtained to assess the presence of cement leakage and leakage sides. Cement leakages were grouped into the four following sides on axial, coronal and sagittal CT scans (Figure 3): epidural, paravertebral, intradiscal, and mixed. All radiographic evaluations were independently performed in a double-blinded fashion by the same radiologist. All the patients were grouped according to the surgical approach (bipedicular or unipedicular), fracture pathology, fractured segments, number of treated segments, and injected cement volume per segment. The incidence rate of cement leakage and leakage locations were evaluated and compared with the data from similar studies in the literature.

Statistical analysis

Statistical analyses were conducted using SPSS, version 18.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were presented as means and standard deviation. The χ^2 test was performed to determine significant associations between demographic characteristics, fracture pathologies, cement volumes, surgical approaches, fractured segments, and cement leakages. A logistic regression model was used to examine the association between the type of fracture pathology and cement leakage occurrence. P-values of less than 0.05 were used to denote statistical significance.

RESULTS

Bone cement distribution and leakage rate

The mean age (years) of the study population was 64.37 years (range, 24–108 years), and the male–female ratio was 71/94. No significant difference in the proportion of males (n = 71, 43.03%) and females (n = 94, 56.96%) was observed between the groups. Among the 195 fractured segments, most frequent fractures were observed at the T12 (n = 41, 21.02%) and L1 (n = 65, 33.33%) levels.

Among the 195 fracture segments, 168 (86.15%) were treated using the bipedicular approach, and among the 165 patients, 79 (47.87%) had traumatic fractures. The mean volume of injected cement per segment was 3.8 ± 0.7 mL. The number of patients treated for two consequent segments, three consequent segments and two or more non-consequent segments was 17 (10.3%), 1 (0.6%), and 10 (6.06%), respectively. The mean duration of surgery was 39.86 ± 5.6 minutes (range 25–70 minutes). Data obtained from the assessment of cement leakage locations revealed that the intradiscal space was the most common (12.3% of 51) leakage site. Table 1 presents the patients' demographic characteristics, characteristics of fractured segments, and surgical features.

Table 1. Characteristics of the patients

Characteristic	Value
Sex	71 males / 94 females (total 165 patients)
Mean age (range) (years)	64.37 (24–108)
Surgical approach (195 segments)	
Unipedicular	27 (12 right /15 left)
Bipedicular	168
Fractured segments (195 segments)	
T5	1
T6	2
T7	2
T8	6
T9	4
T10	5
T11	7
T12	39
L1	63
L2	28
L3	23
L4	15
Duration of surgery (165 patients)	
Range (minutes)	25–70
Mean (minutes)	39.86
Multiple segments	28 of 165 patients
Two consequent segments	17
Three consequent segments	1
Two or more non-consequent segments	10
Leakage locations	51 of 195 segments
Epidural	6 (3.07%)
Foraminal	4 (2.05%)
Mixed	4 (2.05%)
Paravertebral	13 (6.66%)
Intradiscal	24 (12.3%)
Pathology of fracture (165 patients)	
Osteoporosis	63
Trauma	79
Neoplasm	23

Cement leakage risk factor analysis

According to the postoperative CT scans, cement leakage was detected in 37 of the 165 patients (22.42%) and in 51 of the 195 segments (26.15%). No patients with cement leakage revealed neurological deficits or any other clinical symptoms.

A statistically significant relationship was observed between cement leakage and fracture pathology ($\chi^2 = 12.673$; $p = 0.002$).

The bipedicular approach group yielded a higher cement leakage rate than the unilateral approach group (94.11%, 5.88%, respectively; $p = 0.055$) but no statistical significance was revealed. Table 2 presents the risk factor analysis of cement leakage.

Table 2. Cement leakage (risk factor analysis)

Characteristic	Leakage (n/%)	No leakage (n/%)	χ^2	p
Sex			1.347	0.246
Male	19	52		
Female	18	76		
Pathology of fracture			12.673	0.002
Osteoporosis	6	57		
Trauma	21	58		
Neoplasm	10	13		
Surgical approach			3.672	0.055
Unipedicular	3	24		
Bipedicular	48	120		
Fractured segments			2.496	0.287
Thoracic	10	17		
Thoracolumbar (T12–L1)	27	75		
Lumbar	14	52		
Cement volume			0.023	0.88
≤ 3.8 mL	24	66		
> 3.8 mL	27	78		

DISCUSSION

In a developing society, osteoporotic vertebral compression fractures are frequently observed with the prolongation of life span. Apart from osteoporotic compression fractures, traumatic and neoplasm-related vertebral fractures are frequently encountered in our daily practice. Bed rest and orthosis are typical conventional treatments for vertebral compression fractures, as most are stable fractures without neurological deficits. As an alternative treatment option for vertebral compression fractures without any neurological deficits, percutaneous vertebral augmentation procedures provide many advantages, including early pain relief, shorter hospital stay, and early mobilization that can reduce thromboembolic complications, especially in elderly patients [15]. Since these minimally invasive treatments provide an early return to work, they are the preferred treatment methods for vertebral compression fractures in young adults [16].

Despite being minimally invasive, the complications of PV and PK are not rare; however, in most cases, they have no clinical significance. Persistence of pain, cement leakage, paralysis, allergic reaction to bone cement, pulmonary embolism and bleeding (epidural hemorrhage) are potential complications of these minimally invasive procedures [17]. Among these complications, cement leakage is the most common, which can occur in the epidural, paravertebral or intradiscal spaces [14]. Several studies have focused on the incidence of and risk factors for cement leakage in PK and PV under general anesthesia [18–21].

Lee et al. [6] revealed that the incidence rate of cement leakage per number of treated patients was significantly higher in the PV group than that in the PK group under local anesthesia. The most prominent advantage of PK over PV is the balloon that reduces the cement perfusion pressure during the procedure [3].

The type of anesthesia, amount and viscosity of the bone cement injected, fracture characteristics (type, severity, pathology, segment, etc.), approach (bilateral or unilateral), sex, age, and surgery duration have been assessed as risk factors for cement leakage so far [17, 20].

Especially, elderly patients present with a higher an aesthetic risk because of comorbidities, including cardiopulmonary diseases, that make surgeries in the prone position under general anesthesia significantly more difficult. All PK procedures included in the study were applied under sedoanalgesia, which provides the advantage of perioperative neurological examination and prevention of general anesthesia complications. Lavelle et al. [16] preferred general anesthesia in their 94 cases of kyphoplasty and revealed that elderly patients could not tolerate the procedures in the prone position unless performed under general anesthesia. Cagli et al. [11] have reported four cases of cement leakage (three for PV and one for PK) in their series of 91 PV and PKP cases operated on under local anesthesia. However, both in the study by Cagli et al. [11] and in this study, none of the operations was terminated because of intolerance to the type of anesthesia.

In the literature, this study has the largest sample size to retrospectively investigate the incidence rate of cement leakage specifically in PK procedures under sedoanalgesia.

The pooled studies have shown that the incidences of cement leakage for PV and PK were 59.7% and 18.4%, respectively [17]. In this study, the overall incidence rate of bone cement leakage was consistent with previous reports (51 of 195 segments, 26.15%) (Table 3) [6, 22–25].

Table 3. Recent studies presenting cement leakage rates in percutaneous kyphoplasty procedures

Author	Vertebral segments	Cement leakage	Incidence
Chen et al. [22]	44	34	77.27%
Rebolledo et al. [23]	56	9	16.07%
Vogl et al. [24]	65	42	64.61%
Lee et al. [6]	59	29	49.2%
Mishra et al. [25]	61	9	14.75%

Fracture pathology and severity and cement volume were significant predictors of cement leakage according to previous studies [17, 20, 26]. In addition, this study revealed that only fracture pathology was a statistically

Table 4. Logistic regression analysis among fracture pathology subgroups in patients with cement leakage

Subgroups	Coefficient B	Standard error	Z	p	OR	95% CI
Osteoporosis	-1.99	0.599	3.322	0.001	0.137	0.042–0.442
Trauma	-0.748	0.491	1.524	0.128	0.473	0.181–1.239
Constant	-0.249	0.42	0.593	0.553	0.78	

significant risk factor for cement leakage (Table 4). The incidence of cement leakage in the osteoporosis group was higher than the rest (Figure 4). This finding might be due to the weakness of the cortical bone structure in osteoporotic vertebrae. Although no evident intervertebral cleft was observed in preoperative radiological images, cement leakage may have occurred due to the weak structure of the cortical walls in osteoporotic vertebral bodies that cannot resist the cement perfusion pressure.

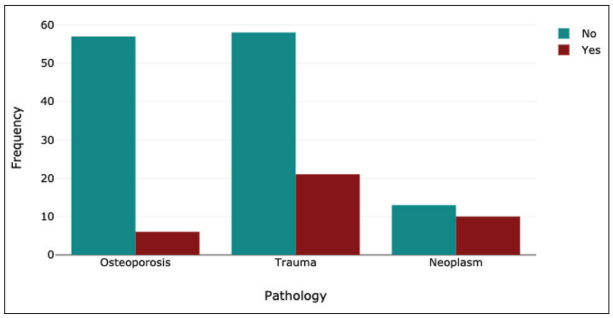

Figure 4. Cement leakage – fracture pathology relationship

The incidence and extent of bone cement leakage invading the spinal canal in the thoracic group were significantly higher than those in the lumbar group (10.1% *vs.* 3.7% and 22.5% *vs.* 11.4, respectively). This finding suggests that the morphological features of the posterior wall of the middle and lower thoracic vertebrae are a risk factor for cement leakage into the spinal canal during PK [13].

Analysis of the leakage locations showed that the intradiscal space was the most prominent side for cement leakage in this case series. Nieuwenhuijse. et al. [26] have reported similar results and attributed this finding to the frequent connection of intravertebral clefts with the intervertebral disc space. The presence of an intravertebral cleft was assumed to be a significant predisposing factor for cement leakage in PV and PK [18].

Some studies have reported that the bilateral percutaneous augmentation approach is more effective for pain relief with the advantage of symmetrical bone cement distribution in the vertebral body [27, 28]. Alternatively, the unilateral approach has significant benefits, including less operation duration and X-ray exposure. Most recent studies have revealed that the amount of bone cement introduced was significantly less in the unilateral approach [8, 12]. However, no definite conclusion has been made regarding whether cement volume is a risk factor for cement leakage. Chen et al. [22] have found that the unilateral approach decreases the incidence of cement leakage according to the meta-analysis of randomized controlled trials involving unilateral and bilateral percutaneous vertebral augmentation for osteoporotic compression fractures. Five of six trials in that meta-analysis included PK procedures, and the following factors were compared between the groups: operative method, surgical approach (unilateral/bilateral), sex, age, number of treated vertebrae, and cement volume. In that study, the type of anesthesia was not examined as a risk factor for cement leakage. This study identified that cement volume and surgical approach were not risk factors for cement leakage in PK under sedoanalgesia ($p = 0.88$ and $p = 0.055$, respectively). Meanwhile, the bipedicular approach group had a higher incidence rate of cement leakage than the unipedicular approach group. This could be attributed to the wider distribution of bone cement via the bipedicular approach that resulted in more cement leakage. Although this finding is consistent with the results of the study by Chen et al. [22], it did not reveal a statistical significance ($p = 0.055$).

The mean operation duration was 39.86 minutes, and 20 of the 165 patients underwent surgery for multiple-segment fractures. Nevertheless, the mean operation duration in this study was consistent with those in previous studies [3, 8].

Due to the retrospective nature of this study, operation comparison is not suitable for the random, control, and blind methods. Despite this limitation, we believe that the number of patient cases available is adequate to accept the results as meaningful.

CONCLUSION

Sedoanalgesia is not a risk factor for cement leakage in PK. However, sedoanalgesia offers a safe anesthesia option to avoid possible complications. Only fracture pathology was shown to be a potential risk factor for cement leakage in PK.

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Анализа фактора ризика од цурења цемента у перкутаној кифопластици – да ли седоаналгезија повећава ризик?

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САЖЕТАК

Увод/Циљ Неколико студија је оценило врсту анестезије као могући фактор ризика за цурење цемента у поступцима перкутане аугментације кичме. Ова студија има највећу серију у литератури која открива податке о учесталости цурења цемента у перкутаној кифопластици под седоаналгезијом.

Циљ студије био је процена могуће повезаности између седоаналгезије и цурења цемента у кожним процедурама кифопластике.

Методе У овој студији ретроспективно је прегледано 195 прелома вертебралне компресије лечених перкутаном кифопластиком под седоаналгезијом код 165 пацијената. Процењена је повезаност између седоаналгезије и цурења цемента у перкутаним поступцима кифопластике.

Резултати Просечна старост истраживане популације била је 64,37 година (распон 24–108 година), а однос мушкараца и жена био је 71/94. Није уочена значајна разлика у уделу мушкараца (n = 71, 43,03%) и жена (n = 94, 56,96%) међу групама. Међу 195 преломљених сегмената, најчешћи преломи су примећени на нивоима Т12 (n = 41, 21,02%) и Л1 (n = 65, 33,33%).

Закључак Седоаналгезија није фактор ризика за цурење цемента у перкутаној кифопластици и нуди сигурну могућност анестезије како би се избегле могуће компликације.

Кључне речи: фрактура компресије кичме; перкутана кифопластика; цурење цемента; седоаналгезија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Detection of hypotension during spinal anesthesia for caesarean section with continuous non-invasive arterial pressure monitoring and intermittent oscillometric blood pressure monitoring in patients treated with ephedrine or phenylephrine

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SUMMARY

Introduction/Objective Despite frequent side effects such as hypotension, spinal anesthesia (SA) is still one of the best anesthetic methods for elective cesarean section (CS). Intermittent, oscillometric, non-invasive blood pressure monitoring (NIBP) frequently leads to missed hypotensive episodes.
The objective was to compare continuous non-invasive arterial pressure (CNAP) monitoring with NIBP in the terms of efficiency to detect hypotension.

Methods In this study, we compared CNAP and NIBP monitoring for hypotension detection in 76 patients divided into two groups of 38 patients treated with ephedrine (E) or phenylephrine (P), during three-minute intervals, starting from SA, by the end of the surgery.

Results In E group, significantly lower mean systolic blood pressure (SBP) values with CNAP compared with NIBP ($p = 0.008$) was detected. By monitoring CNAP, we detected 31 (81.6%) hypotensive patients in E group and significantly lower number, 20 (52.6%), with NIBP ($p = 0.001$), while in P group CNAP detected 34 patients (89.5%) and NIBP only 18 (47.3%), $p = 0.001$. By monitoring CNAP, we detected significantly higher number of hypotensive intervals in E and P groups ($p < 0.001$). Umbilical vein pH was lower within hypotensive compared with normotensive patients in E and P groups, with CNAP and NIBP, respectively ($p < 0.001$, $p = 0.027$ in E, and $p = 0.009$, $p < 0.001$, in P group).

Conclusion CNAP is more efficient in hypotension detection for CS during SA, which allows faster treatment of hypotension, thus improving fetal and maternal outcome.

Keywords: spinal anesthesia; cesarean section; hemodynamic monitoring; hypotension

INTRODUCTION

Spinal anesthesia (SA) is the method of choice for elective cesarean section (CS) despite the fact that it can cause various side effects such as hypotension [1–9]. General anesthesia due to possible difficult intubation and aspiration can lead to the numerous complications [1].

During CS, SA causes hypotension in approximately 50–90% of patients [2, 10] because of the sympathetic blockade [6]. Hypotension is usually accompanied by maternal nausea, vomiting, shivering, respiratory and neural problems [8]. Hypotension leads to the reduction in utero-placental blood flow, and umbilical blood acidosis which can reflect on the vitality of the newborn, Apgar score. Because of potential maternal and fetal side effects, hypotension must be treated immediately, which implies to the significance of more frequent and precise monitoring of maternal blood pressure (BP) [8, 10].

Hypotension can be overcome by using different vasopressors. Phenylephrine increases venous constriction and arterial constriction binding to α1v and α1a adrenergic receptors, which increases BP [5, 11, 12, 13]. Ephedrine is non-catecholamine sympathomimetic agent, acting through α, β1, and β2 adrenergic receptors. Ephedrine has predominant indirect mode

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of action, which explains its relatively slow and prolonged effect [5, 11, 12].

During the past years, continuous non-invasive arterial pressure (CNAP) monitoring is being used in obstetrics, but not routinely. CNAP monitor use allows that side effects of SA during the caesarean section can be minimized or avoided by rapid detection of BP changes. The CNAP monitor uses volume clamp method described by Penáz et al. [14] as "vascular unloading." CNAP measure blood volume in an artery and kept constant by applying external pressure. Changes in external pressure keep the arterial blood volume constant and corresponds to the changes of arterial pressure [15]. CNAP monitor is not used in patients with aortic regurgitation, arterial vascular disease, hypothermia, low perfusion index – PI < 1. Hemodynamic parameters measurement by classic NIBP monitor might reduce the chance of recurrent hypotensive episode to be detected and thus avoided. There is no clinical guideline for optimal NIBP cycles. Most of the studies analyzed one- to five-minute cycles. Often NIBP measurement causes discomfort in patients due to the arm clamping [16]. If a precise BP measurement is required, continuous invasive BP monitoring is used, which involves the placement of an arterial line.

The main goal of this study was to investigate differences between two different types of monitoring: NIBP and CNAP in the terms of number of detected hypotensive episodes and maternal and newborn characteristics, and to see which of the technique is more confident and reliable. Our hypothesis is that CNAP might detect higher number of hypotensive episodes, compared with NIBP.

METHODS

The study was performed as comparative, prospective, and randomized. The study was conducted in accordance with the Declaration of Helsinki of 1975, revised, in 2013, and the protocol was approved by the Ethics Committee of the Dr Dragiša Mišović – Dedinje University Hospital Center in Belgrade no. 01-5293/23. All patients, 76 in total, gave their written informed consent. All patients were of American Society of Anesthesiologists (ASA) 1 or 2 physical statuses. The subjects were primiparous or multiparous patients in the term pregnancy. All patients were scheduled for elective CS, according to obstetric indications and had been examined by the anesthesiologist the day before surgery. Inclusion criteria were; age of the patients between 18 and 40, one fetus, body weight between 50 and 100 kg, and height 150 cm or higher, difference between arterial pressure of the left and right arm have not exceeded 5 mmHg, while exclusion criteria were: less than 36 weeks gestation, cardiovascular diseases, pre-eclampsia, hypertension, and contraindications for SA. The patients were divided into two groups of 38 each, and selected to receive either ephedrine or phenylephrine by a computer-generated randomization table.

Ephedrine, (Galenica Senese, Monteroni d'Arbia, Italy), E group received infusion at a 5 mg/min immediately after SA during the first three minutes. In the cases of more than 20% of the drop of systolic blood pressure (SBP) than the baseline, rescue bolus dose of 5 mg of ephedrine was given intravenously (IV). Then, the infusion was continued. If SBP values increased more than 20% of baseline values, the infusion was interrupted.

Phenylephrine (Sintetica Spinal Anesthesia, Sintetica, London, United Kingdom), P group received infusion at a 25 μg/min dose, starting two minutes prior to SA, and for the next three minutes. In the cases of reduced SBP more than 20% of baseline the patients received rescue bolus dose of 50 μg of phenylephrine, intravenously and infusion was continued. In the cases of bradycardia, the patients received 0.5 mg atropine, intravenously. If SBP was higher than 20% of baseline, phenylephrine infusion was aborted. Both infusions were administered via infusion pump (Argus 600S, Argus Medical AG, CH 3627 Heimberg, Switzerland).

Patients were in the supine position, with the operating table tilted 15 degrees to the left.

In our cohort, heart rates (HR) lower than 60 per min were defined as bradycardia. The drop of SBP values for more than 20% of baseline value was defined as hypotension, while the increase of more than 20% of baseline SBP value was defined as hypertension.

All patients were treated with 50 mg of ranitidine intravenously, one hour preoperatively through an IV cannula inserted into the right arm. All patients received 500 ml of Hartmann's solution before entering the operating room and antibiotic 30 min preoperatively. During the CS the infusion of Hartmann's solution was resumed. Baseline values of BP, HR, electrocardiogram, and oxygen saturation (SpO_2) were obtained with DASH® 4000 monitor (GE Medical Systems Information Technologies, USA). Mean values of first three successive measurements NIBP on the surgery table were used as baseline values of NIBP, and were recorded every three minutes. NIBP cuff was placed on left arm of the patients.

BP was measured and recorded with LIDCO Rapid^{V2}CNAP (LIDCO Ltd, London, UK) hemodynamic monitor, as well. LIDCO Rapid^{V2}CNAP contains a module for non-invasive continuous monitoring of arterial pressure using a double finger cuff with integrated infra-red (IR) photo sensor and air bag. Measured IR signal allows tracking blood volume in the finger. The finger cuff is consisted of the pressure gauge for measuring pressure for each heartbeat (beat to beat). The graph for continuous BP is recorded by CNAP module and is analyzed by Pulse CO^R algorithm.

Double finger cuff attached to the index and middle finger of the right arm.

The CNAP monitor was calibrated before the first measurement to the value of the arterial BP of the brachial artery measured by the NIBP monitor. Calibration was automatic and manual in the event of a drop in BP when values from the NIBP monitor are entered manually. Lidco Rapid CNAP technology is also reliable during the application of vasoactive drugs because it uses the protected VERIFY algorithm for autocorrection of changes in arterial tone.

Baseline CNAP is represented by mean CNAP value in the first minute after the monitor calibration. Time from CNAP and NIBP monitors were concordant. BP was measured on both hands at each patient's (on the right arm via CNAP, and on left arm via NIBP monitor). Both hands were at heart level. NIBP measured SBP at three-minute intervals. At the same time, at each patient SBP was cyclically compared at both monitors. Hypotension treatment was based on SBP values monitored with CNAP.

Bupivacaine-spinal (Marcaine® Spinal Cenexi-Fontenay), 0.5% 2–2.2 ml, 10–11 mg was given in L3/4 intervertebral space. SA was given with 25 G "pencil point" spinal needle (Pencan® B.Braun Melsungen AG Germany) in the sitting position. Then, the patients were returned to their supine position, with the operating table tilted 15° to the left.

We have analyzed the number of hypotensive patients detected by CNAP and NIBP monitor, in both groups, the number of hypotensive episodes detected by CNAP and NIBP monitor, in both groups, pH analysis of umbilical vein, analysis of Apgar score in the first and fifth minute (HR, respiration, muscle tone, reflex irritability, and skin color). Apgar score was calculated as sum of points (0–10); where each parameter carries 0–2 points.

The power of the study at 90% is the result of the assessment of sample size justification, and has been performed before the start of the study. The sample size was determined by Altman nomogram and confirmed by calculation with the formula was defined with a total of 76 patients. The data collected were processed in SPSS v. 19.0 (IBM Corp., Armonk, NY, USA) software. For statistical analysis we used Kolmogorov–Smirnov normality test, then parametric and non-parametric Student's t-test, Mann–Whitney, Pearson's correlational test, χ^2 test, and Fisher's exact test for analysis of frequency distribution; p values < 0.05 were considered as significant.

RESULTS

In this cohort, we investigated 76 patients planned for CS under SA, treated with two different vasopressors, 38 treated with ephedrine and 38 treated with phenylephrine. In both groups we analyzed and compared 1500 intervals measurements SBP (750 per group) in three-minute intervals starting with SA, up to the end of the delivery and surgery. Mean time of data collection was 59 min per patient.

Table 1. Patient characteristic data

Characteristics	Group ephedrine (n = 38)	Group phenylephrine (n = 38)	p
Age (year)	32 (4)	30.9 (3.6)	0.203
Weight (kg)	82.1 (9.8)	74.8 (8.8)	0.003*
Height (cm)	169.7 (5.2)	166.9 (6.3)	0.064
Gestational age (weeks)	38.8 (0.5)	38.8 (0.6)	0.692
Parity	2 (1–3)	2 (1–3)	-
ASA Class I	24 (63.2%)	24 (63.2)	-
ASA Class II	14 (36.8%)	14 (36.8)	-

*significant p < 0.05, mean (SD), median (min–max), n (%); Student's t-test, χ^2 test; ASA – American Society of Anesthesiologists

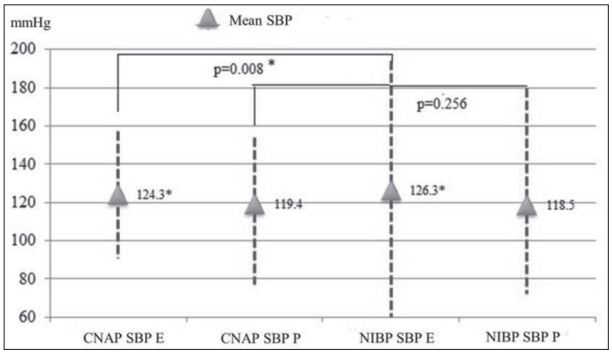

Figure 1. Comparison of mean SBP between E and P groups. Mean systolic blood pressure (SBP) in mmHg measured with CNAP and NIBP methods in ephedrine (E) and phenylephrine (P) groups; CNAP – continuous non-invasive arterial pressure; NIBP – non-invasive blood pressure monitoring; p-values < 0.05 were considered as significant and is presented by *.

Patient characteristics were shown in Table 1. Patients from E group were of greater body weight (p = 0.003).

Table 2. shows fetal characteristics measured by the two methods (CNAP or NIBP) in hypotensive and normotensive patients within E and P groups. Umbilical vein pH was lower within hypotensive compared with normotensive patients in E and P groups, with CNAP and NIBP, respectively (p < 0.001, p = 0.027 in E, and p = 0.009, p < 0.001, in P group) (Table 2). Apgar score in the first and fifth minute did not change significantly, when compared hypotensive and normotensive patients in E and P groups

Table 2. Fetal outcome (pH and Apgar score) in normotensive and hypotensive patients within ephedrine and phenylephrine groups

Group Ephedrine	Continuous non-invasive arterial pressure device		Intermittent oscillometric arterial pressure measurement			
	normotensive	hypotensive	p	normotensive	hypotensive	p
pH	7.381 (0.055)	7.342* (0.065)	< 0.001	7.365 (0.030)	7.359* (0.040)	0.027
Apgar minute 1	9 (8–9)	9 (8–9)	-	9 (8–9)	9 (8–9)	-
Apgar minute 5	10 (9–10)	10 (9–10)	-	10 (9–10)	10 (9–10)	-
Group Phenylephrine	Continuous non-invasive arterial pressure device (CNAP)		Intermittent oscillometric arterial pressure measurement (NIBP)			
	normotensive	hypotensive	p	normotensive	hypotensive	p
pH	7.363 (0.063)	7.337* (0.067)	0.009	7.361 (0.036)	7.341* (0.036)	< 0.001
Apgar 1 minute	9 (8–9)	9 (8–9)	-	9 (8–9)	9 (8–9)	-
Apgar 5 minute	10 (9–10)	10 (9–10)	-	10 (9–10)	10 (9–10)	-

*significant p < 0.05, mean (SD), median (min–max), Student's t-test, Mann–Whitney test

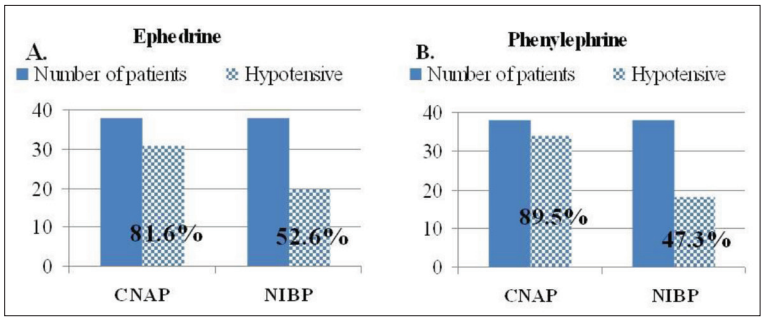

Figure 2. Percentage of hypotensive patients by CNAP and NIBP monitor in E and P groups; the percentage of patients with at least one SBP decline by more than 20% from baseline, detected with CNAP or NIBP in ephedrine (E) and phenylephrine (P) groups; CNAP – continuous non-invasive arterial pressure; NIBP – non-invasive blood pressure monitoring

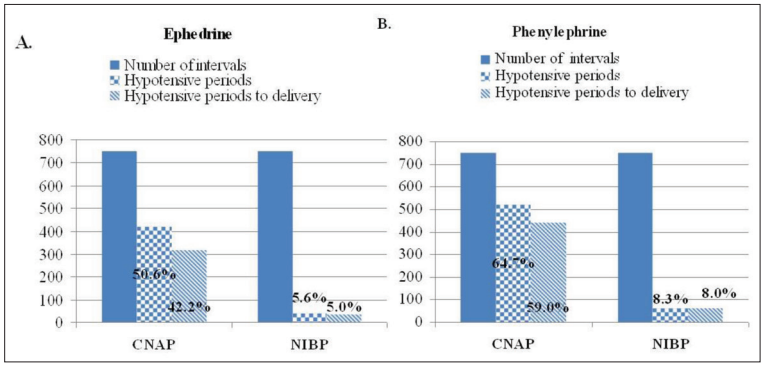

Figure 3. The incidence of hypotensive episodes in E and P groups by CNAP and NIBP monitoring. Incidence of hypotensive episodes in the period from spinal anesthesia to the end of the surgery and in the period from spinal anesthesia to the delivery in A-ephedrine (E), and B-phenylephrine (P) groups with CNAP and NIBP monitors; CNAP – continuous non-invasive arterial pressure; NIBP – non-invasive blood pressure monitoring

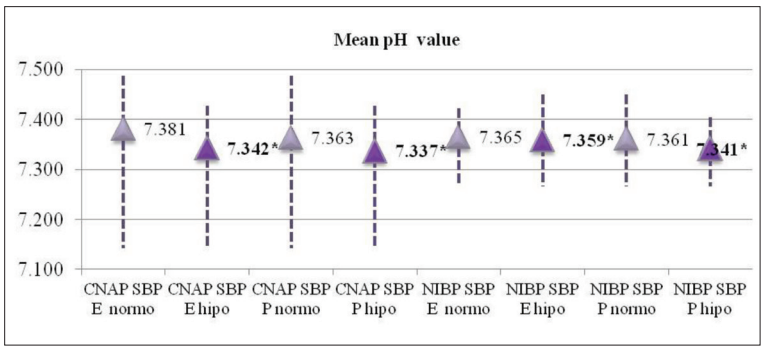

Figure 4. Umbilical vein pH differences within hypotensive and normotensive groups between CNAP and NIBP monitors; mean umbilical blood pH values within normo and hypotensive patients in ephedrine (E) and phenylephrine (P) monitored with CNAP and NIBP monitor; CNAP – continuous non-invasive arterial pressure; NIBP – non-invasive blood pressure monitoring; significant $p < 0.05$ is presented by *.

on both monitors (Table 2). Mean values SBP measured with both monitors in E and P groups were presented in Figure 1. We detected significantly higher SBP values in E group, measured by both CNAP and NIBP methods (124.3 CNAP and 126.3 NIBP), compared with P group (119.4 CNAP and 118.5 NIBP), with $p < 0.001$.

In E group, we detected significantly lower mean SBP values with CNAP compared with NIBP ($p = 0.008$, Figure 1). In P group, we did not detect any difference in SBP values between two methods ($p = 0.256$, Figure 1).

Percentage of hypotensive patients by CNAP and NIBP monitor in E and P groups was shown in Figure 2. In E group by CNAP method, 31 (81.6%) patients experienced hypotension, while significantly lower number of patients experienced hypotension, according to NIBP monitoring, 20 (52.6%), ($p = 0.001$, Figure 2). In P group, hypotension was detected within 34/38 (89.5%) patients by CNAP monitoring, while according to NIBP monitoring 18 (47.3%) patients had hypotension ($p = 0.001$, Figure 2).

In E group, during the 750 measurements of SBP per every 3 min, hypotension was detected in 420 (50.6%) measurements with CNAP, while only in 42 (5.6%) measurements with NIBP ($p < 0.001$, Figure 3). In P group, CNAP monitor detected hypotension in 521 (64.7%) cycles of measurement, while with NIBP only 62 (8.3%) measurements indicated hypotension ($p < 0.001$, Figure 3).

Significantly higher incidences of hypotensive intervals were detected to the moment of the delivery with CNAP monitor (42.2% hypotensive episodes in E group and 59% in P group, i.e., in 83.3–91.2% of cases, Figure 3). NIBP monitor did not show any significant differences in both groups. (5% hypotensive episodes in E group and 8% in P group, i.e., in 89–96% of cases, Figure 3). In the cases of hypotensive periods to delivery, CNAP showed significantly higher number compared with NIBP in both, E and P groups ($p < 0.001$, Figure 3).

Mean values of umbilical vein pH were lower within hypotensive compared with normotensive patients in E and P groups, with CNAP and NIBP measurements, respectively ($p < 0.001$, $p = 0.027$ in E, and $p = 0.009$, $p < 0.001$, in P group) (Figure 4).

Additionally, we performed correlational analysis between E and P groups (Table 3), which additionally confirms results from umbilical pH analysis presented on Figure 4. Lower pH values within hypotensive patients are confirmed in correlational analysis. We detected negative correlation with moderate correlational coefficient -0.468 with very low p value ($p < 0.001$, Table 3, Pearson's product moment) between mean pH values and number of hypotensive episodes on E group, which means that higher number of hypotensive episodes might be associated with lower pH values in E group and *vice versa*.

DISCUSSION

Up to now, there has been no precise definition of hypotension in the literature and practice. Majority of the studies

Table 3. Associations between SBP, hypotension incidence, and pH in E and P groups

Parameter	pH E	pH P
SBP	**rho = 0.161****	**rho = -0.116****
	p < 0.001	**p = 0.002**
ΔSBP	**rho = -0.236****	rho = -0.035
	p < 0.001	p = 0.358
Incidence of hypotension (number of patients)	**rho = -0.468****	**rho = -0.108****
	p < 0.001	**p = 0.004**
Incidence of hypotension in number of intervals	**rho = -0.100****	rho = 0.046
	p = 0.006	p = 0.216

Correlation at the 0.01 level (2-tailed)-** was considered as significant; SBP – systolic blood pressure; E – ephedrine; P – phenylephrine; Pearson's correlational test

use the drop of 20% of baseline BP, or use the value of systolic BP below 100 mmHg as hypotension [17]. Besides the hypotension definition, type of monitoring also may impact on efficiency of hypotension detection and thus its prevention and treatment [10, 18, 19]. Stenglova and Benes [19] reviewed and emphasized that even a short period of hypotension, especially if they are more frequent, may significantly influence on postoperative recovery.

Ilies et al. [10], Juri et al. [18] are among the first authors who compared differences in number of hypotensive episodes between continuous and intermittent monitoring.

Although hemodynamic changes during CS have already been measured continuously [10, 18, 20, 21], to the best of our knowledge, this is the first study that investigates differences in hypotensive episodes by using DASH® 4000 monitor, non-invasive intermittent oscilloscopic compared with parameters measured with continuous LIDCO Rapid^{V2}CNAP monitoring system within the patients treated with E and P vasopressors.

Juri et al. [18] compared ClearSight™ system (Edwards Lifesciences, Irvine, CA, USA) with classical BP monitoring within 40 patients and have shown ClearSight™ system use resulted in lower rates of hypotension and nausea than use of regular oscillometric BP monitor.

Han et al. [16] give the advantage to CNAP monitoring compared with NIBP monitoring in the hemodynamic stability maintenance, and maternal and fetal outcome. Their study has shown similar incidence of detected hypotensive periods in both groups (NIBP-N and CNAP-C). Significantly lower incidence of severe hypotension was detected in C group, because it was significantly earlier discovered and treated.

In our research, we have compared results of SBP and umbilical vein pH measured with both, CNAP and NIBP monitoring systems. Interestingly, we detected significantly lower mean values of SBP with CNAP compared with NIBP measurement in E group, but not in P group. Number of hypotensive patients significantly differed between CNAP and NIBP in both, E and P groups. In E group, according to CNAP monitor, 81.6% of patients experienced hypotension, and 52.6% according to NIBP, while in P group, CNAP detected 89.5%, and NIBP only 47.3% hypotensive patients. Similarly, Ilies et al. [10], compared two techniques CNAP by CNAPTM Monitor 500, (CNSystems Medizintechnik, Graz, Austria), and oscillometric [non-invasive arterial pressure measurement, (NIAP)]. They also showed that CNAP detected lower values of BP, than NIAP. CNAP detected hypotension, within 91% patients, while NIAP only within 55%. Of the total number of three-minute intervals, CNAP detected 39% as hypotensive and NIAP 9%. This may be due to differences in protocols, differences in vasopressors used, and their mode of application.

In our research, we have also measured number of hypotensive episodes up to the end of the surgery, where we have also found significantly higher number detected with CNAP compared with NIBP in both, E and P groups.

Numerous studies have shown that hypotension leads to the decrease in pH umbilical blood [22] or a lower Apgar score [23].

Similarly, Ilies et al. [10], in our research, mean umbilical vein pH values were lower within hypotensive patients, on both, CNAP and NIBP in E and P groups. Apgar scores at the first and fifth minute were not different between hypotensive and normotensive mothers.

The major limitation of the study was that we measured SBP at three-minute intervals. But, if we had been measuring with one- or two-minute intervals with NIBP, discomfort of patients would be much greater.

CONCLUSIONS

This study has found that hypotension during CS is more readily detected with CNAP than with NIBP monitor. Our results showed that in both examined groups of vasopressors on both monitoring systems, lower pH values were detected within hypotensive patients.

Continuous monitoring enables clinicians to track and detect hypotension more precisely and efficiently than intermittent. Not only the type of monitoring is important, but also the type of vasopressor, as well. Further researches are needed which will involve much detailed information on hemodynamic changes and patients' outcome at different time points during the surgical procedure.

Conflict of interest: None declared.

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Откривање хипотензије током спиналне анестезије за царски рез континуираним неинвазивним праћењем артеријског притиска и интермитентним осцилометријским праћењем крвног притиска код болесница третираних ефедрином или фенилефрином

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САЖЕТАК

Увод/Циљ Упркос честим нежељеним ефектима као што је хипотензија, спинална анестезија је и даље техника избора за планирани царски рез. Интермитентно неинвазивно праћење крвног притиска често не детектује хипотензивне епизоде. Циљ ове студије је био да се упореди континуирано неинвазивно праћење артеријског притиска са интермитентним неинвазивним праћењем крвног притиска у смислу ефикасности у откривању хипотензије.

Методе Упоређивани су системи за континуирано неинвазивно праћење артеријског притиска и интермитентно неинвазивно праћење крвног притиска ради детекције хипотензије код 76 болесница подељених у две групе од по 38 болесница, третираних ефедрином (Е) или фенилефрином (Ф), на свака три минута, почевши од спиналне анестезије па све до краја операције.

Резултати У групи Е су детектоване знатно ниже средње вредности систолног крвног притиска континуираним неинвазивним праћењем артеријског притиска у поређењу са интермитентним неинвазивним праћењем крвног притиска ($p = 0,008$). Континуираним неинвазивним праћењем артеријског притиска детектована је 31 (81,6%) хипотензивна болесница у групи Е и знатно мањи број, 20 (52,6%) болесница, интермитентним неинвазивним праћењем крвног притиска ($p = 0,001$), док је у групи Ф континуираним неинвазивним праћењем артеријског притиска детектована хипотензија код 34 болеснице (89,5%), а интермитентним неинвазивним праћењем крвног притиска код 18 (47,3%) болесница, $p = 0,001$. Континуираним неинвазивним праћењем артеријског притиска детектован је знатно већи број хипотензивних епизода у групама Е и Ф ($p < 0,001$). *pH* вредности умбиликалне крви биле су значајно ниже код хипотензивних у односу на нормотензивне болеснице у групама Е и Ф, и са континуираним неинвазивним праћењем артеријског притиска и интермитентним неинвазивним праћењем крвног притиска, респективно ($p < 0,001$, $p = 0,027$ у групи Е, и $p = 0,009$, $p < 0,001$ у групи Ф).

Закључак Континуирано неинвазивно праћење артеријског притиска је много ефикасније у откривању хипотензије током царског реза у спиналној анестезији, што омогућава бржи третман и мање нежељених ефеката код мајке и новорођенчета.

Кључне речи: спинална анестезија; царски рез; хемодинамско праћење; хипотензија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The reasons for unusable lipemic blood plasma in transfusion treatment

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SUMMARY

Introduction/Objective The increased presence of lipid particles in blood is one of most common reasons that transfusion units are unusable. The risk factors for lipemic plasma in donated blood are not completely known. The aim of this study is to identify the factors that influence plasma to be fatty so that we can prevent further storage costs and eliminate unusable transfusion units.

Methods This case–control study was conducted in 2017, and 1552 respondents were included in the study. The control group included 1502 subjects whose blood was not lipemic, while 50 patients with lipemic blood were selected for the case group. The presence of lipemic blood was assessed by inspection, while data were collected by clinical laboratory tests and a questionnaire.

Results Our findings show that multiple blood donors with lipemic blood were significantly older ($p < 0.0005$) and have higher systolic and diastolic pressure ($p < 0.0005$), high triglyceride levels ($p < 0.0005$), and lower levels of hemoglobin ($p < 0.0005$). Additionally, the presence of lipemic plasma was associated with female sex ($p = 0.002$), blood type ($p = 0.016$), heart disease ($p < 0.0005$), smoking ($p < 0.005$), diabetes ($p = 0.001$), lipid intake prior to blood donation ($p < 0.005$) and venipuncture therapy ($p < 0.0005$). Systolic pressure is a reliable predictor of lipemic blood (AUROC = 0.901, $p < 0.0005$).

Conclusion Our study provided a rational explanation and identified some of the risk factors that may help identify potential donors with lipemic blood.

Keywords: blood transfusion; blood donors; plasma; preventive measures; cholesterol; triglyceride

INTRODUCTION

The availability of safe blood and blood products has always been a key strategy for addressing health-related challenges [1, 2, 3]. In transfusion practice, blood and blood components with changed plasma color are often present [4]. Color changes occur due to factors such as hemolysis, bacterial contamination, bubble formation, the presence of clots and fibrin strands and bright yellow to brown lipemic plasma with a specific "strawberry milkshake" appearance [4]. The increased presence of lipid particles in the blood is called lipemia and is one of most common reasons why transfusion units are unusable [4]. The causes of occurrence are different, but lipemia is usually associated with excessive nutrition [2, 5]. Donors who eat a fatty meal before donating blood are known to have an increased plasma triglyceride concentration for several hours. [6]. Other causes of lipemia include conditions such as obesity, diabetes mellitus, Cushing disease, acromegaly, nephritic syndrome, hypothyroidism, pregnancy and the use of various medications [4].

Increased blood fat values are associated with atherosclerotic diseases and heart disease and greatly increase the possibility of the occurrence of blood pressure and stroke [7]. Low-calorie nutrition and some foods, such as vitamins, minerals, and unsaturated fatty acids (omega 3), reduce the level of fat in blood [7].

There are no up-to-date international transfusion guidelines [4]. Therefore, some transfusion centers use visual inspection to detect the turbid appearance of plasma [8]. Further, the effects of lipemic plasma or platelet donations on recipients are not known [4]. Similarly, some countries consider lipemic units acceptable for transfusion [4]. However, excessive lipemia obstructs testing of all blood components and is a rational reason to discard such blood units [4]. This has been applied in our practice in compliance with the Blood Safety Strategy implemented by the Government of the Republic of Montenegro and Institute for Blood Transfusion of Montenegro since 2006 and in accordance with EU Directives 2002/98 EC and the WHO resolution on the availability, safety and quality of blood products.

We tried to discover the collaboration and the origin of the factors that affect the occurrence of increased fat content in donated blood. Knowledge about risk factors and what

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is causing the risk may provide options for the prevention of lipemic plasma donation. The presence of large numbers of such transfusion units in the future could lead to an even greater increase in costs related to the process and length of this type of treatment [1, 9].

METHODS

Ethical approvals

The study was conducted at the Blood Transfusion Institute of Montenegro, Bar Organizational Unit, Bar, Montenegro. Patients included in the study gave their informed consent, and the research project was approved by the ethics committees of the University Medical Center Kragujevac, Serbia. Additionally, the study adhered to the Principle of Good Clinical Practice and the Declaration of Helsinki at all times.

Study design and study population

This case–control study was conducted in 2017. In the observation period, 1639 respondents self-reported as potential blood donors, of whom 127 were rejected as ineligible. The survey included the remaining 1552 respondents (1512 seemingly healthy service providers and 40 patients treated with venipuncture). Of the 1512 healthy donors, 10 gave lipemic blood (Table 1).

Table 1. Study participants

Respondents	n	Normal plasma (control group)	Turbid plasma (case group)
Potential blood donors	1639	-	-
Rejected as ineligible	127	-	-
Seemingly healthy service providers	1512	1502	10
Patients treated with venipuncture	40	0	40
Total	1552	1502	50

The respondents were divided into two groups. The control group consisted of 1502 subjects whose blood was not lipemic and consisted exclusively of healthy donors. For the group of cases, 50 subjects with lipemic blood were selected, which consisted of the healthy donors who gave lipemic blood – 10 previously mentioned persons – as well as patients treated with therapeutic venipuncture – 40 sick persons (Table 1).

The basic criteria for assessing donor eligibility were 18–65 years of age, body weight over 55 kg, hemoglobin values (in males, higher than 135 g/l; in females, higher than 125 g/l), blood pressure values (systolic 120–150 mmHg; diastolic 80–100 mmHg) and the presence of elevated glycemia (greater than 6.1 mmol/l). To examine the factors whose elevated values affect the appearance of lipemic blood, we included 40 patients undergoing venipuncture (hypertension, other cardiovascular disease, obesity, and blood with an elevated erythrocyte count) in the study. According to the clinical and laboratory findings, these subjects are not eligible as donors and based on the presence or absence of blood fat, were grouped into a control or a case group. Subjects who were undergoing therapeutic venipuncture included persons 65 years and older who weighed significantly more than 55 kg and had elevated values of the parameters tested (blood pressure, hemoglobin levels, and glucose levels) and/or the presence of chronic diseases (diabetes and cardiovascular disease).

Data collection

Before giving blood, all subjects routinely had their blood type and Rh factor determined and laboratory glucose and hemoglobin values, body weight, and blood pressure values measured. Respondents completed a questionnaire compiled according to European blood donation directives, providing data on sex, age, habits (alcohol and smoking), the presence and type of chronic diseases, previous injuries and surgeries, and the possible presence of infectious and blood-transmissible diseases. Based on the survey questionnaire and clinical laboratory analyses, part of the analyzed data was collected, and donor eligibility was assessed.

Blood collection and laboratory analyses

A total volume of 350–450 ml of blood was collected into standardized blood bags of foreign production (Terumo Corporation, Tokyo, Japan). Citrate-phosphate-dextrose-adenine (CPD) and CPD A1 were used as anticoagulants in the blood bags, each with a duration of 28–42 days. The majority of blood was collected at the Blood Transfusion Department in Bar (80%), while the rest of the blood was collected as voluntary blood donations in the field (20%). The blood units taken were stored at 4°C. After 3–5 hours, by inspection, we detected and recorded the presence of turbid and greasy contents in the bags. Milky and fatty units were removed, while unchanged units were sent for centrifugation and then divided into fractions. All blood units were processed according to the Standard Operational Procedures for treatment with blood and converted into two fractions: fresh frozen plasma and concentrated erythrocytes [1, 10]. Plasma units in which milky color and lipemic content were detected were recorded and eliminated from further use, as were erythrocytes obtained by this procedure. The processing was performed by adequately trained staff on the appropriate standardized equipment.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY, USA). Continuous variables were presented as the mean ± standard deviation. Comparisons between two groups were analyzed by t-test or the Mann–Whitney U-test. Comparisons of categorical data between the groups were performed by the χ^2 test or the Fisher's exact test. Univariate and multivariate binary logistic regression analyses, including odds ratios, were performed to determine the effects of each factor on the dependent variable

Table 2. Lipid levels in the study

Types of analyses mmol/l	Turbid plasma SD	Turbid plasma %	Normal plasma SD	Normal plasma %	SD 95% CI	p χ^2
Total cholesterol	0.98	1.96	1.88	0.12	-0.10 (-0.63–0.54)	
Desirable (< 5.2)	36.97	73.94	1360.5	90.57		
Borderline high (5.2–6.1)	9.24	18.48	124.6	8.25		
Low (> 6.2)	2.52	5.04	15.02	1		
HDL	0.11	0.22	4.95	0.33	4.84 (4.43–5.29)	< 0.01
High (> 1.55)	0.25	0.5	688.96	45.87		
Medium (1.03–1.54)	4.29	8.58	711.94	47.4		
Low (< 1.03)	45.35	90.7	96.12	6.4		
LDL	0.86	1.72	21.02	1.4	20.17 (18.46–22.054)	< 0.01
Low (< 1.55)	0.315	0.3	132326	88.1		
Medium (1.55–4.52)	3.94	6.08	139.68	9.3		
High (> 4.53)	45.9	91.8	18.02	1.2		
Triglycerides	0.87	1.75	24.7	1.6	23.83 (21.82–26.057)	< 0.01
Normal (< 1.70)	1.6	3.2	1108.73	73.8		
Borderline high (1.7–2.25)	0.75	1.5	184.30	12.3		
High (2.26–5.64)	25.6	51.2	181.27	12.1		
Very high (> 5.65)	21.1	42.35	3	0.2		
Total	50	100%	1502	100%		

HDL – high-density lipoprotein; LDL – low-density lipoprotein

Table 3. Numerical variables in relation to lipemic blood

Variable	Not lipemic blood	Lipemic blood	p
	Arithmetic mean +SD	Arithmetic mean + SD	
Age	40.74 ±11.72	57.1 ± 12.47	< 0.0005
Systolic pressure (mmHg)	129.77 ± 6.62	156.1 ± 15.98	< 0.0005
Diastolic pressure (mmHg)	86.29 ± 5.58	102.8 ± 10.46	< 0.0005
Hemoglobin (g/l)	143.88 ± 5.58	138.08 ± 4.66	< 0.0005
Weight (kg)	84.68 ± 5.84	87.84 ± 6.8	0.002

Table 4. Lipemic blood compared to categorical variables

Variable		Lipemic blood	Non-lipemic blood	p
Sex	Male	40 (2.8%)	1395 (97.2%)	0.002
	Female	10 (8.5%)	107 (91.5%)	
Blood type	A	11 (1.8%)	591 (98.2%)	0.041
	B	13 (5.6%)	221 (94.4%)	
	AB	4 (3.8%)	102 (96.2%)	
	0	22 (3.6)	588 (96.4%)	
Professional qualifications	Basic and less	16 (15.8%)	85 (84.2%)	< 0.0005
	Medium	33 (2.3%)	1381 (97.7%)	
	High and higher	1 (2.7%)	36 (97.3%)	
Retiree	No	47 (3%)	1500 (97%)	0.001
	Yes	3 (60%)	2 (40%)	
Heart disease	No	42 (2.7%)	1496 (97.3%)	< 0.0005
	Yes	8 (57.1%)	6 (42.9%)	
High blood glucose	No	48 (3.1%)	1502 (96.9%)	0.001
	Yes	2 (100%)	0 (0%)	
Venipuncture therapy	No	28 (1.9%)	1484 (98.1%)	< 0.0005
	Yes	22 (55%)	18 (45%)	

(fatty blood). A receiver operating characteristic (ROC) curve was generated, and the area under the curve (AROC) was calculated. Sensitivity and specificity for the optimal cut-off value were calculated. Differences were considered significant at $p < 0.05$.

RESULTS

During the study, out of the 1639 people who volunteered for donation, a total of 127 were rejected (7.8%) for various reasons. Seemingly healthy service providers (1512) and patients treated with venipuncture (40) constituted a group of 1552 respondents. Of this number (1552), 50 individuals donated lipemic blood that was then discarded (3.2%), of which 10 units were from seemingly healthy donors and 40 units were from sick persons treated with venipuncture (Table 1). In developed countries of Europe, this percentage ranges 0.05–0.15%.

The total cholesterol level was 0.1 (-0.63 to -0.54) higher in turbid/lipemic plasma cases than in the control group. Additionally, high-density lipoprotein cholesterol levels were higher in donors with turbid plasma than in the control group 84 (4.43–5.29), and low-density lipoprotein cholesterol was 20.17 (18.46–22.05). The value of triglyceride was also higher at 23.83 (21.82–26.05) in donors from the case group compared to those from the control group who gave normal plasma (difference, 95% CI) (Table 2).

The donors whose blood was lipemic were significantly older ($p < 0.0005$) and had higher systolic and diastolic pressure ($p < 0.0005$), a higher body mass index ($p = 0.022$), and a lower level of hemoglobin ($p < 0.0005$) (Table 3). Women ($p = 0.002$), diabetic patients ($p = 0.001$), and donors with heart disease who were treated with venipuncture ($p < 0.0005$) had a higher percentage of lipemic blood (Table 4). Interestingly, the occurrence of lipemic blood depended on the blood group ($p = 0.041$), professional qualification ($p < 0.0005$) and occupation ($p < 0.0005$) (Table 4). Fear, Rh factors, injuries, alcoholism, psychoactive substances, suspicion of the presence of transmissible diseases, places of blood collection, other diseases and seasons were not statistically significantly related to the donation of unusable lipemic units.

The univariate binary logistic regression showed that the appearance of fatty blood was influenced by age ($p < 0.0005$), systolic pressure ($p < 0.0005$), diastolic pressure ($p < 0.0005$), hemoglobin level ($p < 0.0005$), female sex ($p = 0.001$), blood group A ($p = 0.016$), primary schooling ($p < 0.0005$), working status retiree ($p < 0.0005$), and venipuncture therapy ($p < 0.0005$) (Table 5). Multivariate binary logistic regression showed

Table 5. Influence of examined variables on the occurrence of lipemic blood

Variable	Univariate binary regression		Multivariate binary regression	
	Risk quantity	p	Risk quantity	p
Age	1.132 (1.099–1.165)	< 0.0005		
Systolic pressure (mmHg)	1.168 (1.139–1.197)	< 0.0005	1.166 (1.138–1.196)	< 0.0005
Diastolic pressure (mmHg)	1.246 (1.201–1.293)	< 0.0005		
Hemoglobin (g/l)	0.766 (0.716–0.818)	< 0.0005		
Female	3.259 (1.586–66.98)	0.001	3.218 (1.185–8.738)	0.022
Blood group A	0.435 (0.221–0.856)	0.016		
Primary school	7.845 (4.165–14.777)	< 0.0005		
Pensioner	47.872 (7.814–298.282)	< 0.0005		
Therapeutic venipuncture	64.778 (31.326–133.95)	< 0.0005		

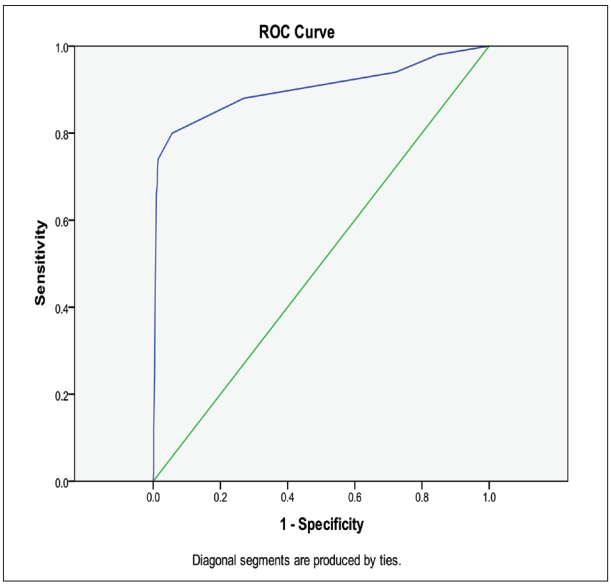

Figure 1. Receiver operating characteristic (ROC) curve for systolic pressure; systolic pressure may be a marker indicating to lipemic blood (the area under the ROC = 0.901, p < 0.0005) if we use systolic pressure cut-off value of 140 mmHg (sensitivity = 0.740, specificity = 0.985; negative predictive value = 0.991, and positive predictive value = 0.627); 94.3% of blood donors with systolic pressure above 150 mmHg had lipemic blood

that the appearance of fatty blood affected systolic pressure (p < 0.0005) and female sex (p = 0.022) (Table 5). The risk quantity for systolic pressure was 1.166 (1.138–1.196), and for females it was 3.218 (1.185–8.738) (Table 5).

The ROC curve shows that systolic pressure may be a marker indicating lipemic blood (AUROC = 0.901, p < 0.0005) (Figure 1).

DISCUSSION

Blood treatment is an expensive process, and blood collection has always been extremely demanding and difficult, especially in countries where the standard of living is quite low. The leading cause of unusable blood units in our research is the presence of fat content in fresh frozen plasma produced immediately after collecting blood. We showed that the percentage of unused lipemic blood units is 22.1%, which is quite high. The reasons for unusable plasma units are also found in some insufficiently educated blood donors in terms of diet before giving blood. As all the blood collected in our blood transfusion department is processed into fresh frozen plasma, it is only then that it is possible to notice the fat content in the bag with the plasma. Such a plasma bag, due to the unauthorized presence of fat inside, automatically becomes unusable [11, 12]. In line with this, milky plasma due to the presence of fat constitutes the strictest ban on its use in transfusion treatment [13]. Vassallo and Stearns [3] reported a detailed study of the occurrence of lipemic plasma, its composition – particularly the level of triglycerides that is significant for the onset of many diseases and draws attention to the habits of donors, risk factors and the possibility of removing these phenomena. de Kort et al. [14] observed the reasons for the refusal of blood donors following the relationship between the Dutch and the general population, as well as the possibility of disease occurrence with the popularization of a healthy lifestyle. Some authors try to introduce new methods for treating various metabolic diseases, especially fatty liver and diabetes [15]. This is possible by the identification of bioactive lipids and their mechanisms of action [16].

The problem of the presence of fat in donor blood and the consequent association with the onset of cardiovascular diseases has long attracted the attention of many authors [1, 2, 17, 18, 19]. Wittock et al. [20] observed the demographic characteristics of donors across Europe, bringing them into the relationship between the presence of fat in the blood and the onset of cardiovascular diseases. One of the leading causes of these diseases is the presence of fat in donor blood [20]. On the appearance of fat in donor plasma, Peffer et al. [2] pointed out in his study that it is linked to risk factors and the occurrence of many heart and blood vessel diseases. The aim of this study was to objectively determine clouding and to identify risk factors for cloudy plasma [2]. Donors that have given cloudy plasma have a less favorable cardiovascular profile than other donors [2]. The most common independent risks are consuming dinner, high levels of triglycerides and smoking [2]. Adverse health behaviors (smoking, poor diet, higher body mass index, and unhealthy lifestyle) combined with risk factors (hyperlipidemia, hypertension, and diabetes) lead to the development of cardiovascular diseases (85–95%) [17]. Elimination of unhealthy habits and using aspirin can help in the treatment [17]. O'Neill et al. [21] found several factors associated with what we assessed to be "appropriate" documentation of risk factors sufficient for cardiovascular risk assessment, such as an

increasing number of clinical encounters, male sex, and increasing BMI and age. The focus of the research was the relationship between the composition of lipid plasma and the appearance of cardiovascular diseases, as well as elevated serum lipid levels and the appearance of coronary heart disease [18, 19]. Many risk factors that lead to the onset of this disease have been described [19]. Goel et al. [1] showed the risks of cardiovascular disease due to the presence of fat in donor blood and the manner of their care and treatment. Otherwise, cardiovascular diseases prolong the length of treatment for sick donors, shorten their length and quality of life and permanently eliminate them from the blood donation process [2, 12].

Some of the authors have also observed sociological moments that influence donor motivation for giving blood [1, 22, 23]. Their goal is to increase the number of healthy blood donors. In two independent studies, the authors showed a change in the behavior of blood donors, according to the diverse social circumstances in which they are found. They emphasize the importance of sociological institutions in increasing the number of fully healthy blood donors [22, 23]. Unequivocally, it is easier to motivate a satisfied donor to give blood [24]. In our community, quite a large number of blood donors are unemployed, and they have a major problem supporting themselves; therefore, it is difficult to motivate them to give blood. In addition, they have poor and irregular nutrition, which certainly affects the presence of fat in their blood [25].

Most authors advocate mandatory testing of the level of fat in blood donors. In this way, it would be possible to profile the production of lipids in blood donors, which would contribute to more effective treatment of persons with an increased content of fat in their blood [26]. The presence of fatty blood from donors suggested the standardization of detection through testing, as well as documentation that contributes to the optimal resolution [27]. In a case–control study, Si et al. [28] analyzed 61 lipidomic markers in baseline plasma using targeted nuclear magnetic resonance spectroscopy. Pechlaner et al. [10] showed patents for cardiovascular diseases biomarkers that refer to the standardization of blood lipidemia measurements. Beginning in 2016, in our practice, all donors with a recorded finding of increased fat in plasma bags, present in two consecutive cases after giving blood, are personally informed of the findings and are obliged to undergo a medical examination.

Our study indicates that older donors, higher blood pressure, lower levels of hemoglobin, increased body weight, profession pensioner, venipuncture therapy, and some blood groups significantly increase the risk of fat presence in blood or plasma (Tables 3 and 4). The reason is irregular diet, low social status of donors, and the more frequent occurrence of disease among elderly persons. We showed that the value of systolic pressure is a reliable predictor of lipemic blood (Figure 1). Previous research has shown the association between the presence of fat in the blood and older age and the time of day when the blood was taken [29]. Female sex and lower education levels (primary school and less) also lead to a higher risk of blood being fatty (Table 4). It has been proven that women are more inclined to increase body mass than men. People with lower levels of education consume higher amounts of fat in their diets compared to people with higher education levels [14]. The blood of donors with blood group A has a lower risk of being fatty than the blood of donors in other blood groups. This data has to be regarded with certain amount of reserve due to the fact that there was a relatively small number of tested donors with blood type A (11 donors). Our findings could be verified in a more extensive study in the future. Blood group B donors have a higher risk of fat presence in their blood. In our community, the highest percentage of individuals in blood group B are members of the Roma population, and their diet can explain the increased presence of fat in the blood of donors with this blood group (Table 5).

We have also introduced continuous education of blood donors by blood transfusion teams in our service, which, through lectures and written flyers for donors, point out the danger of the presence of an elevated level of fat in the blood, resulting in severe cardiovascular disease. A healthy lifestyle is proposed, as well as proper nutrition with reduced intake of fat through meals.

CONCLUSION

Our study provided a rational explanation and identified some of the risk factors that may help in the identification of potential donors with lipemic blood.

Determining the presence of these risk factors in donors and excluding them from the blood donation process can reduce the cost of storage and elimination of lipemic blood units. Additionally, such testing can assist in the early diagnosis and timely treatment of some chronic diseases of potential "healthy" donors. The detection of such blood donors and the speed of their care and treatment must be priorities in the future. Further, larger studies are necessary to confirm the effects of lipemic blood units and the safety of their recipients.

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NOTE

Authors Dragan Radonjić and Saša Raičević have contributed equally to this work.

Conflict of interest: None declared.

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Разлози неупотребљивости липемичне крвне плазме у трансфузиолошком лечењу

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САЖЕТАК

Увод/Циљ Повишено присуство липидних честица у крви је један од најчешћих разлога неупотребљивости трансфузиолошких јединица. Фактори ризика за липемичну плазму код давалаца нису потпуно познати.

Циљ рада је био утврђивање фактора који утичу на настанак липемичне плазме, чиме би се спречили, последично, даљи трошкови складиштења и уклањања неупотребљивих трансфузиолошких јединица.

Методе Студија случаја и контрола спроведена је током 2017. године и укључена су 1552 испитаника. Контролна група је обухватала 1502 испитаника чија крв није била липемична, док је у испитивану групу одабрано 50 болесника са липемичном крвљу. Присуство липемичне крви утврђивано је инспекцијским прегледом, док су подаци прикупљени лабораторијским тестовима и анкетним упитником.

Резултати Наши налази показују да вишеструки даваоци крви, чија је крв липемична, припадају следећим категоријама: значајно старији ($p < 0,0005$), имају виши систолни и дијастолни притисак ($p < 0,0005$), висок ниво триглицерида ($p < 0,0005$) и нижи ниво хемоглобина ($p < 0,0005$). Такође, присуство липемичне плазме повезано је са женским полом ($p = 0,002$), крвном групом ($p = 0,016$), болестима срца ($p < 0,0005$), пушењем ($p < 0,005$), дијабетесом ($p = 0,001$), као и са уносом масне хране пре давања крви ($p < 0,005$) и терапије венепунктуром ($p < 0,0005$). Систолни притисак је поуздан предиктор липемичне крви (*AUROC* = 0,901, $p < 0,0005$).

Закључак Наша студија је пружила рационално објашњење и идентификовала је неке од фактора ризика који могу помоћи у идентификацији могућих давалаца липемичне крви.

Кључне речи: трансфузија крви; даваоци крви; плазма; мере превенције; холестерол; триглицериди

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The impact of COVID-19 pandemic on suicide attempts in the Republic of Serbia

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SUMMARY

Introduction/Objective Previous studies suggest that the number of suicides and suicide attempts will increase due to the COVID-19 pandemic. The aim of this study was to investigate the impact of the COVID-19 pandemic on the frequency and characteristics of suicide attempts in the Republic of Serbia.

Methods The study observed two periods: the period from March to August 2020 (the COVID period) and the same period of the previous year (the non-COVID period). The observation during the mentioned periods encompassed patients who were examined at the Dr. Laza Lazarević Clinic for Mental Disorders in Belgrade due to suicide attempts (1987 persons during COVID period and 2300 persons during the non-COVID period).

Results Concerning suicide attempts, a statistically significant difference between the observed periods was registered in respect to the total number of monthly clinical examinations, monthly distribution of suicide attempts, patients' gender and age, mode of suicide attempt, and the diagnostic category. Binary logistic regression determined that statistically significant factors that can influence the suicide attempt were year, months, patients' gender and age, and diagnostic category.

Conclusion COVID-19 pandemic creates the increased exposure of the people to suicide risk factors, which points to the significance of consistent monitoring of mental health during the COVID-19 pandemic and thereafter.

Keywords: suicide; suicide attempts; COVID-19; pandemic

INTRODUCTION

In January 2020, the World Health Organization declared the COVID-19 outbreak to be a public health emergency of international concern, with a high risk of disease spreading to all countries around the world. In March 2020, the World Health Organization made an assessment that COVID-19 should be characterized as a pandemic disease [1]. The clinical spectrum of COVID-19 varies from asymptomatic forms to clinical conditions characterized by respiratory failure that necessitate mechanical ventilation and support in an intensive care unit, as well as life treating sepsis, septic shock, and multiple organ dysfunction syndrome [2]. Therefore, medical workers and public health professionals are focused on treating individuals with COVID-19, as well as on preventing the spread of corona virus in the general population, but they pay less attention to the psychiatric consequences of the COVID-19 crisis [3].

Previous studies suggest that number of suicides and suicide attempts may increase due the COVID-19 pandemic [3, 4]. Global responses such as social isolation and psychical distance have heightened depression, anxiety, loneliness, anger, irritability, relationship conflicts, post-traumatic stress disorder, economic uncertainty, fears, and increased use of psychoactive substances [5]. All of these have been previously identified as risk factors for suicide behavior, especially in vulnerable categories (such as psychiatric patients), and the population that was not considered to be a risk for suicide prior to the COVID-19 pandemic [6].

Through its specialized organizational unit (Psychiatric Emergency Department), the Dr. Laza Lazarević Clinic for Mental Disorders is the only one psychiatric institution in Belgrade (having about 2,500,000 inhabitants) that takes care of suicide attempts, as well as other urgent psychiatric conditions.

Considering the data from current literature and the lack of data for the territory of the Republic of Serbia, the aim of this study was to investigate the impact of the COVID-19 pandemic on the frequency and characteristics of suicide attempts in the Republic of Serbia.

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METHODS

This is a retrospective study that includes two periods: the period from March to August 2020 (the COVID period) and the same period of the previous year (the non-COVID period). The mentioned two periods referred to the patients who were examined for suicide attempts at the Dr. Laza Lazarević Clinic for Mental Disorders, Belgrade. The approval for the study was obtained from the Ethics Committee of the Clinic (decision No. 7108/2020), and the study was conducted in accordance with the Declaration of Helsinki.

At the Psychiatric Emergency Department of the Clinic, medical histories of all the examined patients in the observed periods were searched in order to find suicide attempts, which was the only inclusion criterion. During the non-COVID period, 2300 persons were examined at the Psychiatric Emergency Department, 139 (6.04%) of which were suicide attempts. However, during the COVID period, 1987 persons were examined at the same department, 159 (8%) of which were suicide attempts. The patients' data noted from medical history were as follows: gender, age, residence, method of attempting suicide (self-poisoning, self-injury by a sharp object or a weapon, hanging, jump from height, and self-ignition), and psychiatric diagnosis.

Descriptive statistical methods, methods for testing statistical hypotheses, and regression analysis were used to analyze the data. Statistical differences were tested at a significance level of $p \leq 0.05$. All statistical analyses were conducted using the IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

During the non-COVID period, most of the clinical examinations were done during April (17.4%) and July (20.1%); during the COVID period, most of the clinical examinations were performed during June (18.5%) and August (18.4%) (Figure 1). A statistical significance between these two observed periods was registered in respect to the number of total clinical examinations distributed by months ($\chi^2 = 23.207$; $p = 0.000$).

During the non-COVID period, most suicide attempts were noted in March, July, and August; during the COVID period, the highest percentage of suicide attempts was recorded during May and August (Table 1). A statistically significant difference was noticed in the distribution of suicide attempts during the observation periods (Table 1). In the non-COVID period, the largest number of patients who attempted suicide were females (64%). All the patients were 18–86 years old, and most of them were living in Belgrade. Almost 60% of them attempted suicide by self-poisoning, and 35.3% of them belonged to the F20–F29 diagnostic category (Table 1). On the other hand, in the COVID period, most of the persons who tried to commit suicide were males, 18–92 years old, living in Belgrade (Table 1). Like in the non-COVID period, during the COVID period, over 50% of patients attempted suicide by self-poisoning and belonged to the F20–F29 diagnostic category (Table 1). A statistically significant difference between these two observed periods was noticed for month, gender, method of suicide attempt, and diagnostic category (Table 1).

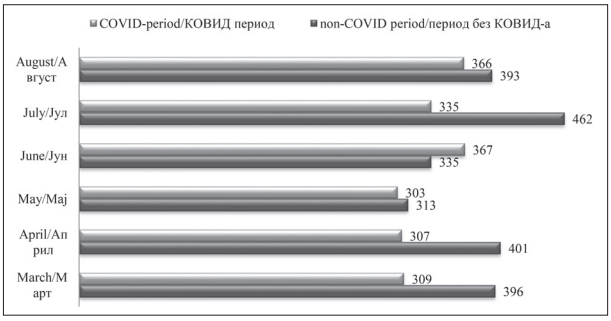

Figure 1. Total number of clinical examinations done at the Psychiatric Emergency Department of the Clinic in the two observed periods

During the COVID period, a statistical significance between genders in terms of month, residence, method of suicide attempt, and diagnostic category was not registered (Table 2).

Binary logistic regression determined that statistically significant factors influencing suicide attempt were year (COVID and non-COVID period), month, gender, age of patients, and their diagnostic category (Table 3).

DISCUSSION

Globally, the data and the research connected with the topic of suicide during the current pandemic are missing. The reports on the suicide rate and the successful suicide attempts are generally rare in real time, that is, there is a time delay in their publishing, which, in the current situation, is extremely important due to the need for timely response of the society and the health system to this challenge.

Our study, performed in the observed COVID period, has established that the final absolute number of patients who have attempted suicide is higher in comparison to the non-COVID period. The majority of published studies with the topic of suicide during COVID-19 pandemic are either study cases or cross-sectional surveys on non-representative samples, which have not provided us with the clear data in the change of suicide rate [7]. The only study that compared the period of the first four weeks of the pandemic with the same time period previous year, and whose subjects were patients reporting to the urgent psychiatric department, has actually shown the decrease in the number of patients attempting suicide [8]. The research performed on pregnant women in China has shown an increased level of suicidal thoughts during the pandemic in comparison to the thoughts of pregnant women in the same stage of pregnancy, just prior to COVID-19 pandemic [9]. Keeping in mind that the pandemic is still ongoing and that the performed researches, including ours, have observed only the first period of the pandemic, it can be expected, based on the study results from the previous

Table 1. Data about persons with attempted suicide

Characteristics	non-COVID period n (%)	COVID period/ n (%)	χ^2/U	p
Month				
March April May June July August	28 (20.1) 26 (18.7) 13 (9.4) 10 (7.2) 28 (20.1) 34 (24.5)	24 (15.1) 26 (16.4) 40 (25.2) 16 (10.1) 17 (10.7) 36 (22.6)	16.927	0.005*
Gender				
male/ female/	50 (36) 89 (64)	82 (51.6) 77 (48.4)	7.316	0.007*
Age (years)				
X ± SD; Med (min–max)	41.6 ± 14.6; 40 (18–86)	44.6 ± 17.3; 41 (18–92)	-1.281	0.200
Residence				
Belgrade region other regions in Serbia	118 (84.9) 21 (15.1)	144 (90.6) 15 (9.4)	2.248	0.134
Method of attempting suicide				
self-poising self-injury (sharp object, weapon, etc.) other (hanging, jumping from height, ignition)	83 (59.7) 24 (17.3) 32 (23)	80 (50.3) 42 (26.4) 37 (23.3)	4.002	0.135
Diagnostic category (ICD-10)				
F20–F29 F30–F39 other diagnosis	49 (35.3) 43 (30.9) 47 (33.8)	37 (23.3) 27 (17) 95 (59.7)	20.306	0.000*

U – Mann–Whitney test;
*statistically significant

Table 2. Patients attempting suicide during the COVID period, distributed by gender

Characteristics	Males n (%)	Females n (%)	χ^2/ U	p
Month				
March April May June July August	16 (19.5) 10 (12.2) 25 (30.5) 6 (7.3) 7 (8.5) 18 (22)	8 (10.4) 6 (20.8) 15 (19.5) 10 (13) 10 (13) 18 (23.4)	7.931	0.160
Age (years)				
X ± SD; Med (min–max)	43.7 ± 17.5; 41 (19–92)	45.5 ± 17.2; 44 (18–87)	-1.281	0.200
Residence				
Belgrade region other regions in Serbia	75 (91.5) 7 (8.5)	70 (90.9) 7 (9.1)	0.015	0.902
Method of attempting suicide				
self-poising self-injury (sharp object, weapon, etc.) other (hanging, jumping from hight, ignition)	36(43.9) 25 (30.5) 21 (25.6)	44 (57.1) 18 (22.1) 16 (20.8)	2.845	0.241
Diagnostic category (ICD-10)				
F20–F29 F30–F39 other diagnosis	20 (24.4) 10 (12.2) 52 (63.4)	17 (22.1) 17 (22.1) 43 (55.8)	2.756	0.252

U – Mann–Whitney test;
*statistically significant

Table 3. Binary logistic model concerning suicide attempts

Independent variables	95% CI	p
Year	6.234	0.013*
Month	24.319	0.001*
Gender	5.772	0.016*
Age	-0.009	0.012*
Residence	0.642	0.423
Diagnostic category	76.270	0.000*

*Statistically significant

pandemics that the suicide rate will increase. The epidemic of the Spanish flu was connected to the increased death toll caused by suicide, and it has also been established that the reductions in social interaction and fears caused by the epidemic were the factors that influenced the increase of this rate [10]. The study by Yip et al. [11] also showed a significant increase in the suicide rate in people over the age of 65 during the SARS epidemic in 2003. That research showed that the increase in suicide rate is connected with the fear of getting infected, with fears that the person might become a burden to the family, anxiety, social isolation, and distress. Many adverse risk factors which existed during these epidemics exist during the COVID-19 breakout as well. However, there are significant differences between COVID-19 and the previous pandemics, especially when we compare their virulence, speed at which the disease is spreading, death rate, and the level of socio-economic influence, which, to some extent, limits our ability to predict the influence of COVID-19 pandemic on mental health and suicide rate [12].

The results of our research show that, in the observed COVID period of time, males have attempted suicide more often, that they were on average 41 years old, and that they most often attempted suicide by self-poisoning. Comparing COVID and non-COVID periods, it can be noticed that in the COVID period, although in both periods the most common way of suicide attempt was self-poisoning, the number of people who tried suicide in this way decreased, and the number who tried suicide by self-injury increased. Researches related to the period of the COVID-19 pandemic, even when performed on a small number of test subjects, or represented as case studies, also show that men attempted and committed suicide more often [8, 13]. The most common method of suicide, according to the available data, was either by jumping or hanging [14, 15, 16]. According to the results of the available researches, those who are facing higher risk are males who are under pressure of meeting traditional expectations, hide their feelings, do not take much care of themselves, postpone looking for medical help when they need it, are unemployed or have lost their job, have problems in establishing/ maintaining emotional connections, or use psychoactive substances [17, 18].

According to our research, even though the people who have attempted suicide in the COVID period have mostly suffered from psychosis belonging to the schizophrenia spectrum, we have noticed a significant reduction in the percentage in the number of these patients in the general pool of patients, in comparison to the non-COVID period. Our study has shown that, during the COVID period, there has been an increase in the number of patients suffering from organic disorders, anxiety and stress related disorders, substance-related disorders, as well as personality and behavior disorders that have attempted suicide. Organic disorders usually appear in people belonging to the older age group, who are, according to the results of the previous researches, under a greater risk of suicide during the epidemic, both due to the increased prevalence of already known risk factors connected to suicide, and to the imposed measures targeted at the control of the spread of the virus, which increase social isolation and psychological vulnerability [19]. More researches conducted during the period of the pandemic show the increase in substance-related disorders, as well as the fact that people who had already been the consumers of psychoactive substances have increased the consumption of those substances during the period of the pandemic [20, 21]. According to a study by Ferrando et al. [22], dealing with psychiatric emergencies during the height of the COVID-19 pandemic in the suburban New York City area, the most common reason for reporting to the emergency psychiatric service was depression and suicidal ideation, as in the pre-COVID period. In the same study, a significant increase in the number of people with anxiety disorders was present, compared to the pre-COVID period, as is the case in our study. No study, to our knowledge, has dealt, in particular, with the diagnostic categories of patients attempting suicide during the COVID-19 pandemic. According to our study, comparing the data obtained in relation to gender during the COVID period, it was noted that women who attempted suicide were older than men and used self-poisoning as a method of suicide more often. Comparing the diagnostic categories, women who attempted suicide had an equal prevalence of psychotic and affective disorders, while men were more likely to suffer from psychosis than from affective disorders.

The factors that may increase suicidal risk during the pandemic, especially in the vulnerable groups (such as people with a previous history of a psychiatric disorder, people over the age of 65, people who have previously attempted suicide, health care professionals working with COVID-19-infected patients, COVID-19-infected people, people recovering from COVID-19, as well as people whose family member or a friend has died from COVID-19) are social isolation, anxiety, fear of getting infected, insecurity, chronic stress, economic consequences, and the reduced availability of doctors working in the non-COVID system [3, 12, 23].

Social isolation and quarantine are important measures in the fight against spreading of COVID-19 pandemic, but they also have negative effects on the psychic health of humans and are connected to the appearance of depression, generalized anxiety disorder, suicidal thoughts and behavior, especially in vulnerable categories, since social interaction is an important factor of both emotional and social stability [3, 23].

Anxiety and the fear of getting infected are connected to the fear of the unknown, but could also be induced by the news and information about COVID-19 pandemic to which the people are exposed through all types of media [12]. Worries and concerns might lead to the development of anxiety disorders, depression, and insomnia [24]. Li et al. [25] have analyzed on-line posts of 17,865 users of Chinese social networks, comparing the period immediately prior to COVID-19 and the COVID period, and have noted the increase in negative emotions, such as anxiety and depression during the period of the pandemic. Huang and Zhao [26] have performed a web-based study on 7236 subjects in China during the COVID-19 pandemic period, which showed that more than one-third of the subjects met the criteria for generalized anxiety disorder, while depression prevalence was 20.1% and insomnia prevalence 18.2%. Insomnia also represents an isolated factor of suicidal risk [27].

The measures aimed at combating the epidemic have left significant consequences on the world economy and have caused global economic recession [23]. Millions of people worldwide have lost their jobs, while many others fear the loss of their jobs, experience material insecurity and are afraid for their financial future. Unemployment and the fear of losing one's job represent important risk factors for the development of depressive symptoms [3]. A study by Nordt et al. [28] has found that the suicidal risk connected to unemployment was increased by 20–30%. Kawohl and Nordt [29] have estimated in their study that, owing to the increase in the worldwide unemployment rate due to COVID-19 pandemic, the number of suicides will be increased by between 2135 and 9570 cases yearly.

Many patients are afraid of the infection and avoid coming to check-ups, which in psychiatric patients, as a vulnerable category, might lead to their own decision to stop taking their therapy, and it might also lead to disorder relapse, the appearance of depressive symptoms and suicidal thoughts and behavior [30].

CONCLUSION

Suicide can be prevented in many cases, which is why it is extremely important to formulate measures and strategies for its prevention. Early detection of people under an increased risk of suicide, people expressing suicidal behavior or verbalizing suicidal thoughts is, along with timely psycho-social and pharmaco-therapeutic interventions, imperative in preventing a tragic outcome.

Even though there are still no researches which clearly show the increase in the suicide rate during the current pandemic, the fact that is supported by the results of our research as well, COVID-19 outbreak has been connected to the increased exposure of people to suicide risk factors, which tells us that it is important to continue following the

mental health influenced by the COVID-19 pandemic. The repeated cross-sectional and longitudinal researches of the influence of the COVID-19 pandemic on mental health and suicide rate are important because of the collection of real time data, as well as the following of patients' needs, so that the available resources could be targeted at those parts of the system used for the protection of mental health, which suffer the highest pressure.

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Утицај пандемије ковида 19 на покушаје самоубиства у Републици Србији

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САЖЕТАК

Увод/Циљ Претходна истраживања указују да ће се услед пандемије ковида 19 број самоубистава и покушаја самоубиства повећати.

Циљ овог истраживања је био да се испита утицај пандемије ковида 19 на учесталост и карактеристике покушаја самоубиства у Републици Србији.

Методе Истраживање је укључило два периода: од марта до априла 2020. године (период ковида) и исти период током године која је претходила (период без ковида). Поменути периоди су се односили на болеснике који су због покушаја самоубиства били прегледани у Клиници за психијатријске болести „Др Лаза Лазаревић" у Београду (1987 особа током периода ковида и 2300 особа током периода без ковида).

Резултати Статистички значајна разлика између два посматрана периода забележена је у погледу укупног броја прегледа посматрано по месецима, дистрибуције покушаја самоубиства, пола и старосног доба болесника, начина покушаја самоубиства и дијагностичке категорије. Бинарном логистичком регресијом утврђено је да су фактори који могу статистички значајно утицати на покушаје самоубиства били година, месец, пол и старосно доба болесника, као и дијагностичка категорија.

Закључак Пандемија ковида 19 ствара услове за повећану изложеност људи факторима ризика за самоубиство, што потенцира значај континуираног праћења менталног здравља људи у току пандемије ковида 19 и после ње.

Кључне речи: самоубиство; покушај самоубиства; пандемија ковида 19

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Regulatory and clinical perspective on patient access to antidiabetic medicines in Slovenia

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SUMMARY
Introduction/Objective Three novel classes of antidiabetic medicines have been introduced into the market in the last decade, namely dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose co-transporter 2 inhibitors. Many factors influence patient access to these medicines and their utilization in clinical practice: these need to be explored.
The aim of the study was to gain an insight into patient access to antidiabetic medicines in Slovenia from a regulatory and clinical point of view.
Methods A focus group with five Slovenian experts (representatives of regulatory bodies and prescribers of antidiabetic medicines) was performed in January 2019. The discussion was audiotaped upon obtaining written consent from the experts and transformed into a verbatim transcript. Two researchers independently analyzed the content of the discussion, using NVivo 11 to identify main themes and subthemes.
Results Slovenia provides satisfactory patient access to antidiabetic medicines; however, prescribing restrictions and unequal access to diabetologists in the Slovenian regions may limit patient access to novel antidiabetic medicines. Prescribing restrictions should be aligned with the new evidence on cardiovascular benefit of some antidiabetic medicines. A national registry of patients with diabetes should be established in order to obtain reliable data on patient outcomes and improve the quality of patient care.
Conclusion Patient access to antidiabetic medicines could be significantly improved not only in Slovenia but also in other countries by changing prescribing restrictions, establishing national registries of patients with diabetes, and involving multidisciplinary teams in diabetes care.
Keywords: diabetes mellitus; antidiabetic medicines; patient access; focus groups; diabetes care

INTRODUCTION

Slovenia has a social Bismarck-type health insurance system, which is mainly financed through compulsory health insurance provided by the Health Insurance Institute of Slovenia (HIIS) and mainly funded by payroll taxes. The HIIS is also involved in medicine reimbursement decision-making. The Reimbursement Committee evaluates applications for medicine reimbursement and makes a recommendation, while the HIIS makes the final decision [1]. All antidiabetic medicines in Slovenia are fully covered by compulsory insurance; however, even for these medicines the HIIS can introduce various measures to control medicine expenditure, e.g., prescribing restrictions, reference pricing.

The estimated prevalence of diabetes in Slovenia is 6.9% and every year about 4.7 in 1000 people start antidiabetic therapy [2]. Three novel classes of antidiabetic medicines have obtained marketing authorization in the EU since 2006, namely dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and sodium-glucose co-transporter 2 inhibitors (SGLT2i). A recent study, which evaluated patient access to novel antidiabetic medicines in 11 European countries, showed that, in 2016, the proportion of novel antidiabetic medicines consumption in Slovenia was lower than in most other European countries included in the study [3]. The uptake of novel antidiabetic medicines in Slovenia was similar to that in Sweden and Italy, accounting for less than 10% of total antidiabetic medicines consumption, while in Spain and Austria it accounted for more than 25%. There may be many factors affecting patient access to antidiabetic medicines in Slovenia that should be investigated in order to plan appropriate measures to optimize patient access to these medicines and their outcomes.

The aim of the study was to gain an insight into patient access to antidiabetic medicines in Slovenia from a regulatory and clinical point of view.

METHODS

A semi-structured focus group with five Slovenian experts was performed in January 2019. The Consolidated Criteria for reporting Qualitative Research (COREQ) were followed when conducting and reporting on this focus group [4].

Research team

The research team consisted of four members working in an academic environment: two faculty professors, a postdoctoral researcher with a PhD in pharmacoeconomics, and a

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Table 1. A set of questions used to lead a discussion

Patient access to antidiabetic medicines and utilization of antidiabetic medicines in Slovenia
List positive aspects of patient access to antidiabetic medicines and utilization of antidiabetic medicines in Slovenia. • From the clinical perspective • From the system perspective
List key challenges of patient access to antidiabetic medicines and utilization of antidiabetic medicines in Slovenia. • From the clinical perspective • From the system perspective
Influence of differences in patient access to antidiabetic medicines on health outcomes
What impact do differences in patient access to antidiabetic medicines have on health outcomes?
Opportunities for improvement
What are the most important measures to improve patient access to antidiabetic medicines and diabetes management in Slovenia? • At system level • At clinical practice level

second-year doctoral student. The researchers are familiar with qualitative study designs and have conducted several focus groups and other types of qualitative studies [5, 6, 7].

Selection of participants

A purposive sampling technique was used with the aim to gather a heterogeneous group of experts who do not only have an in-depth insight into the healthcare system and patient access to antidiabetic medicines, but also the ability to influence diabetes management in Slovenia.

To obtain the regulatory point of view, we invited representatives of two institutions involved in medicines' regulation, namely the HIIS and the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP). To obtain the clinical perspective, we invited representatives of physicians (diabetologists and general practitioners) who work as clinicians with patients with diabetes and who have been actively involved in the development, implementation, and monitoring of the Slovenian national diabetes program. One of the key objectives of the program is to ensure access to comprehensive, integrated, equal, effective, and safe patient care, which also includes provision of patient access to antidiabetic medicines [8]. Initially, seven experts were invited to participate in the discussion via e-mail: one from each of the two regulatory bodies and five physicians. Two physicians could not participate in the discussion due to other obligations. The focus group consisted of five experts:

- Two diabetologists with more than 20 years of experience in managing patients with diabetes, working at two of the leading Slovenian hospitals in different regions (D1, D2);
- A representative of general practitioners working at a community health center with more than 10 years of experience in family medicine, and a member of the coordination working group at the Ministry of Health that is responsible for the implementation of the national diabetes program (GP) [8];
- A representative of the HIIS from the Department for Medicines with more than 20 years of experience in medicine reimbursement decision-making (HIIS);
- A representative of JAZMP from the department focusing on access to medicines, health technology assessment, and medicine pricing (JAZMP).

Study design

A semi-structured panel discussion was held in an academic environment in January 2019. The discussion was facilitated by a postdoctoral researcher, who was previously trained in facilitating discussion by the faculty professors. The faculty professors observed the discussion and the doctoral student took notes on non-verbal communication. The discussion lasted one and a half hours and was audiotaped upon obtaining written consent from all the participants. No ethical approval was required for this study.

The discussion began with a brief introduction of each focus group member. After the introduction, the facilitator posed a set of open-ended questions, which are listed in Table 1. The questions were based upon literature review and the results of a pharmacoepidemiological analysis that evaluated patient access to novel antidiabetic medicines in 11 European countries [3]. At the end of the discussion, the experts had the opportunity to expose any additional comments or suggestions.

Data analysis

A verbatim transcript of discussion was made by the facilitator of the focus group. It was subjected to content analysis with NVivo 11 qualitative data analysis computer software package (QSR International, LLC, Burlington, MA, USA) to identify main themes and subthemes of the discussion. Two researchers independently coded the data based on key expressions. Each researcher developed a separate coding tree with main themes and subthemes. After comparing the coding trees, they reached an agreement on the final themes and subthemes. Then one of the researchers set a new theme hierarchy based upon the agreement, while the second researcher reviewed the final coding hierarchy.

RESULTS

Four main themes were derived from the discussion, which are presented in Tables 2, 3, and 4, with key quotes from participants.

Table 2. Quotes supporting themes Patient Access to Antidiabetic Medicines and Factors that Influence Patient Access to Antidiabetic Medicines

Patient Access to Antidiabetic Medicines
Patient access to antidiabetic medicines in Slovenia
[JAZMP]: "Slovenia provides good patient access to medicines, not only in the field of diabetes, but in other fields as well." [D1]: "Patients, who benefit the most, with best expected health outcomes, have access to medicines. Patients in whom smaller benefit is expected do not have such access to medicines. I assume that the greatest benefits with regard to health outcomes are covered with our access to medicines."
Comparison of patient access to antidiabetic medicines in Slovenia and other countries
[D1]: "Slovenia provides better patient access to antidiabetic medicines compared to the countries of the former Yugoslavia (e.g., Croatia, Serbia) and Eastern Europe; however, in terms of patient access to novel antidiabetic medicines, Slovenia is still a little behind compared to some other countries [e.g., Spain, Austria, Germany]." [JAZMP]: "Some smaller European countries, e.g., Cyprus, Malta, already have problems with the availability of older medicines. I would like to emphasize that the Reimbursement Committee is trying to do its best to enable good patient access to older medicines."
Lower prescribing rate of insulin in Slovenia compared to Nordic countries
[D1]: "A lot of insulin, basal insulin, is being prescribed in Nordic countries." [D2]: "Swedes routinely monitor HbA1c levels and introduce insulin when target HbA1c levels cannot be achieved using oral antidiabetic medicines." [D1]: "Slovenian patients often remain on triple therapy, which is expensive. And triple combination therapy is allowed by the health insurance institute, whereas Swedes initiate insulin earlier in the course of type 2 diabetes."
The proportion of novel antidiabetic medicines consumption is lower than in other countries
[HIIS]: "With regard to utilization of novel antidiabetic medicines, Slovenia is comparable to Sweden, but not to Austria and Spain." [D1]: "Sweden has higher consumption of GLP-1RA compared with Slovenia."
Factors that Influence Patient Access to Antidiabetic Medicines
Prescribing restrictions
[GP]: "Some groups of patients benefit from novel antidiabetic medicines. Prescribing restrictions are influenced by medicine prices and the number of patients with type 2 diabetes; however, they are necessary for the sustainability of the healthcare system." [JAZMP]: "The Reimbursement Committee is trying to set prescribing restrictions so that patients most in need and patients with greatest expected benefits get the medicines." [D2]: "What has been bothering me for several years is that certain medicines can be prescribed only by diabetologists. Some Slovenian regions provide poorer patient access to diabetologists, which automatically affects patients' access to medicines that can be prescribed only by diabetologists." [D1]: "New evidence in diabetology represents a huge challenge. New studies of some novel antidiabetic medicines showed benefit in terms of treatment outcomes in patients with established cardiovascular disease. This evidence is so important that it will be challenging not to provide certain patients with these medicines or to treat them with older medicines without this evidence."
Medicine prices
[HIIS]: "Older medicines are generally a bit more expensive in Slovenia, because the market is small, which makes it harder to negotiate. And there is only one or two manufacturers, and we are really careful in order to keep them on the market. However, apparently we are better negotiators for novel medicines."

D1 – diabetologist 1; D2 – diabetologist 2; GP – general practitioner; HIIS – representative of the Health Insurance Institute of Slovenia; JAZMP – representative of the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia; GLP-1RA – glucagon-like peptide-1 receptor agonists

Table 3. Quotes supporting theme Influence of Patient Access to Antidiabetic Medicines on Patient Outcomes

Influence of Patient Access to Antidiabetic Medicines on Patient Outcomes
Treatment approach to improve patient outcomes
[D2]: "Multifactorial approach had the greatest influence on patient outcomes. Not only diabetes but also lipids, blood pressure, and other measures." [D1]: "Cardiocentric approach will be crucial in the following years. In addition to multifactorial approach, also choosing the right medicine with regard to these outcomes." [D1]: "Studies with DPP-4i did not show benefits, but they are safe in the early stage in addition to metformin. However, for such a diagnosis (established cardiovascular disease) SGLT2i and GLP-1RA are more appropriate."
Outcomes of patients with diabetes in Slovenia
[HIIS]: "Cardiovascular outcomes of Slovenian patients are significantly improving. The mortality rate is decreasing rapidly. We have global indicators. With the exception of amputations for which I don't know where we stand, we are doing very well with regard to global health indicators, those most important ones." [HIIS]: "We need to know what the incidence of the second most important outcome [amputations] is. I find it unacceptable that the medical profession has no data on the incidence of amputations." [D1]: "The medical profession does not have this data. This is divided among several specialties and the acknowledgment of that." [D2]: "We also need data on the incidence of blindness, end-stage kidney failure, etc."

D1 – diabetologist 1; D2 – diabetologist 2; GP – general practitioner; HIIS – representative of the Health Insurance Institute of Slovenia; DPP-4i – dipeptidyl peptidase-4 inhibitors; GLP-1RA – glucagon-like peptide-1 receptor agonists; SGLT2i – sodium-glucose co-transporter 2 inhibitors

Patient access to antidiabetic medicines

From the experts' point of view, Slovenia provides satisfactory patient access to antidiabetic medicines. Slovenia provides good patient access to older antidiabetic medicines, which should not be taken for granted. In addition, Slovenia provides better patient access to antidiabetic medicines than other countries of the former Yugoslavia and Eastern Europe, while it is still a little behind with regard to patient access to novel antidiabetic medicines when compared to some other EU countries, e.g., Spain, Austria, and Germany. Furthermore, Slovenia has a lower prescribing rate of insulins than the Nordic countries, especially Sweden. The experts also highlighted the problem

Table 4. Quotes supporting theme Suggestions for Improving Patient Access to Antidiabetic Medicines

Suggestions for Improving Patient access to Antidiabetic Medicines
Change in prescribing restrictions
[D1]: "It is important to change prescribing restrictions in order to provide better patient access to medicines." [D1]: "Now that we have evidence of cardiovascular benefit, Slovenia should open the door at least a little bit for patients at high risk, high cardiovascular risk. Especially for SGLT2i." [HIIS]: "According to this discussion, SGLT2i are a group of medicines for which it would be reasonable to open the door at least a little bit. This is the group from which everyone would benefit the most." [D2]: "GPs are qualified to prescribe DPP-4i and SGLT2i. These medicines have more or less evaluated safety profiles, so safety aspects should not be a barrier for prescribing." [GP]: "GPs are generally somewhat reluctant to prescribe novel antidiabetic medicines. Additional training on these medicines should be provided to GPs. In such a case, we would probably start prescribing these medicines. Nevertheless, physicians prefer to prescribe medicines with which they are familiar. They know what the side effects are and what to expect."
Establishment of national registry
[D2]: "Until we have a registry, we won't have reliable data on amputations." [D2]: "What has been missing in Slovenia for several years is a unified registry of patients with diabetes. This should be a national project. Until we have a registry, we won't know what is going on with diabetes in Slovenia." [GP]: "I would like to refer to the nurses in the FMRCs. I think that in the future we could have a complete national registry. Nurses should write down all patient data once a year. Or this data could be collected elsewhere. We need a joint system. There is such a mess of data, some data is here and some data is there. Some patients are registered in reference clinics, some are not."
Involvement of other potential medicine prescribers
[D2]: "Nurses in FMRCs should be legally and professionally enabled to change therapy. England is a good model of this practice… Nurses in foreign countries titrate medicines, they don't prescribe them. The prescription is still written by a physician." [JAZMP]: "Nurses don't have in-depth knowledge of pharmacotherapy… Pharmacists have more knowledge of pharmacotherapy than nurses. In my opinion, we need to consider multidisciplinary teams."
Improvement of the concept of FMRCs
[D2]: "A lot of money is spent for very little benefit. That's what bothers me about the concept of FMRCs. However, I think the basic idea of involving FMRCs in the management of patients with diabetes was excellent." [HIIS]: "The potential of FMRCs is unexploited and the concept is not clear." [HIIS]: "Nurses in the FMRCs are providing individual counseling. I think it would be reasonable to perform group education for patients with diabetes. The concept of FMRCs should be upgraded."

D1 – diabetologist 1; D2 – diabetologist 2; GP – general practitioner; HIIS – representative of the Health Insurance Institute of Slovenia; JAZMP – representative of the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia; DPP-4i – dipeptidyl peptidase-4 inhibitors; FMRC – family medicine reference clinic; SGLT2i – sodium-glucose co-transporter 2 inhibitors

that in Slovenia, triple combination therapy is often used instead of insulin (Table 2).

Factors that influence patient access to antidiabetic medicines

The panel agreed that prescribing restrictions are necessary for the sustainability of the healthcare system, but pointed out that they limit patient access to novel antidiabetic medicines. Some antidiabetic medicines, namely DPP-4i and SGLT2i, can only be prescribed by diabetologists, but patients in Slovenia do not have equal access to diabetologists, which affects their access to these medicines. In addition, the experts agreed that new evidence on cardiovascular benefit of certain antidiabetic medicine groups will pose a challenge for both decision-makers and prescribers of antidiabetic medicines in order to provide access to these medicines for patients with established cardiovascular disease. On the other hand, the representative of JAZMP argued that Reimbursement Committee sets prescribing restrictions so that patients most in need and those with greatest expected benefits have access to medicines.

Another factor that may influence patient access to antidiabetic medicines are medicine prices. In comparison with other countries, older medicines are generally more expensive in Slovenia, while novel antidiabetic medicines are less expensive (Table 2).

Influence of patient access to antidiabetic medicines on patient outcomes

The experts agreed that the multifactorial treatment approach has the greatest influence on the outcomes of patients with diabetes. In their opinion, in the future, antidiabetic medicine will be selected based on the cardiovascular risk of the individual patient. Patients with established cardiovascular disease will be treated with medicines with proven cardiovascular benefit, namely SGLT2i and GLP-1RA.

The experts also discussed the influence on outcomes of patients with diabetes in Slovenia. They agreed that both mortality rates and the number of people with diabetes who experience cardiovascular events in Slovenia have been decreasing in recent years. Yet, they pointed out the lack of data on other outcomes, namely amputations, retinopathies, and kidney failure (Table 3).

Suggestions for improving patient access to antidiabetic medicines

The experts expressed the need to change prescribing restrictions, especially for SGLT2i, to provide these medicines to patients at high cardiovascular risk. They also argued that GPs should be able to prescribe DPP-4i and SGLT2i to ensure more equal patient access to these medicines.

One of the diabetologists suggested involving other healthcare professionals in prescribing antidiabetic medicines. Another expert emphasized the need to establish multidisciplinary teams in diabetes care. One attempt to do this was the introduction of family medicine reference clinics (FMRCs) at the primary level of the healthcare system. The general opinion of the experts was that the implementation of FMRCs was an excellent idea; however, they agreed that their potential is unexploited.

The experts repeatedly stressed the need to establish a Slovenian national registry of patients with diabetes in order to obtain more reliable data on these patients' outcomes (Table 4).

DISCUSSION

The participants agreed that Slovenia provides satisfactory patient access to antidiabetic medicines that is comparable with most European countries. Some countries, such as Spain, Austria, and Germany, provide better patient access to novel antidiabetic medicines than Slovenia [3]. However, Slovenia provides good patient access to older antidiabetic medicines, while some smaller European countries already had problems with the availability of older antidiabetic medicines, especially metformin.

The most important factor that may affect patient access, especially to novel antidiabetic medicines, is prescribing restrictions. Several prescribing restrictions apply to novel antidiabetic medicines, e.g., SGLT2i and DPP-4i can only be prescribed by diabetologists and neither of these groups of medicines can be used as first-line therapy. Another antidiabetic medicine group, GLP-1RA, could also be prescribed by GPs, but only to patients with a body mass index equal to or greater than 30 kg/m^2 who are already receiving maximum doses of dual oral combination therapy [9]. However, GPs are reluctant to prescribe GLP-1RA due to lack of knowledge about these medicines.

Due to unequal access to diabetologists across Slovenian regions, patients living in regions with poorer access to diabetologists (especially in eastern Slovenia) may have poorer access to DPP-4i and SGLT2i [10]. Prescribing restrictions of SGLT2i and GLP-1RA should be changed to align with new evidence on the cardiovascular benefit of some medicines of the SGLT2i and GLP-1RA drug classes [11].

In subsequent years, cardiovascular prognosis will probably be the key factor influencing the choice of antidiabetic medicine for individual patients. Cardiovascular outcomes and mortality rates of patients with diabetes in Slovenia are improving, but there is a lack of reliable data on other outcomes, especially amputations. A national registry of patients with diabetes is needed, following the example of, e.g., Sweden and Denmark [12, 13]. Sweden has the best diabetes care in Europe and its national registry is a key factor in the quality of patient care [14]. The experts saw the potential for establishing a registry in Slovenia using FMRCs, where nurses could set up and maintain a national registry of patients with diabetes. FMRCs have been established to provide preventive screening for some chronic diseases (including diabetes), to identify and monitor risk factors, and provide patient education [15]. They play an important role in detecting diabetes early and in providing early access to care for these patients, including early access to antidiabetic medicines that can be prescribed by a GP. In the experts' opinion, the concept of FMRCs was promising but should be upgraded. One area for improvement is in providing group rather than individual education for patients with diabetes. The model of FMRCs may serve as a basis for involving multidisciplinary teams in diabetes care and improving patient care.

The present study provides insight into patient access to antidiabetic medicines from a regulatory and clinical point of view and identifies factors that influence it. In addition, it proposes measures to improve patient access to antidiabetic medicines and patient outcomes, which apply not only to Slovenia but also to other countries. Our study has some important strengths. COREQ criteria were followed for performing and reporting this study. To ensure study validity, the discussion was audiotaped and transcribed verbatim. Two coders independently identified main themes and subthemes of the discussion and jointly interpreted the results.

Nevertheless, some limitations arise when interpreting the findings. First, the study involved only one focus group; however, the group members represented key stakeholders (regulatory bodies and clinicians), who not only have an in-depth insight into patient access to antidiabetic medicines, but also the ability to influence diabetes management in Slovenia. The number of representatives of regulatory bodies with specific knowledge on the study topic in Slovenia is limited, which makes it more difficult to conduct series of focus groups with different representatives of regulatory bodies; doing so would most likely not add to the results. We could conduct another focus group including only representatives of clinicians, but in this case different stakeholders would not be able to interact and discuss each other's opinions, which is one of the main advantages of focus groups. Second, although the focus group facilitator encouraged all participants to express their opinions, some clinical aspects were discussed more specifically by diabetologists only. Third, transcripts and study findings were not returned to the experts for additional feedback and confirmation. However, all four researchers who attended the focus group discussed the study findings. During the discussion, no specific questions arose regarding the interpretation of the study results.

CONCLUSION

Slovenia provides satisfactory patient access to antidiabetic medicines; this is mainly affected by prescribing restrictions and unequal access to diabetologists across Slovenian regions. The most important measure to improve patient access to antidiabetic medicines, not only in Slovenia but also in other countries, is changing prescribing restrictions. In addition, national registries of patients with diabetes should be established to monitor patient outcomes.

Multidisciplinary teams should be involved in diabetes care. The Slovenian model of FMRCs may serve as a basis for establishing multidisciplinary teams; however, the activities of these clinics should be clearly defined from the beginning at the national level, involving representatives of all stakeholders in diabetes care.

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Регулаторна и клиничка перспектива доступности антидијабетика болесницима у Словенији

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САЖЕТАК

Увод/Циљ У последњој деценији уведене су три иновативне врсте антидијабетика, а то су инхибитори дипептидилне пептидазе-4, аналози глукагона слични пептиду-1 и инхибитори натријума и глукозе 2. Неколико чињеница утиче на доступност ових лекова болесницима, те треба истражити њихову употребу у клиничкој пракси.

Циљ студије био је да се стекне увид у доступност антидијабетика болесницима у Словенији са регулаторне и клиничке тачке гледишта.

Методе Фокусна група са пет словеначких стручњака (представници регулаторних тела и корисници антидијабетика) састала се у јануару 2019. године. Дискусија је снимљена звучним записом, а после добијања писмене сагласности стручњака направљен је писани транскрипт. Двоје истраживача су независно анализирали садржај дискусије, користећи *NVivo* 11 да идентификују главне теме и подтеме.

Резултати Словенија пружа задовољавајући ниво доступности антидијабетика болесницима, међутим, ограничења у прописивању лекова и неједнак приступ дијабетолозима у словеначким регионима могу ограничити приступ болесника иновативним антидијабетичарима. Ограничења у прописивању лекова треба ускладити са новим доказима о кардиоваскуларним предностима одређених антидијабетика. Потребно је успоставити национални регистар болесника са дијабетесом како би се добили поуздани подаци о исходима лечења и побољшао квалитет неге болесника.

Закључак Неопходно је побољшати доступност антидијабетика болесницима не само у Словенији већ и у другим земљама променом ограничења за прописивање лекова, успостављањем националног регистра болесника са дијабетесом и укључивањем мултидисциплинарних тимова у лечење дијабетеса.

Кључне речи: дијабетес; антидијабетичари; приступ болесницима; фокусна група; лечење дијабетеса

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Rapidly progressive pulmonary fibrosis in COVID-19 pneumonia

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SUMMARY

Introduction COVID-19 pneumonia does not have a characteristic course and prognosis. Many facts still remain hidden, mainly why certain patients develop complications with serious tissue damage and whether it causes a permanent organ impairment. If and when will fibrosis develop in COVID-19 pneumonia requires further research, but a link between the amount of tissue afflicted and the development of fibrosis exists.

Case outline A previously healthy, non-smoker, woman with minor symptoms on admission had suddenly developed a serious respiratory insufficiency and whose radiographic finding on computed tomography scan had shown a serious progression with the development of fibrosis in a matter of days. The exact mechanism and correlation of this clinical course remains unknown; however, it is clear that the pulmonary fibrosis is caused by COVID-19 pneumonia. Follow-up computed tomography scan, performed 50 days after initial symptoms, had shown a partial regression of consolidations and post-inflammatory fibrosis.

Conclusion Pulmonary fibrosis is the most severe complication of COVID-19 infection on the respiratory system. Who, when or if a patient will develop any complication is still unclear, as well as whether these changes are reversible? Also, the number of recovered patients who later develop some chronic complications remains to be seen.

Keywords: COVID-19; pneumonia; pulmonary fibrosis

INTRODUCTION

Near the end of 2019, in Wuhan, China there was a significant number of patients with viral pneumonia with uncharacteristic clinical manifestation and unpredictable clinical course. Shortly thereafter the cause was identified as coronavirus, and the World Health Organization had classified it as COVID-19 infection, more specifically as SARS-CoV-2 [1].

Previously, coronavirus had caused gastrointestinal symptoms in humans, and was predominantly pathogen that infects animal species [2]. In previous seven months, as of time of writing this report, this virus is one of the most common infectious agents in humans, and can lead to respiratory, cardiovascular, gastrointestinal and other difficulties. Currently, clinical manifestation of this infection is of a relatively severe course, with frequent development of complications and (one or more) organ failures, with a possibility of a lethal outcome [3]. Many clinical studies have shown that organ damage caused by COVID-19 can be irreversible [4]. Considering that coronavirus still shows new characteristics, many facts are still unknown, such as the path of transmission, period of incubation, clinical presentation, typical radiographic and laboratory findings and specific treatment.

CASE REPORT

Female patient, non-smoker, aged 45, with no previous history of any pulmonary or other medical diseases, has been hospitalized at our Clinic due to suspicion of COVID-19 infection. She presented with fever (up to 38°C), fatigue, muscle and joint pain which began a day prior to hospitalization. Initially, she was examined in the regional medical center, chest X-ray had shown a discrete reticular pattern paracardial to the right and biochemical results have shown a slightly elevated C- reactive protein (10 mg/l). Considering the positive epidemiological exposition, she was highly suspected of COVID-19 infection and was administered to our Clinic. On admission the patient was conscious, with a fever (37.8°C), eupneic, acyanotic, anicteric, with normal coloration of the skin and visible mucosa, with no signs of peripheral lymphadenopathy and fresh hemorrhagic syndrome. Auscultation of lungs had shown normal respiratory sound, O_2 saturation of blood measured on room air was 98%. Heart rate was tachycardic, rhythmic, with no murmurs, heart rate was 95 bpm, arterial tension was 120/80 mmHg. ECG had shown sinus rhythm, with no ST and T abnormalities. Laboratory findings were within referential values, except slightly elevated C-reactive protein (CRP) 9.1mg/l and interleukin 6 (IL-6) 13.1 pg/ml. Chest X ray had

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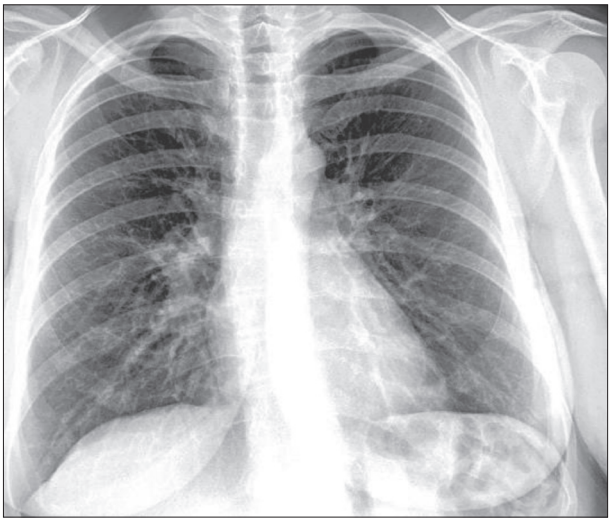

Figure 1. Chest X-ray on admission, with signs of diffuse bronchovascular markings

shown emphasized bronchovascular markings (Figure 1). Serological analysis for COVID-19 were initially negative, as well as the first two nasopharyngeal swabs. However, the third swab came back positive, and the patient was started with COVID-19 treatment suggested by the National protocol for COVID-19 infection, provided by the Ministry of Health of Serbia (third generation cephalosporins, chloroquine, anticoagulant and poli-vitamin treatment). After the beginning of treatment, clinically the patient felt well, with the exception of daily elevations of body temperature (up to 39°C). On the fifth day of hospitalization, there was an elevation of CRP (23.7 mg/l) and IL-6 (35.7 pg/ml); serum iron was decreased (4.3 umol/ml) with newly discovered mild thrombocytopenia (142×10^9) and leucocytes count of 3.6×10^9. Follow-up chest X-ray did not show any significant changes compared to the one on admission. Fluoroquinolone was added to the treatment. On the seventh day of hospitalization, as a part of reevaluation of the disease, a CT scan was performed which had shown multiple bilateral and subpleural oval areas of ground glass opacification with a minimal reaction of interlobular interstitium, with the exception of X segment, in which was an area 6 × 3.2 cm, with evident interlobar septal thickening with fibrosis and bronchiectasis. The location of the areas with ground glass opacification were as follows: the left lung 2.5 × 1.5 cm in the upper lobe, 2.8 × 2.4 cm in the lingula, 5.4 × 2 cm in the VI segment, roughly 4.5 cm in the IX, and 1.5 cm in the X segment; the right lung in the posterior part of the upper lobe 5.7 × 2 cm, 7 × 3 cm in the VI segment, and up to 1.5 cm in the VIII segment. There were several lymph nodes up to 1 cm in the 4R and 5L group (Figure 2).

On the tenth day of hospitalization, there was an acute worsening of the general state of the patient with a sudden development of hypoxia (O_2 sat 92%). There was a further increase of the inflammatory factors (CRP 138.6 mg/l, fibrinogen 4.9 g/l, ferritin 544 ug/l, IL-6 63 pg/ml), with a significant increase of presepsin 1340 pg/ml. There was also a pathological finding of the liver enzymes (AST 54 U/l, ALT 49 U/l). Chest X ray had shown further progression of the finding, with diffuse consolidation, especially peripherally in the basal regions (Figure 3). The patient was put on a triple antibiotic treatment (third antibiotic was a derivate of imidazole), and was placed on a continuous controlled oxigenotherapy. Considering the presence of both clinical and radiological worsening, as well as the further increase of the inflammatory factors, it was decided to administer tocilizumab in the dose of 40 mg parenterally, followed by systemic corticosteroid therapy (methylprednisolone, 2 mg/kg with successive decrease of the dose). After the change of the treatment, the respiratory insufficiency is further worsened (arterial blood gas test had shown pH 7.46, pO_2 7.78 kPa, pCO_2 5.07 kPa, lactates 2.2 mmol/l, O_2 sat 91%), which lead to the administration of the high flow oxygenator. The treatment proved successful, there was an improvement of the arterial blood gas test pH 7.49, pO_2 11.5 kPa, pCO_2 4.44 kPa, O_2 sat 95.5%, starting from the 13th day of the hospitalization the patient did not have any fever, and felt significantly better, however, she was still dependent on high flow oxygenator. New lab results have shown a normalization of the bloodwork as well as CRP (2.5 mg/l), and a relatively higher value of IL-6 (195 pg/ml), which was expected after the initiation of the immunosuppressive therapy. The control chest X-ray has started to show initial signs of the regression; however, it did show a certain degree of the newly developed pulmonary fibrosis (Figure 4). The further administration of

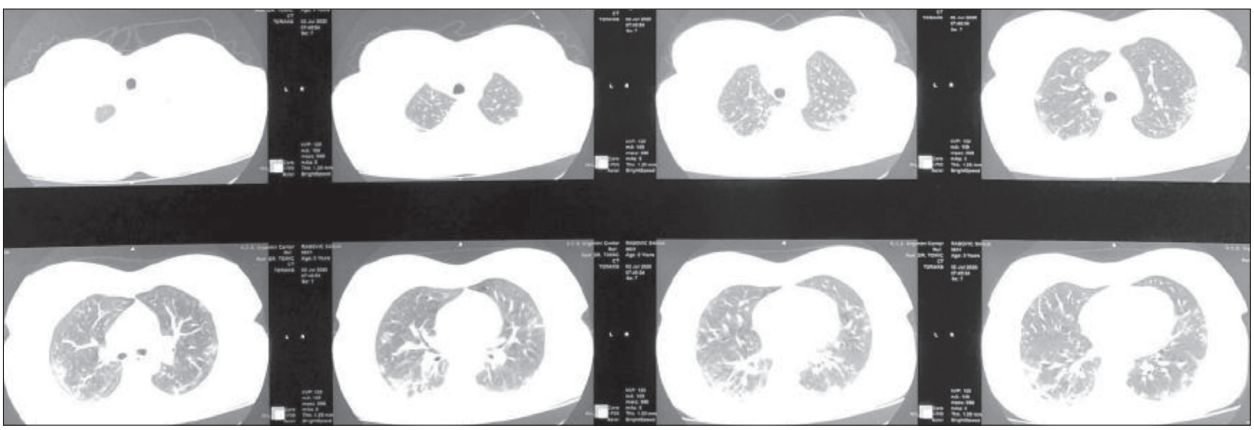

Figure 2. First computed tomography scan showing multiple subpleural ground glass opacifications

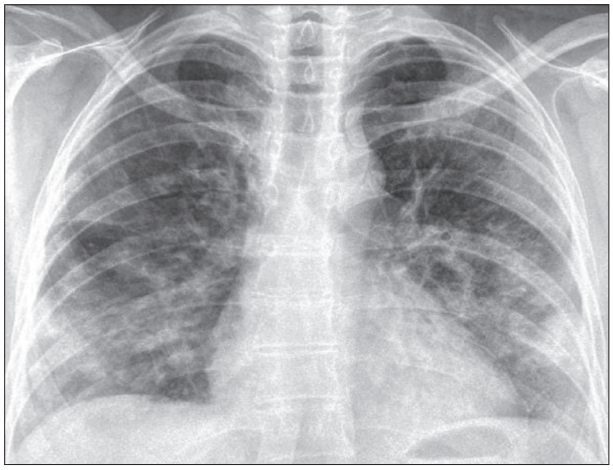

Figure 3. Follow-up chest X-ray now showing the changes initially seen only on the computed tomography scan

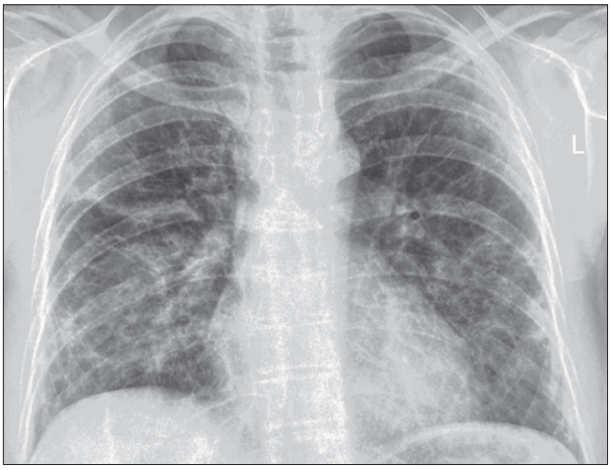

Figure 4. Follow-up chest X-ray after immunosuppressive treatment and high flow oxygenator, showing a certain degree of regression, however areas with fibrosis still remain

the corticosteroid treatment had led to the improvement of the arterial blood gases (pH 7.47, pO_2 9.5 kPa, pCO_2 4.8 kPa, O_2 sat 96%, the results were without O_2 support). With these improvements, the patient was discharged, and continued treatment from home.

The follow-up CT scan was performed 50 days after the first day of hospitalization. It had shown that subpleural, in both lungs, the previously found ground glass regions remained (right I and II segment, left I and II segment) which were interpreted as an inflammation in resolution. However, in the VI segment, in the right lung, there was a zone of consolidation with a negative areal bronchogram, and a thickening of the interstitium with a distortion of the pulmonary bronchi; bilaterally in the IX and X segment there is a thickening of the interstitial septa- all of the changes are attributed to the post inflammatory fibrosis. The follow-up pulmonary function had shown a certain degree of restriction (FVC 96%, FEV1 100%, FEV1/FVC 88.52; diffusion capacity for CO TLCOc 59%, KCOc 73%).

Written consent to publish all shown material was obtained from the patient.

DISCUSSION

We have stated that COVID-19 pneumonia has an uncharacteristic clinical presentation and an unpredictable outcome. Many characteristics still remain undiscovered, and the main enigma is why certain patients develop complications, and whether or not there is a permanent disfunction to the afflicted organs. In this case report we will discuss what is known regarding the pathophysiological mechanism of the COVID-19 infection of the respiratory system. It is known that COVID-19 enters the respiratory cells through angiotensin-converting enzyme 2 receptors (ACE2) [5]. If a certain organism causes an intensive immune response, known as "cytokine storm," it leads to the hypercoagulability and further lung damage [6]. The damaged tissue is repaired with scar tissue, which has no function, and leads to the state known as pulmonary fibrosis. Whether or not the pulmonary fibrosis will develop after COVID-19 pneumonia is still unknow, but it could be hypothesized that there is a correlation between the amount of infected tissue and the degree of fibrosis.

We have chosen to present this case in order to show how the clinical course, radiographical and laboratory findings can change in a relative short period of time, in this case in less than 48 hours. It is important to note that our patient was a relatively young woman, with no previous known diseases, no history of smoking and no professional exposition to any known respiratory agents. On admission she did not show any signs or symptoms of any organ failure. Between sixth and tenth day, the patient suffered a worsening of the symptoms and developed acute respiratory insufficiency with radiological progression. CT scan could probably show the existing pathological findings earlier than chest X-ray. The first CT scan performed on the eighth day since the start of the symptoms had shown the beginning of the lung scaring. There are two possible explanations for the development of the pulmonary fibrosis which are most probable: first is that the virus was present much longer prior to the manifestation of the first symptoms and had time to damage the lungs. The second possibility is that the virus caused the "cytokine storm" which led to the pulmonary fibrosis. The only certain causality is that COVID-19 pneumonia has led to the pulmonary fibrosis. The control CT scan had shown that there still are areas of consolidations, as well as areas with pulmonary fibrosis.

Current knowledge regarding the sequelae of COVID-19 infection is lacking. Regarding the respiratory system, pulmonary fibrosis could be considered the most severe complication of COVID-19 infection. It is still unclear who, when or if a patient will develop this complication. As of writing of this article, there are roughly 20 million infected people, with round 13 million who have recovered from COVID-19 infection [7, 8]. How many of the recovered patients will have any complications, and if those complications are reversible, only time will tell.

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Conflict of interest: None declared

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Рапидно прогресивна плућна фиброза код пнеумоније изазване ковидом 19

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САЖЕТАК

Увод Пнеумонија изазвана ковидом 19 има некарактеристичну клиничку слику и непредвидив ток. Многе чињенице су остале неразјашњене, а главна енигма остаје зашто се код неких болесника развијају компликације са последичним оштећењем ткива и да ли ће те промене трајно нарушити функцију захваћених органа. Да ли ће се и када развити фиброза плућа после пнеумоније изазване ковидом 19 засад није познато, али јасно је да постоји корелација између обима захваћеног ткива вирусом и развоја ове болести.

Приказ болесника Приказујемо болесницу без хроничних болести, непушача, без професионалне изложености, која је при пријему била доброг општег стања и без знакова попуштања било ког органа. У року од неколико дана рапидно се погоршало опште стање, развила се респираторна инсуфицијенција и радиолошки су уочене масивне консолидације обострано, са појединим зонама у којима су биле ожиљне промене. Да ли је вирус био дуже присутан и да ли су прве тегобе наступиле после већ обимног нарушавања плућног ткива или су уочене фиброзне промене последица „цитокинске олује" није познато. Јасно је да су фиброзне промене последица пнеумоније изазване ковидом 19. Контролни снимак компјутеризованом томографијом грудног коша показао је да су промене у плућима присутне дифузно, обострано у свим лобулусима, делом консолидација (50 дана од почетка тегоба), а делом консолидација у резолуцији, уз присутне фиброзне промене као постинфламаторне секвеле.

Закључак Фиброза плућа је најтежа секвела коју овај вирус може проузроковати на респираторном систему. Ко, када и да ли ће развити фиброзу плућа и даље остаје неразјашњено. Колики проценат опорављених болесника има или ће развити неку од хроничних компликација показаће време, као и то да ли су присутне промене реверзибилне.

Кључне речи: ковид 19; пнеумонија; плућна фиброза

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Report on four cases of the rarest benign splenic tumor – myoid angioendothelioma, with literature review

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SUMMARY

Introduction Myoid angioendothelioma of the spleen is an extremely rare form of a benign splenic tumor. There is no characteristic symptomatology for this disease.

Case outline We present four patients operated on for myoid angioendothelioma of the spleen. Three patients were without problems while one had nonspecific problems. Two patients underwent laparoscopic surgery and two underwent open splenectomy. In all patients, the definitive diagnosis was confirmed by histopathological examination.

By reviewing the aforementioned medical databases of published papers in English, we found a total of eight cases of myoid angioendothelioma of the spleen. In addition to the mentioned number, we have added our series of cases.

Conclusion Twenty-one years after the discovery of myoid angioendothelioma of the spleen, the small number of cases presented in the literature is still a limiting factor in making conclusions and in learning lessons about this disease

Keywords: spleen; tumor of the spleen; splenectomy; laparoscopy

INTRODUCTION

Myoid angioendothelioma of the spleen (MEA) is an extremely rare form of benign splenic tumor. As most benign tumors of the spleen, vascular malformations in combination with stromal cells are responsible for the development of MEA [1].

There is no characteristic symptomatology for this disease. Patients are mostly asymptomatic, and sporadically there may be symptoms in the form of nonspecific pain below the left costal arch, abdominal discomfort, nausea and vomiting, which may occur sporadically [2].

MAE is diagnosed accidentally, most often as an incidental finding within other diagnostic foci. Initially, it can be detected by ultrasonography of the abdomen, although computed tomography (CT), as well as magnetic resonance imaging (MRI) have much greater specificity and sensitivity. The most authoritative, and at the same time the most accurate diagnosis is histopathological verification [3, 4].

Splenectomy (laparoscopic or copen) is the only curative treatment modality. Laparoscopic splenectomy should certainly be preferred over open splenectomy because of the numerous advantages and benefits achieved by this approach [5].

Our study aims to implement our series of MAE cases into current literature data. We also wanted to show that, in addition to the already known benefits of laparoscopic splenectomy over open splenectomy, preserving the integrity of the preparation does not affect the definitive histopathological finding, and that there is absolutely no difference whether the spleen is delivered in fragments or as a complete sample.

CASE REPORTS

Case 1

A 54-year-old female patient was referred to our hospital for additional diagnostics and further treatment due to a lesion in the spleen, which had previously been verified with ultrasound. On admission, the patient's general health status was good, she had no comorbidities and reported no complaints. Within additional diagnostics, an abdominal CT scan was performed. The finding confirmed the existence of a lesion in the spleen, 52 × 50 mm in size, which was, according to its characteristics, most consistent with a splenic tumor. We indicated that surgical treatment was necessary and proceeded to perform laparoscopic splenectomy in the standard manner, with the use of hem-o-lok clips for the vascular elements of the splenic hilum (Figure 1). Hospitalization was uneventful, with no complications. On the

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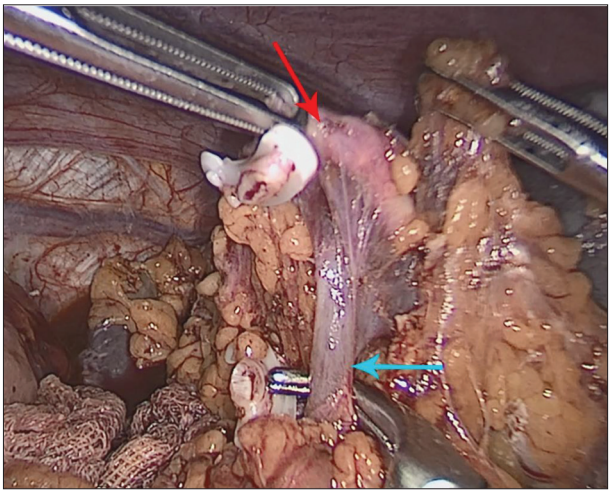

Figure 1. Intraoperative presentation of the hemostatic technique for the vascular elements of the spleen hilum; the red arrow indicates the splenic artery and the blue arrow indicates a splenic vein

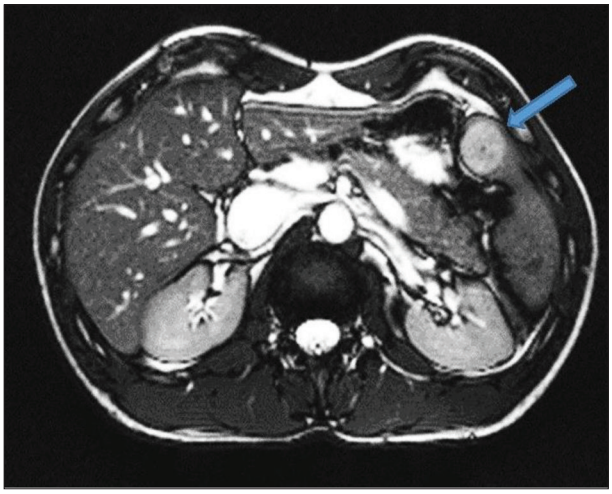

Figure 2. Magnetic resonance imaging examination showed a solitary lesion in the lower pole of the spleen, with peripheral rim enhancement on arterial phase

third postoperative day the patient was prescribed appropriate therapy and discharged from hospital to complete recovery at home.

Case 2

A 26-year-old male patient was hospitalized for surgical treatment. Previous MRI of the abdomen showed tumorous lesions in the spleen, 45 × 40 mm (Figure 2). After adequate preoperative preparation, the patient was operated on in general anesthesia. Laparoscopic splenectomy was performed, in the standard manner, with the application of the hanging spleen technique, as was done in the previously described case. The surgery itself, as well as postoperative recovery, were uneventful, with no complications. The patient was discharged from hospital on the third postoperative day.

Case 3

A 58-year-old male patient was hospitalized for surgical treatment of a previously verified tumorous lesion in the spleen. This lesion had been diagnosed with an abdominal MRI scan, as an incidental finding within diagnostic procedures and testing focused on other health issues. The patient, whose general health status was good and who had no comorbidities, was treated surgically. The surgical procedure and postoperative recovery were uneventful, with no complications. The patient was discharged on the fifth postoperative day.

Case 4

A 69-year-old male patient was admitted to hospital for health status assessment and additional diagnostics. Prior to hospitalization, the patient felt discomfort in the upper left quadrant of the abdomen with occasional nonspecific pain in the same region. Ultrasound of the abdomen showed a lesion in the spleen. The patient was then referred for further treatment. After hospital admission, a CT of the abdomen was performed. The scan verified a lesion in the spleen, 55 × 60 mm in size, which, according to its characteristics, was consistent with a splenic tumor. Surgical treatment was indicated, and open splenectomy was performed, as in Case 3, described above. Postoperative recovery was uneventful and with no complications, and the patient was discharged from hospital for further recovery at home on the fifth day after the procedure.

All the patients whose cases are described above were prescribed prophylactic antibiotic therapy at discharge, and were also given instructions regarding necessary postoperative immunization, in keeping with the current guidelines found in literature and guidebooks on the prevention and treatment of postsplenectomy infections.

All the spleen samples were sent for definitive histopathological and immunohistochemical analysis, which confirmed that, in all four of the described cases, the lesions were MAE of the spleen. In one of the patients, however, overlap was detected, i.e., in addition to MAE, the existence of splenic cord capillary hemangioma was also confirmed.

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. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

MEA of the spleen is an extremely rare form of a benign splenic tumor. It was described for the first time in 1999 by Kraus and Dehner [6]. By reviewing the aforementioned medical databases of the published papers in English, we found a total of eight cases of MEA. In addition to the

Table 1. Characteristics of all included studies and our studies

Author	Country	Year	Study design	Age	Sex	Histopathology confirmation	Treatment Laparoscopy or Open surgery	Accompanying disease	Signs and symptoms
Kraus M. D. [6]	USA	1999	Case series	3 7 43	Female Male Female	In all three cases: may represent proliferations of myoid elements native to the spleen	Case 1: not reported Case 2: not reported Case 3: open surgery	Case 1: Beckwith–Wiedemann syndrome Case 2: None Case 3: Cystic mucinous pancreatic neoplasm	Case 1: not reported Case 2: abdominal discomfort Case 3: not reported
Karim R. Z. [4]	Australia	2004	Case report	51	Male	Yes	Not clear	Renal calculi and degenerative spinal disc disease	Abnormal liver function test results
Chan Y. F. [7]	Australia	2005	Case report	8	Male	Yes	Partial splenectomy and removal of the splenic lesion	Wilms' tumor	Fever, lethargy, vomiting and bone pain
Jang K. Y. [1]	South Korea	2013	Case report	41	Female	Yes	Open surgery	Rectal cancer, hypertension and asthma	Incidentally discovered while searching for metastasis of rectal cancer
Geramizadeh B. [3]	Iran	2017	Case report	38	Female	Yes	Open surgery	None	Epigastric abdominal pain and fullness
Shah A. A. [10]	India	2018	Case report	11	Male	Yes	Laparoscopic splenectomy	Wilms tumor (kidney)	No symptoms and signs, discovered on routine ultrasound (follow up after Wilms tumor)
Milosavljević V. (present study)	Serbia	2020	Case series	57 32 65 74	Female Male Male Male	Yes	Case 1, 2. Laparoscopic splenectomy Case 3, 4. Open surgery	None	No symptoms and signs, discovered on routine ultrasound and incidentally on computed tomography, magnetic resonance

mentioned number, we have added our series of cases and showed it in Table 1, all of it to update and add to the current literature data.

Including data from our case series, the distribution by gender is slightly higher in men compared to women 7/5.

The symptomatology of this disease is mostly absent. Rarely, there may be a pain in the upper left quadrant of the abdomen, as well as a feeling of discomfort in the abdomen [7, 8].

Due to the absence of specific symptoms, like other benign tumors of the spleen, MAE is a real diagnostic challenge. They are almost always discovered accidentally as an incidental finding as part of other diagnostic tests and foci [9, 10]. They are initially detected by ultrasound examination of the abdomen, although it is certainly necessary to perform one of the more modern diagnostic methods such as CT, MRI, or positron emission tomography for better verification, determination of characteristics, and differential diagnosis [11].

The definitive and only authoritative diagnosis is made by histopathological and immunohistochemical examination [2, 5, 12].

All patients presented in our study underwent histopathological and immunohistochemical verification. Definitive histopathological findings revealed a well-circumscribed tumor composed of numerous capillary caliber vessels implanted in an eosinophilic matrix with pulp stromal cells. Further immunohistochemical examination revealed strongly positive staining of the vascular lining cells for CD34 and CD31, while stromal cells stained positive for smooth muscle actin, desmin, and myosin. Staining for S100, CD8 and CD21 was not present in either lining. Therefore, a diagnosis of MEA of the spleen was confirmed.

Some authors advocate preoperative histopathological analysis of changes in the spleen using fine-needle aspiration [13].

From our previous experience in the treatment of benign tumors of the spleen, we do not share the opinion that the use of fine-needle aspiration is necessary if it is known that any tumor change in the spleen requires surgical treatment, i.e., splenectomy [2, 5, 14, 15]. Special attention should certainly be paid to the fact that the fine-needle aspiration sample can often be inconclusive, and the intervention itself, like all other invasive procedures on the spleen, carries a certain type of risk for complications [16].

As in the case of other benign splenic tumors, splenectomy is the only curative treatment modality to be applied for MAE [2, 17]. According to the literature data presented so far in Table 1, out of a total of eight cases, only one underwent laparoscopic splenectomy. During that time, we performed laparoscopic splenectomy in two patients, and open splenectomy was performed in two patients due to

technical reasons and to the insufficient experience of the surgeons who performed the operations.

Due to the numerous advantages and benefits that laparoscopic splenectomy provides, it should always be given priority over open splenectomy [2, 5, 14, 16, 18].

Since it is a benign tumor of the spleen, it is possible to perform partial splenectomy, especially in younger people [19]. In general, the small number of cases described so far, as well as the lack of reliable information on the application of partial splenectomy in the treatment of MAE, are a limiting factor [20].

Twenty-one years after the discovery of MAE, the small number of cases presented in the literature is still a limiting factor in making conclusions and in learning lessons about this disease. Each subsequent case should be approached individually to possibly gain new, significant, and necessary information and knowledge. Laparoscopic splenectomy has proven to be a safe, easily applicable, and effective treatment modality for MAE. It can be said that it is the modality of choice both as surgical treatment and as diagnostics and should always be applied when there are suitable conditions, technical equipment, and trained staff. It remains to be seen in the future whether there are conditions for the application of partial splenectomy in MAE on a larger sample of patients, which would certainly improve treatment and provide a better, more comfortable postoperative lifestyle, especially in younger patients.

Conflict of interest: None declared.

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Приказ четири случаја најређег бенигног тумора слезине – миоидног ангиоендотелиома и преглед литературе

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САЖЕТАК

Увод Миоидни ангиоендотелиом је веома редак бенигни тумор слезине. Не постоји карактеристична симптоматологија за ово обољење.

Приказ болесника Представљамо четири болесника оперисана због миоидног ангиоендотелиома слезине. Три болесника су била без тегоба, док је један имао неспецифичне тегобе. Два болесника су оперисана лапароскопски, а два отвореном спленектомијом. Код свих болесника дефинитивна дијагноза је потврђена хистопатолошким прегледом.

Дискусија Прегледајући поменуте медицинске базе података објављених радова на енглеском језику, пронашли смо укупно осам случајева миоидног ангиоендотелиома слезине. Поред поменутог броја, додали смо и нашу серију случајева.

Закључак Двадесет и једну годину после открића миоидног ангиоендотелиома слезине мали број случајева представљених у литератури је и даље ограничавајући фактор у доношењу закључака о овој болести.

Кључне речи: слезина; тумор слезине; спленектомија; лапароскопија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Necrotising fascitis – a life-threatening infection: case reports and literature review

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SUMMARY

Introduction Necrotizing fasciitis is a rare, severe, aggressive infection, life-threatening surgical emergency that spreads quickly, characterized by extensive necrosis of the deep and superficial fascia, associated with significant morbidity and mortality.

Case outline We are presenting two case reports with necrotizing fasciitis: a 54-year-old male patient, obese, with hypertension and untreated perianal fistula with severe infection of perianal region, perineum and scrotum, and a 64-year-old female patient with diabetes mellitus and heart disease, with severe infection of the lower extremity, anterior abdominal wall, inguinal and gluteal region, in which the entry point of infection were microlesions of the skin after shaving. Both patients were treated by emergency extensive surgical necrectomy with eradication of the deep infection source, with all conservative treatment measures. One patient was treated with hyperbaric oxygen therapy, the other was not because of cardiac and pulmonary contraindications.

Conclusion Better treatment outcome requires a multidisciplinary approach (cardiologist, endocrinologist, nephrologist, orthopedist, surgeon). Rapid and extensive surgical necrectomy is necessary to increase the success of the treatment of patients with this infection.

Keywords: necrotizing fasciitis, surgical debridement, severe infection

INTRODUCTION

Necrotizing fasciitis (NF) is a rare, severe, bacterial life-threatening infection, characterized by spreading rapidly, affecting subcutaneous tissue, fascia and sometimes muscles, an infection with high mortality rate, especially in patients with comorbidities [1].

The incidence of this infection is 1–4/100.000 persons per year. Many studies present different mortality data for NF, but what they have in common is that it is still extremely high [1, 2, 3]. In a population-based study in the United States, it was reported that overall mortality was 7.5%. Some studies reported mortality rate up to 70% with higher rates in underdeveloped countries. The modern new studies report mortality rate between 20–40% [4].

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CASE REPORT 1

In September 2019, a 54-year-old man was admitted to the Department of General Surgery at the General hospital of Novi Pazar. The patient was febrile, languid, hypotensive, tachycardic, obese, with changes on the skin of the perianal region, about 3 × 3 cm in size, a slight bullous change on the surface and palpatory evident tissue fluctuation below the change. History of the present illness: untreated perianal fistula. Past medical history was positive for hypertension.

When admitted, an incision was made and a large amount of green-brown liquid content was obtained with an extremely unpleasant odor. Laboratory findings during hospitalization are shown in Table 1. Intensive conservative treatment started with empirical antibiotics (ceftriaxone, gentamicin, and metronidazole), insulin therapy, fluid replacement, analgesics, and other supportive therapy, with monitoring of vital parameters. After 24 hours of treatment erythematous changes occurred on the skin with obvious rapid spread of infection to the perineum and scrotum, as well as to both gluteal regions, also increased local pain, biochemical inflammatory parameters and development of clinical signs of sepsis (s-Procalcitonin 21.08, The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score 11). Extensive surgical excision of the infected parts of the perianal region, broadly into each gluteal region was made, as well as excision of scrotal skin with opening of all testicular sheaths and opening inguinal canals on both sides. The wound was left to heal *per secundam intentionem* (Figure 1).

A wound swab taken for microbiological analysis was positive for Klebsiella spp. Treatment was continued with antibiotics (imipenem, vancomycin, and metronidazole) and regular wound dressing two to three times daily.

Postoperatively, 48 hours after surgical reintervention, necrectomy, was performed. On the fifth postoperative day there was a worsening of the patient's general condition which was

Table 1. Laboratory parameters during the hospitalization

Parameters	Patient 1			Patient 2		
	Day 1	Day 2	Day 7	Day 1	Day 2	Day 7
Glycemia (mmol/L)	41	20	12	32	24	10
CRP (mg/L)	403.7	397	134	350	305	140
Creatinine (μmol/L)	222	160	103	158	142	122
Urea (mmol/L)	26.8	23	19	24	20	12
Na+ (mmol/L)	135	134	135	135	133	136
WBC (10^9/L)	26	28	16	27	23	15
RBC (10^{12}/L)	4.08	3.81	3.21	4.34	4.01	3.98
HGB (g/L)	121	114	101	129	123	124

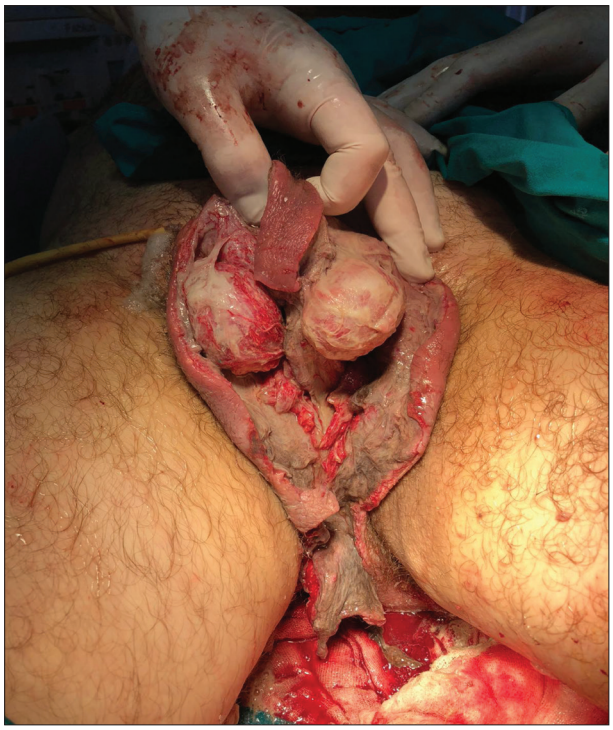

Figure 1. Infection of scrotum and perineum after surgical necrectomy

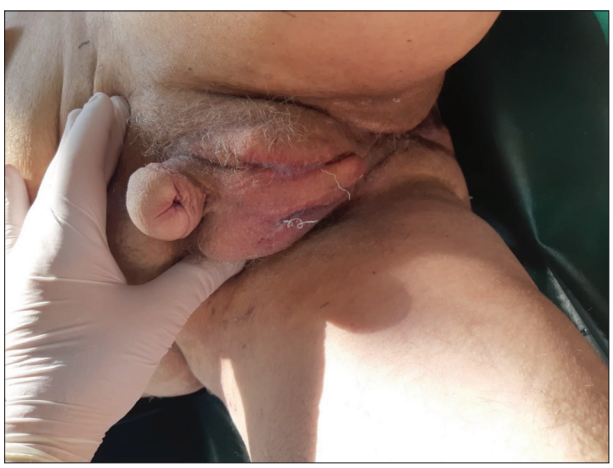

Figure 2. At the end of the treatment for patient 1

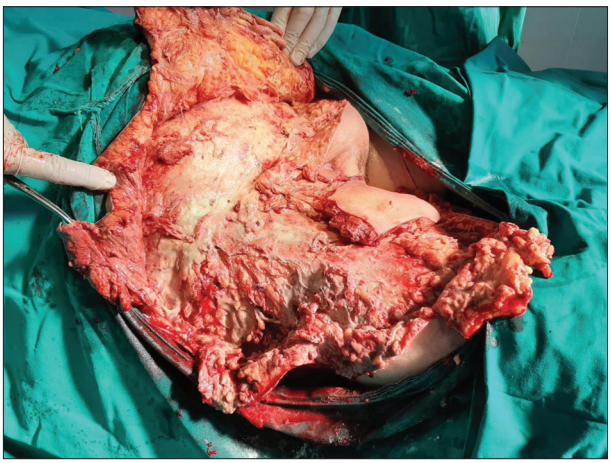

Figure 3. Local status of infected area in the beginning of treatment

complicated by the appearance of pulmonary edema and heart failure. After the improvement of the general condition, on the 10th postoperative day, hemodynamically stable, with neat vital parameters, the patient was transported to a tertiary health care institution for treatment with hyperbaric oxygen therapy (HBOT). Prior to HBOT, colon surgery was performed according to Hartman procedure. He was treated in a tertiary institution for 40 days after which he was discharged for outpatient treatment with a regular wound toilet and occasional surgeon's control. Four months following the treatment the patient had fully recovered (Figure 2).

CASE REPORT 2

In September 2019, a 64-year-old female patient was admitted to the Department of General Surgery at the General Hospital of Novi Pazar. On admission she was febrile, languid, hemodynamically unstable, with pretibial edema, septic, less mobile. For over 15 years she has been a diabetic on insulin therapy.

On admission, an infection of the skin of the groin region on the right, about 6 × 2 cm in size, was noticed, where the skin was erythematous, painful, with the presence of subcutaneous air enhancements.

Biochemical parameters during hospitalization are shown in Table 1 (s-Procalcitonin 23.12, LRINEC score 10). Four hours after admission an extensive excision of the skin and subcutaneous tissue was made, all the way to the fascia of right femoral and pubic region, anterior abdominal wall in the infraumbilical region, pubic and right gluteal region, to the macroscopically visible healthy tissue (Figure 3). The wound was left to heal *per secundam intentionem*. After necrectomy antibiotic treatment was started: imipenem, vancomycin, and metronidazole, and other supportive therapy with daily wound toileting, two to three times a day.

Postoperatively, a decrease in biochemical inflammatory parameters occurs. Surgical reintervention, necrectomia, 48 hours after the first surgery, was performed. Microbiologically isolated *Pseudomonas aeruginosa* in the

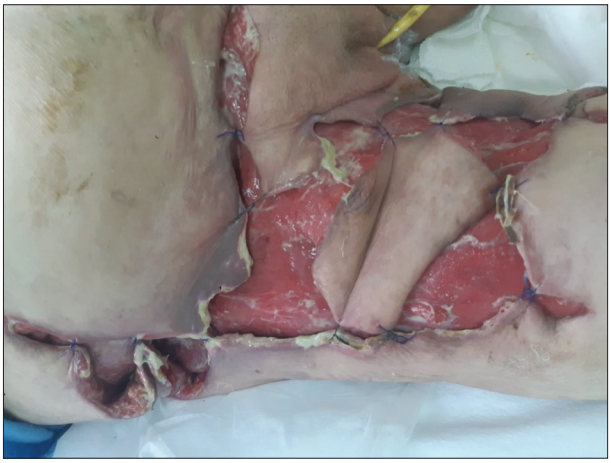

Figure 4. At the end of the treatment for patient 2

wound swab was sensitive to administered antibiotics. HBOT treatment was not performed due to cardiac and pulmonary contraindications. On the control swab the microbiological findings showed *Staphylococcus aureus* and *Klebsiella spp*. Due to a large skin defect, to prevent skin contracture, situational sutures were repeatedly placed on the skin (Figure 4) but to no avail. The patient was in good general condition, neat vital parameters, no local signs of infection, and after 45 days of hospitalization, the skin defect was reconstructed by a plastic surgeon.

We obtained verbal and written consent from the patients to publish the case report. This article was planned in compliance with the Patient Rights Directive and ethical rules by considering the principles of the Declaration of Helsinki.

DISCUSSION

NF is severe and potentially fatal, aggressive infection associated with significant morbidity and mortality. Some literature data reported that the prevalence of NF is about 1–4 cases per 100,000 populations; men are commonly affected, with a male-to-female ratio of 3:1 [1]. However, there are studies showing different results, so, male to female ratio by Eke et al. [5] is approximately 10:1, and in the study of Kim et al. [6], men accounted for 67.1%.

Most commonly, it is a polymicrobial infection caused by aerobic and anaerobic bacteria, most commonly from the genitourinary and digestive tract, but also from the skin [7]. However, some recent studies suggests that the prevalence of monomicrobial NF is as high as 60–80% [8]. Tsai et al. [8] state that the infections have more rapid and fulminant form if they are caused by Gram-negative microorganisms. Jabbour et al. [9] state that *Pseudomonas* and *Proteus* infections were the most commonly associated microorganisms among non-survivors in their study.

In presented cases, *Pseudomonas* and *Klebsiella* were isolated as the only pathogenic microorganisms.

There is no age predilection for NF, but patient age is a significant predictive factor for treatment outcome. Middle-aged patients as well as those over 50 years of age are more likely to be infected [10], have a worse prognosis, especially if they have accompanying comorbidities [1, 11]. In the study by Chalya et al. [11], the median age of patients was 34 years, while Schröder et al. [12] analyzed the occurrence of NF in children [13]. Advanced age is independent and strong predictor of mortality, mainly due to the increased incidence of comorbidities.

Diabetes mellitus is the most common comorbidity in patients with NF, and in addition to it, there are chronic alcoholism, chronic renal failure, arterial hypertension, immunosuppression, systemic disorders, cirrhosis, obesity, local trauma. Jabbour et al. [9] stated that in their study diabetes was present in 64%, followed by hypertension and renal impairment, and compared to a survivor group, these comorbidities were higher among non-survivors. In a study by Tarchouli et al. [10], diabetes was present in 38% of the cases and the mortality rate in heart disease was significantly higher. In the study of van Stigt et al. [14] the most frequent comorbidity was cardiovascular disease.

The disease usually involves anterior abdominal wall (20%), the scrotum (30%), and perineum (50%) [1].

Patients usually have symptoms that manifest as local pain, fever, malaise, hypotension, and poor general condition. Tissue swelling, erythema, crepitations, odor, skin necrosis, bullous changes can be seen. What is important is that the visible change of the skin is much smaller than the tissue infection under the skin, so it is necessary to recognize NF when the cutaneous changes are small. Mitchell et al. [15] reported that the lower limb was the most frequent site of infection, with 53%, and severe pain (76%) and swelling (83%) were the most common presenting features. Jabbour et al. [9] stated that the lower limb/thigh (53%) was the most frequent site of infection, followed by perineum (25%), and the sacral region had significantly higher frequency in non-survivors. Misiakos et al. [13] stated, the mostly infected site was perineum (46.8%), then lower limbs (35.5%), diabetes mellitus was the most common comorbidity (40.3%) and tenderness and local pain were the most common symptoms.

The symptomatology and local indicators of the infection in our cases mainly coincide with the literature data. Both patients were admitted in a serious condition with both local and systemic symptoms. The first patient presented with a history of comorbidity: irregularly treated arterial hypertension was only reported, while he also suffered from untreated perianal fistula and obesity (BMI 37.6). A percussion abscess was present from which the infection may have spread. The second patient was a cardiac patient with a long history of diabetes, on insulin therapy, with signs of diabetic angiopathy and neuropathy. Locally, in the groin region, after shaving a skin infection occurred with liquid secretion and unpleasant odor, and the infection began to spread.

For successful treatment of NF timely diagnosis or suspicion of NF, aggressive resuscitation of the patient, broad spectrum antibiotics administration, and early and radical surgical intervention are essential. A diagnosis is generally based on a clinical presentation. Laboratory tests and radiological imaging have a significant place in infection severity prediction and treatment outcome [16, 17, 18].

This is why scoring systems have been developed as predictors of the severity of infection. LRINEC is a scoring system designed to differentiate NF from other soft tissue infections [13]. The LRINEC score for the first patient was 11 and 10 for the second patient, which put them in the high-risk group.

Urgent and radical surgical treatment, with removal of necrotic and devitalized tissue, is mandatory and a major factor for good outcome in patients with NF. The mortality rate can be nine times greater when primary surgery is performed 24 hours after the onset of symptoms [13]. Several studies stated that all patients underwent 1–10 radical surgical debridement, with an average of 2.5 [1]. HBOT is a useful procedure for some infections, but it has not been proved that it is essential part of the treatment [1].

Both our patients were with a high LRINEC score, probably due to late arrival for a surgical examination. Radical surgical intervention was done 24 hours after admission in the first case and four hours after admission in the second. In both cases, surgical reinterventions were performed, but in the first case colon surgery (according to Hartman) was necessary due to rectal necrosis. HBOT was used in the first patient, however not in the second because of contraindications. In both cases intensive measures of conservative treatment and intravenous administration of antibiotics were applied. In both cases there was a complete recovery of the patients.

NF continues to be a serious disease with a high mortality rate and challenging diagnosis. Surgeons must be aware of the importance of rapid diagnosis and treatment to prevent mortality.

Conflict of Interests: None declared.

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Некротизирајући фасцитис – инфекција опасна по живот: прикази болесника и преглед литературе

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САЖЕТАК

Увод Некротизирајући фасцитис је ретка, тешка и агресивна инфекција која се брзо шири и представља хируршко стање опасно по живот, карактерише се опсежном некрозом дубоких и површинских фасција и повезана је са значајним морбидитетом и смртношћу.

Прикази болесника Представљамо два случаја некротизирајућих фасцитиса: 54-годишњег болесника, гојазног, с хипертензијом и нелеченом перианалном фистулом, с тешком инфекцијом перианалне регије, перинеума и скротума, и 64-годишњу болесницу са дијабетесом мелитусом и срчаном болешћу, с тешком инфекцијом доњег екстремитета, предњег трбушног зида, ингвиналне и глутеалне регије, код које су улазно место инфекције представљале микролезије коже после бријања. Оба болесника лечена су хитном опсежном хируршком некректомијом, уз ерадикацију извора инфекције, и уз све мере конзервативног лечења. Први болесник је лечен и хипербаричном терапијом кисеоником, а други не, због срчаних и плућних контраиндикација.

Закључак Бољи исход лечења захтева мултидисциплинарни приступ (кардиолог, ендокринолог, нефролог, ортопед, хирург). Потребна је брза и опсежна хируршка некректомија како би се повећао успех лечења болесника с овом инфекцијом.

Кључне речи: некротизирајући фасцитис; хируршки дебридман; тешка инфекција

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Pregnancy- and lactation-associated osteoporosis with vertebral fractures

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SUMMARY

Introduction Pregnancy- and lactation- associated osteoporosis (PLO) is a rare disease for which the pathophysiological mechanism is as yet incompletely known. The incidence of PLO is 0.4 in 100,000 women. It is considered that the number of undiagnosed patients is even higher. PLO can lead to multiple fragility compression fractures in the spinal vertebrae.

Case outline We present the case of a 30 years old woman (first-born, breastfeeding child) who came for examination due to lower back pain that occured after childbirth without any apparent cause. The patient was found to have low levels of vitamin D and low bone mineral density on osteodensitometry (established osteoporosis). Magnetic resonance imaging (MRI) examination showed vertebral bodies fractures Th11, Th12 and L4. During therapy, we used vitamin D (800 IU/24 h), alendronate (70 mg once weekly), calcium 1000 mg/24h and thoracic lumbar sacral orthosis (TLSO) as support to spine. After 12 months of treatment osteodensitometry findings were close to normal, control MRI showed no further collapse of vertebral bodies and clinical examination of spine was orderly.

Conclusion PLO is a rare clinical condition and it must be kept in mind in the differential diagnosis in patients having low back pain during or after pregnancy. Early diagnosis and treatment of PLO and regular follow-up of these cases are particularly important. The the stability of the spine in patients with vertebral fractures must be carefully monitored as well as using the TLSO as a support for the spine.

Keywords: osteoporosis; pregnancy; lactation; vertebral fractures

INTRODUCTION

Osteoporosis is the most common bone disease in humans. It is characterized by low bone mass, deterioration of bone tissue and disruption of bone architecture, compromised bone strength and an increase in the risk of fracture. Pregnancy- and lactation-associated osteoporosis (PLO) is a rare disease for which the pathophysiological mechanism is as yet incompletely known [1]. The incidence of PLO is 0.4 in 100,000 women. Approximately 100 cases of pregnancy and lactation-associated osteoporosis were described between 1955. and 2009 [2]. It is considered that the number of undiagnosed patients is even higher. PLO led to multiple fragility compression fractures in the spinal vertebrae [3]. Analysis of diagnosis and treatment of this case can help clinicians to pay attention to the disease and the evaluation of osteoporosis. The clinical signs usually become to manifest in the postpartum period when patients come for examination with more pronounced back pain.

CASE REPORT

A 30-year-old patient (breastfeeding a firstborn child) came in for examination due to lower back pain that occurred after childbirth without any apparent cause. She breastfed for a month and menstruation has returned to normal. She went to a local clinic for treatment, but the pain did not lessen. Her medical history was not remarkable for chronic disease, drug use, smoking or alcohol use. The examination was done one month after the delivery. Examination revealed pain in the lower back and weaker movements in the spine. The performed laboratory findings were shown in Table 1. Ultrasound examination of the abdomen was within physiological limits. The gynecological examination was orderly. Neurological examination showed no signs of neurological diseases. Urological examination showed no signs of urological diseases or problems. The patient was referred for magnetic resonance imaging (MRI) of the spine, which showed compressive fractures of vertebral bodies Th11, Th12 and L4, Figure 1.

Considering the reduced values of vitamin D and the findings of MRI she was referred for

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Table 1. Laboratory findings at the first examination

Blood work	Value	Units	Reference values
WBC	3.7	10^9/l	3.9–10
RBC	4.67	10^{12}/l	3.9–5.9
Hgb	130	g/l	110–180
Plt	190	10^9/l	140–450
CRP	2	mg/l	< 5
Urea	4.4	mmol/l	1.6–7.5
Creatinine	57	umol/l	53–124
Ca (total)	2.36	mmol/l	2.02–2.60
Inorganic P	3.68	mmol/l	0.81–1.62
Vitamin D	40.3	nmol/l	75–250
T3	1.43	ng/ml	0.79–1.58
T4	9.18	µg/dl	4.9–11
TSH	0.791	IU/ml	0.27–4.2 (adults)
PTH	66.3	pg/ml	15–66

WBC – white blood cells; RBC – red blood cells; Hgb – hemoglobin; Plt – platelets; CRP – C-reactive protein; T3 – triiodothyronine; T4 – thyroxine; TSH – thyroid-stimulating hormone; PTH – parathyroid hormone

Table 2. Osteodensitometry test findings during the treatment

Osteodensitometry	First examination	After five months	After 12 months
L1 (BMD g/cm^2)	0.87	0.787	0.987
L2 (BMD g/cm^2)	0.83	0.714	1.143
L3 (BMD g/cm^2)	0.75	0.783	1
L4 (BMD g/cm^2)	0.62	0.754	0.934
Total (lumbar) (BMD g/cm^2)	0.744	0.766	1.014
T score (lumbar)	-2.8	-2.4	0.4
Z score (lumbar)	-2.8	-2.4	-1.9
Neck (BMD g/cm^2)	0.571	0.61	0.98
Total neck (BMD g/cm^2)	0.642	0.668	0.98
T score (femur)	-2.2	-2.2	1
Z score (femur)	-2.2	-2.2	1

BMD – bone mineral density

Table 3. Values of vitamin D in blood during the treatment

Vitamin D (nmol/l)	First examination	After three months	After five months	After 10 months	After 12 months
	40.3	54	72	> 75	> 75

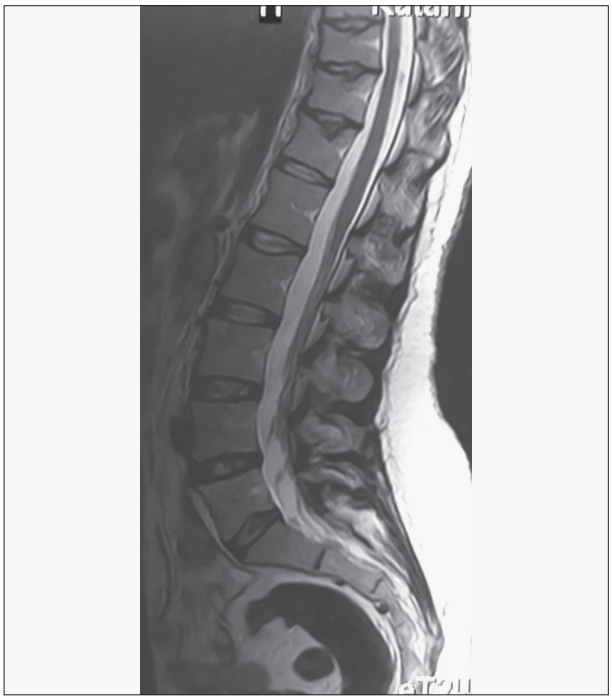

Figure 1. Magnetic resonance imaging of thoracolumbar spine; compressive fractures of the vertebral bodies Th11, Th12, and L4

osteodensitometry test, which confirmed the diagnosis of osteoporosis, Table 2.

Bisphosphonates (alendronate 70 mg once weekly), vitamin D (800 IU/day), calcium (1200 mg/day), analgesics and thoracic lumbar sacral orthosis (TLSO) were prescribed in the therapy and advice was given to stop lactation. The level of vitamin D in the blood was monitored.

After five months, the osteodensitometry test values, although better, still did not satisfy nor did the analysis of vitamin D levels (72 nmol/l), Table 3.

Bisphosphonates and vitamin D were continued in the therapy. The pain in the spinal column stopped, and the

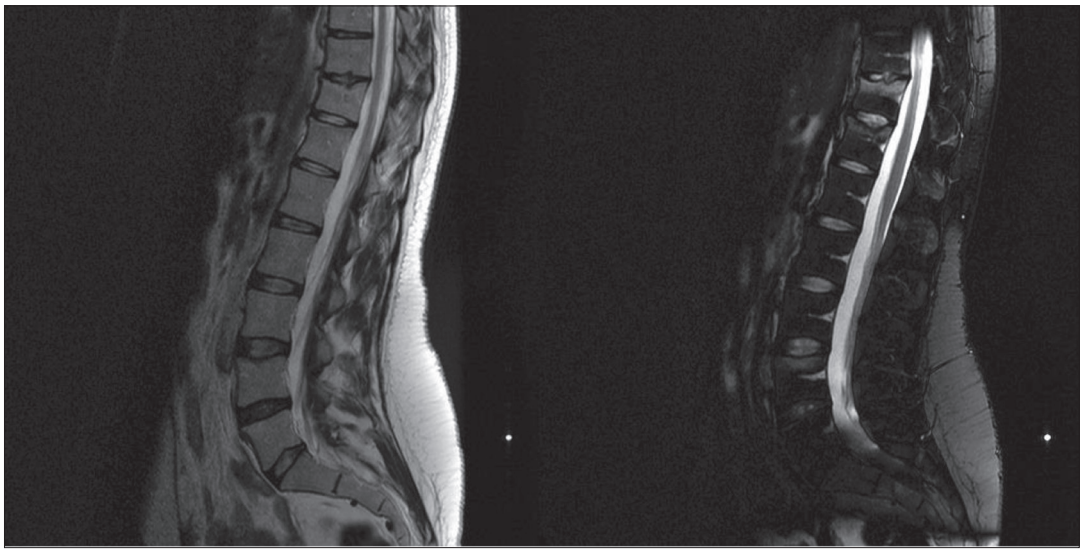

Figure 2. Control magnetic resonance imaging of the thoracolumbar spine after 10 months

movements of the spinal column were normal. Wearing TLSO continued for four hours a day.

Ten and 12 months after the first examination, the control values of vitamin D were normal, and 12 months after first examination the osteodensitometry values were close to normal. The patient had orderly clinical findings. 12 months after initial treatment laboratory findings of bone metabolism are normal and we stopped bisphosphonates and advised the patient to check blood levels of vitamin D every three months. Control MRI after 12 months did not show further vertebral collapse, Figure 2.

Written consent for publication of this article has been obtained by patient.

DISCUSSION

PLO is a condition that is often overlooked, although it was described as early as 1955 [4]. The causes of PLO are still unclear. There are risk factors for PLO development such as smoking, malnutrition, lower calcium and Vitamin D intake, poor mobility, weight gain during the last trimester and oligomenorrhea [5]. Cohen et al. [6] considered that women with PLO may have a low bone remodeling state assessed more than a year postpartum, which increases understanding of the pathogenic mechanism of PLO and also may have underlying osteoblast functional deficits which could affect their therapeutic response to osteoanabolic medications. In our case, there were no risk factors.

Careful analysis of the examination of patients with suspected PLO is required. A comprehensive analysis of other conditions that would lead to osteoporosis is also needed. A detailed evaluation of bone metabolism is extremely important [7]. Our patient was a young woman with normal period who suffered with unexplained pain, has brittle fractures and decreased bone mineral density (BMD). In this case, we first took into consideration the metabolic bone diseases, which had to be carefully identified with osteoporosis and other metabolic bone diseases. In our case we performed complete laboratory findings of bone metabolism, which only showed a reduced level of vitamin D, so we raised the level of vitamin D to normal levels, along with calcium intake.

Bisphosphonates can be used regularly in PLO therapy, and there was increase in BMD after bisphosphonate use in patients with PLO [8, 9, 10]. For increasing BMD can be used teriparatide [11] and also alfacalcidol can be used for PLO joined with vertebral fractures [12]. Osteodensitometry examination of our patient showed a strong decrease in BMD and Z-score, so we decided to use bisphosphonates in therapy. We used bisphosphonates in therapy for 12 months.

Strong loss of bone mass in the vertebral bodies can cause collapse and compressive fractures with strong back pain [13]. Vertebral fractures occur most commonly in PLO and are often multiple [14]. If a vertebral collapse is found, TLSO should be used. Sometimes the stability of the spine is disturbed, so surgical treatment with kyphoplasty is necessary [15]. The stability of the spinal column should be constantly monitored by control MRI. In our case, there was an affection of the vertebral bodies of the Th11, Th12, and L4. With rapid diagnosis and timely therapy for further progression of osteoporosis, we used TLSO for treatment and prevented further vertebral collapse. Our last MRI examination at the end of treatment did not show further collapse of the vertebral bodies. The patient's clinical condition was normal after 11 months.

Breastfeeding produces an obligatory loss of maternal skeletal mineral which contributes to the decline of bone density [16]. All women with developed PLO are advised to stop breastfeeding.

PLO is a rare clinical condition and it must be considered in the differential diagnosis in patients coming with low back pain during or after pregnancy. Although not specified as a diagnostic criterion, the exclusion of other reasons for osteoporosis and progressive clinical course are necessary and helpful in the diagnostic process. At the same time, the monitoring and evaluation of the efficacy of PLO intervention is also very important. The fractures of vertebral bodies related to PLO may be an important cause of disability in the long term. Early diagnosis and treatment of PLO and regular follow-up of these cases are particularly important. The stability of the spine in patients with vertebral fractures must be carefully monitored and the TLSO must be used to support the spine.

Conflict of interest: None declared.

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Остеопороза током трудноће и лактације са преломима кичмених пршљенова

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САЖЕТАК

Увод Остеопороза изазвана трудноћом и дојењем је ретка болест за коју је патофизиолошки механизам још увек непознат. Њена инциденца је 0,4 на 100.000 жена. Сматра се да је број недијагностикованих болесница још већи. Може изазвати компресивне преломе пршљенова.

Приказ болесника Представљамо случај 30-годишњакиње (прворотка, дојиља) која је дошла на преглед због болова у доњем делу леђа, који се јављају после порођаја без икаквог очигледног разлога. Утврђено је да болесница има нижи ниво витамина *D* и ниску густину костију на остеоденситометријском прегледу (утврђена остеопороза). Преглед магнетном резонанцом показао је преломе тела пршљенова *Th*11, *Th*12 и *L*4. У терапији смо користили витамин *D* (800 ИЈ / 24 ч.), алендронат (70 мг једном недељно), калцијум 1000 мг / 24 ч. и спиналну ортозу као потпору кичми. После 12 месеци лечења остеоденситометријски налази су били близу нормале, а контролни преглед магнетном резонанцом није показао даљи колапс тела пршљенова. Клинички преглед кичме је био уредан.

Закључак Остеопороза изазвана трудноћом и дојењем је ретко клиничко стање и мора се имати на уму у диференцијалној дијагнози код болесница које имају болове у леђима током или после трудноће. Рано дијагностиковање, лечење и редовно праћење случајева остеопорозе изазване трудноћом и дојењем посебно су важни. Стабилност кичменог стуба код болесница са преломима пршљенова мора се пажљиво проценити и надгледати, и мора се користити спинална ортоза као потпора кичми.

Кључне речи: остеопороза; трудноћа; лактација; преломи пршљенова

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Infantile hemiconvulsion–hemiplegia epilepsy syndrome associated with *GRIN2A* gene mutation

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SUMMARY

Introduction Infantile hemiconvulsion–hemiplegia and epilepsy (IHHE) syndrome is defined as a specific syndrome in patients < 2 years of age, presenting as a new onset refractory status epilepticus with unilateral motor seizures and acute imaging abnormalities, fever, hemiparesis > 24 hours, and excluding infectious encephalitis.

Case outline We present the results of a follow-up in a 11-year-old girl with IHHE, associated with *GRIN2A* mutation. The girl had normal development until the first febrile hemiconvulsive status epilepticus at the age of seven months. Neuroimaging initially showed right hemisphere edema, followed by progressive right side hemiatrophy. The patient has resistant epilepsy, left side hemiparesis, and good language and cognitive development.

Conclusion Despite IHHE described many years ago, some syndrome's features, including etiology, have remained unexplained. The association between IHHE and *GRIN2A* mutation stated in the current manuscript is described in scientific literature for the first time.

Keywords: infantile hemiconvulsion; hemiplegia epilepsy; *GRIN2A*; status epilepticus

INTRODUCTION

Infantile hemiconvulsion–hemiplegia and epilepsy (IHHE) syndrome is defined as a specific syndrome in a patient younger than two years of age, presenting as a new onset refractory status epilepticus (NORSE). IHHE characteristics are: unilateral motor seizures, high grade fever at the time of onset of refractory status epilepticus (SE), and unilaterally abnormal acute imaging, followed by hemiparesis lasting at least 24 hours, and excluding infectious encephalitis [1]. In a variable period, from a few months to years later, intractable epilepsy emerges in two-thirds to three-fourths of children with IHHE. The mechanisms underlying the IHHE syndrome remain unclear. A neuronal injury induced by venous thrombosis and/or hypoxia, and previous abnormalities of the brain were suggested as an underlying mechanism [2]. Gene mutations associated with IHHE syndrome have been described in the literature, such as *CACNA1A*, *SCN1A, HNRNPU, ATP1A3* genes [3, 4, 5]. Initial acute cytotoxic edema of the affected hemisphere at the time of SE is followed by chronic atrophic changes of the same hemisphere [6]. Clinical presentation is characterized by prolonged hemiconvulsions followed by hemiplegia and medication-resistant epilepsy [6–9]. The motor deficit has a variable course, from definitive hemiplegia to complete resolution [6]. The long-term cognitive outcome following IHHE syndrome has been poorly studied [9].

CASE REPORT

We present an 11-year-old girl with resistant focal epilepsy and left side hemiparesis. The girl was the second child from an uneventful pregnancy and perinatal history. She had normal global development until the first epileptic attack at the age of seven months. The child was febrile (39°C) for three days before the first seizure and had facial exanthema. NORSE started with the head and eyes deviation toward the left side, clonic jerks of the left limbs and impaired consciousness lasting for hours, and repeating in clusters within three days. All hematological, coagulation factors, biochemical and metabolic blood analyses were normal. Cytological, biochemical and microbiological analyses of the cerebrospinal fluid were normal. Fundoscopy was normal. Electroencephalographic (EEG) record showed continuous slow epileptic discharges above the right hemisphere (Figure 1). Urgent brain computed tomography showed edema of the right hemisphere (Figure 2). The girl was treated according to the protocol for SE: benzodiazepine as the first line (intravenously midazolam in a dosage of 0.2 mg/kg), Phenobarbital as a second line (20 mg/kg), and since it was ineffective, midazolam was given in continuous intravenous infusion (0.2 mg/kg/h). Anti-edematous therapy was given (mannitol, dexamethasone). From the fourth day of hospitalization, the infant was seizure-free. Phenobarbital was continued in the maintaining dosage of 5 mg/kg. After two months, focal seizures started in afebrile,

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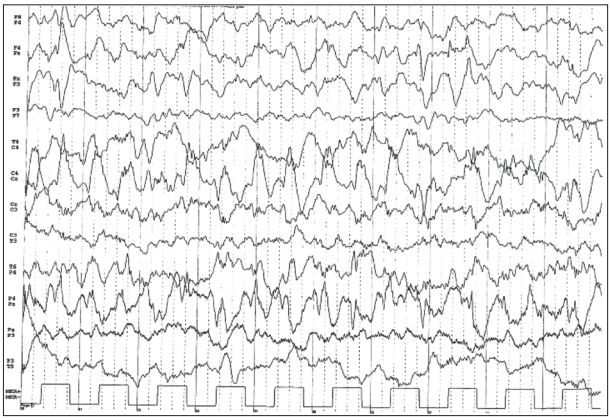

Figure 1. Interictal electroencephalogram during the first day of seizure onset, showing high-amplitude, slow, 2 Hz spikes and waves, above the right centro-parietal region with spreading to the entire right region

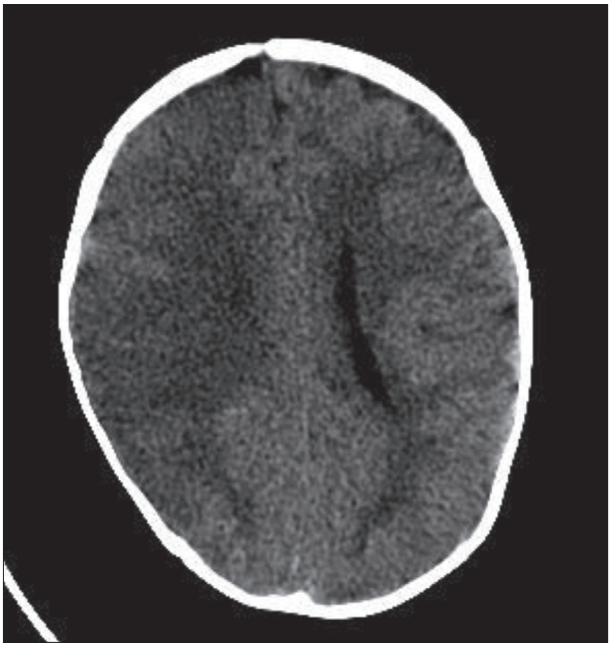

Figure 2. Brain computed tomography scan during hemiconvulsive status epilepticus, showing right cerebral edema

awake state: the infant interrupted activities, had staring, cyanosis, deviation of the head lasting up to two minutes. Left side hemiparesis persisted from NORSE. At the age of 10 months, the child was referred to our clinic. EEG showed asymmetric background activity, slower above the right hemisphere with almost continuous discharges above parietotemporal right region. Brain magnetic resonance imaging (MRI) showed right cerebral white mater hypotrophy. Diagnosis of IHHE was based on the data of febrile refractory hemiconvulsive SE at the early age followed by recurrent focal-onset seizures, persistent hemiparesis, and MR evidence of brain hemiatrophy. Antiepileptic therapy was corrected, phenobarbital was withdrawn, and carbamazepine was introduced leading to seizure control for one year (25 mg/kg). At the age of 18 months, hemiconvulsive seizures reappeared, and clobazam (1.2 mg/kg) was added. At the age of 28 months, brain MRI showed progressive right side hemiatrophy (Figure 3). Despite this progression

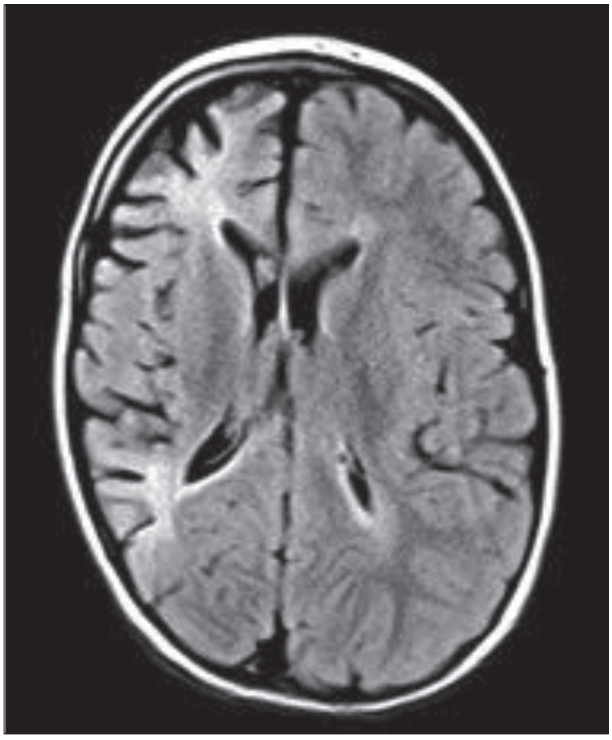

Figure 3. Brain magnetic resonance scan at the age of 28 months, showing progressive right hemisphere atrophy

in brain atrophy, the girl had improvement in global development. Psychological testing showed mild language delay, and developmental quotient of 80–90. Levetiracetam was introduced due to the worsening of seizure control. The girl was continuing to have sporadic focal seizures in frequency up to five seizures per month. At the age of six, the girl started to complain of feeling of fast heart beating, chest pain, and tremor of the hands. If it happened during sleep, the girl awoke and complained of fast heart beating. These episodes were short, repeating up to 10 per day and night. Cardiologist found normal clinical and heart ultrasound findings, while second degree A-V block was registered on 24-hour ECG Holter. Since carbamazepine might contribute to ECG changes, the dosage was reduced and substituted by oxcarbazepine. Two repeated 24-hour ECG Holter recordings over a period of two months showed normal heart rhythm. Since the symptoms were continuing at the age of eight, long-term video EEG was performed. No clinical seizures were observed during the recording, while EEG showed clear asymmetric background activity, slower above the right hemisphere with frequent epileptic discharges. Sulthiame was added, but since the girl became drowsy, the drug was excluded. At the age of nine, topiramate was introduced with good effect to both seizure control and episodes of paroxysmal tachycardia. With current medications (levetiracetam 40 mg/kg/day, clobazam 0.9 mg/kg/day, topiramate 5 mg/kg/day) seizure control was achieved. At the end of the follow-up period, the speech and intelligence are normal, as well as physical findings, and only discrete spastic left side hemiparesis was observed. She goes to a regular school and she is successful in obtaining academic education.

Whole gene sequencing showed that the patient has an extremely rare heterozygous nonsense likely pathogenic variant in the mutation of the *GRIN2A* gene (NM 001134407:c.2776C>T).

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 or comparable ethical standards.

Written consent to publish all shown material was obtained from the patient's caregiver.

DISCUSSION

IHHE was described more than half a century ago, but still many features of the syndrome have remained unexplained [6]. There is a diagnostic challenge since clinical presentation of IHHE has similarities with other neurological disorders, such as Rasmussen's encephalitis, cerebrovascular insult, and mitochondrial disorders, which have to be considered in differential diagnosis. Infective, genetic, and structural underlying causes are proposed in IHHE etiology [10]. There are case reports of acute infantile hemiplegia associated with exanthema subitum caused by *Human betaherpesvirus* 7 (HHV-7) [11]. In our case, at the time of NORSE, exanthema was observed for two days, but PCR for HHV-6 and HHV-7 was not done in the regional hospital. Various gene mutations are associated with IHHE, and this is the first case with IHHE associated with the mutation of the *GRIN1A* gene [3, 4, 5, 12]. *GRIN1A* mutation is associated with different epileptic disorders, such as Rolandic epilepsy, Landau–Kleffner syndrome, and continuous spike waves during slow-wave sleep [13, 14]. A great number of variants in the GRIN genes that encode N-methyl-D-aspartate (NMDA) glutamatergic receptor subunits have been found in patients with neuropsychiatric disorders, including epilepsy. There is evidence that NMDA receptor activation might play an important role in epilepsy, and NMDA receptor antagonists have been considered in treating epilepsy, including SE ($MgSO_4$, felbamate, ketamine). The results of preclinical studies showed that excessive activation of NMDA receptors has been implicated in the pathogenesis of neuronal injury in acute neurologic disorders, and that magnesium reduced NMDA-mediated brain injury [15, 16]. Magnesium normally does not readily penetrate the fully developed blood–brain barrier (BBB), but BBB permeability is greater in infants especially during seizures; thus, systemically administered magnesium may provide effective therapy in these conditions [15]. NMDA receptors play an important role in the induction of programmed cell death during SE [17, 18]. If further genetic investigation shows more frequent association of IHHE with mutation of the genes responsible for NMDA receptors, the strategy for the treatment of hemiconvulsive SE in IHHE syndrome should include NMDA antagonists, such as $MgSO_4$ in high dosage or ketamine [19, 20].

Auvin et al. [2] suggested that anti-edema therapy should be discussed to prevent cell injury, since pathological studies showed that cytotoxic edema in HHE is responsible for neuronal damage playing a role in the development of a later epilepsy. Very aggressive anti-edema treatment by mannitol and corticosteroids, and antiseizure therapy in the acute phase in our patient, did not prevent further damage and epilepsy.

In patients with IHHE, MRI of the brain reveals evidence of abnormal diffusion within the white matter in the acute phase, and hippocampal sclerosis and/or hemiatrophy later in life [2, 21]. In our case, three months after initial brain edema, increased T2 hyperintensity, severe gliosis and unilateral brain atrophy were evident by MRI of the brain. Similar MRI unilateral changes have been described in the literature, only one month after initial hemiconvulsive febrile SE [21]. Recently, some unusual IHHE presentations and etiology were published, such as IHHE in adult cases, or association with cortical dysplasia type III, or cobalamin C deficiency [22, 23, 24].

The long-term cognitive outcome following HHE syndrome has been poorly studied, although mental retardation has been reported in cases with IHHE. A recent study reported that mental retardation is not a uniform feature of the IHHE syndrome and demonstrated that a reorganization of language to the right cerebral hemisphere or its bilateral representation is common in patients with IHHE syndrome affecting the left cerebral hemisphere [9]. In our patient, the right cerebral hemisphere was affected, and language delay was present initially, but during the follow-up, the girl developed normal speech, and had normal intellectual and school performance. A study which included 10 patients with IHHE showed that peri-insular hemispherotomy provides excellent long-term seizure control in patients with drug-resistant hemispheric epilepsy [25]. Recent reports pointed out the rule of inflammation in epilepsy associated with *GRIN2A* mutation and good response to intravenous immunoglobulin, and this therapy might have been considered in our patient as well if other treatment had failed [26].

In conclusion, we suggest further exploration of genetics underlying all cases with IHHE. Our case with IHHE and *GRIN1A* mutation has favorable neurological and cognitive development despite resistant epilepsy from an early age. Since the disorder is very rare, multicenter investigation is recommended, with particular attention to genetics underlying IHHE. It seems that genetic factors contribute to IHHE pathogenesis in addition to all other proposed factors, such as excessive neuronal excitation, hyperthermia, inflammation, and BBB damage [27, 28]. Further investigations are necessary in order to find the answers to present questions about pathogenesis, treatment, and prognosis of IHHE.

Conflict of interest: None declared.

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Синдром инфантилне хемиконвулзије–хемиплегије и епилепсије удружен са мутацијом гена *GRIN2A*

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САЖЕТАК

Увод Синдром инфантилне хемиконвулзије–хемиплегије и епилепсије (ИХХЕ) специфичан је ентитет код болесника млађих од две године. Представља новонастали рефрактарни *status epilepticus* кога карактеришу: унилатерални моторички напади и акутне неурорадиолошке промене на мозгу, фебрилност, хемипареза у трајању већем од 24 сата, у одсуству инфективног енцефалитиса.

Приказ болесника Приказујемо резултате праћења једанаестогодишње девојчице са ИХХЕ удруженим са мутацијом гена *GRIN2A*. Девојчица је имала нормалан развој до првог фебрилног хемиконвулзивног епилептичког статуса у седмом месецу живота. Неурорадиолошки налаз је иницијално показао едем десне хемисфере мозга, а касније прогресивну десностану хемиатрофију мозга. Болесница је имала резистентну епилепсију, левостану хемипарезу и задовољавајући когнитивни развој и говор.

Закључак Иако је ИХХЕ давно описан, бројне карактеристике синдрома, укључујући етиологију, још су увек необјашњене. Удруженост ИХХЕ и мутације гена *GRIN2A* сада је први пут описана у стручној литератури.

Кључне речи: инфантилне хемиконвулзије; хемиплегија; епилепсија; *GRIN2A*; *status epilepticus*

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Quadratus lumborum block in pediatric patients – a case series

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SUMMARY
Introduction The *quadratus lumborum* block (QLB) was the first interfascial plane block introduced to the Leskovac General Hospital thanks to the Kybele Inc. international teaching program in April 2017.
Outlines of cases During the period from April 2017 to December 2019, 22 pediatric patients underwent various surgical procedures and had the QLB type 1 block as a part of a multimodal perioperative pain management plan. Unilateral QLB was provided for unilateral inguinal hernia repair, orchidopexy, testicular torsion repair, and open appendectomy. Bilateral QLB was provided for laparoscopic appendectomy and cholecystectomy. Decreased use of fentanyl and sevoflurane was noticed in the cases when QLB was performed preoperatively. All the patients had well controlled pain.
Conclusion QLB is a simple and safe technique. Clear sonographic landmarks allow it to be easily performed. QLB has great potential to improve and facilitate postoperative pain management.
Keywords: QLB; interfascial plane block; pediatrics

INTRODUCTION

Ultrasound-guided regional anesthesia techniques have decreased the number of failed blocks and increased patient safety [1]. According to published articles and multimodal pain management protocols, interfascial plane blocks have an important place in perioperative pain management. *Quadratus lumborum* block (QLB) was the first interfascial plane block that was introduced to the Leskovac General Hospital in April 2017 [2]. It became a part of a multimodal pain management plan following abdominal, obstetric, gynecologic, and urologic surgery in adults and pediatric patients [3, 4].

REPORTS OF CASES

During the period from April 2017 to December 2019, 253 pediatric patients underwent surgical procedures at the Leskovac General Hospital. Twenty-two of these patients had QLB as a part of a multimodal pain management plan: three following open inguinal hernia repair, two following testicular torsion repair, one following orchidopexy, two after open appendectomy, 12 after laparoscopic appendectomy, and two following laparoscopic cholecystectomy. The patients were 5–17 years old, in good health, without any previous medical history or prior surgery (Table 1).

All surgeries were done under general anesthesia. Anesthesia induction was done using either 2–3 mg/kg of propofol or 4–5 mg/kg of thiopental. A dose at 1–2 μg/kg of fentanyl was given at induction, and repeated if needed. Sevoflurane in a 50% air and 50% oxygen mixture with an end-tidal of 1–2 vol% was used as the maintenance agent. Acetaminophen at a dose of 10–15 mg/kg was used intravenously 15–20 minutes before the end of surgery. QLB was done either after induction of anesthesia, before incision (four patients) or after surgery, before emergence from general anesthesia (18 patients). Unilateral block was provided for unilateral inguinal hernia repair, orchidopexy, testicular torsion repair, and open appendectomy. Patient undergoing laparoscopic surgeries had bilateral QLB. We used levobupivacaine 0.25% or bupivacaine 0.25% at dose of 2 mg/kg (max. 30 ml) (Table 2). We used 22-gauge 50 mm needles for the peripheral nerve block, and the linear ultrasound probe as guidance. Decreased use of fentanyl and sevoflurane was noticed in the cases where QLB was performed preoperatively.

All the patients had well controlled pain. Younger patients (inguinal hernia repair, orchidopexy, and testicular torsion repair) had no pain medications postoperatively. After the emergence from anesthesia, these patients spent their time sleeping and playing with toys. Their parents were very satisfied with the analgesia that was provided. The rest of the patients (13–17 years old) had acetaminophen per request, every six hours (Table 1). Eighteen of 22 patients left the hospital on postoperative day 1. Only patients that underwent open appendectomy and testicular torsion repair stayed in hospital past postoperative day 1. There were no complications regarding block performance.

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Table 1. Demographic, clinical, and acetaminophen consumption data

Type of surgery	Number of patients (male + female)	Age*	ASA	Acetaminophen before the end of surgery (mg/kg)	QLB 1 PreOP / PostOP	Pain treatment 24 hours postoperatively acetaminophen (10–15 mg/kg)
						Number of patients / number of doses
Open inguinal hernia repair	1 + 2	8.3 ± 2.5	I	10	UL 1/2	Ø
Testicular torsion repair	2	11.5 ± 1.5	I	10	UL 1/1	Ø
Orchidopexy	1	10	I	10	UL 1/0	Ø
Open appendectomy	2 + 0	16 ± 1	I	15	UL 1/1	2/4
Laparoscopic appendectomy	10 + 2	15.6 ± 1.38	I	10	BL 0/6	6/Ø
						4/2
						2/4
Laparoscopic cholecystectomy	2 + 0	16 ±1	I	10	BL 0/2	1/2
						1/4

QLB1 – *quadratus lumborum* type 1; PreOP – preoperatively; PostOP – postoperatively; UL – unilateral block; BL – bilateral block; ASA – status according to the American Society of Anesthesiologists;
*mean ± standard deviation

Table 2. Local anesthetic dose recommendation.

Literature	Single shot		Continuous infusion		Maximal dose
	LA and concentration	Dose	LA and concentration	Rate	
Visoiu and Yakovleva [5]	ropivacaine 0.5%	10 ml	ropivacaine 0.2%	5 ml/h or 0.43 mg/kg/h	
Chakraborty et al. [6]	levobupivacaine 0.375%	5 ml	levobupivacaine 0.1%	5 ml/h	
Baidya DK. et al. [7]	ropivacaine 0.2%	0.5 ml/kg	Ø	Ø	
Öksüz et al. [8]	bupivacaine 0.2%	0.5 ml/kg	Ø	Ø	
Aksu et al. [9, 25]	bupivacaine 0.25%	0.5 ml/kg	Ø	Ø	20 ml
İpek et al. [10]	bupivacaine 0.25%	0.5 ml/kg	Ø	Ø	20 ml
Ahiskalioglu et al. [14]	bupivacaine 0.25%	0.5 ml/kg	Ø	Ø	
Yayik et al. [15]	bupivacaine 0.5% and lidocaine 2%	3 ml + 3 ml*	Ø	Ø	
Leskovac General Hospital Protocol	bupivacaine 0.25% or levobupivacaine 0.25%	0.4–0.8# ml/kg	Ø	Ø	2 mg/kg or 30 ml

LA – local anesthetic;
*unilateral block; dose for a three-year-old patient;
#0.4 ml/kg – bilateral block; 0.6–0.8 ml/kg – unilateral block;
2 mg/kg is the maximal dose of bupivacaine and levobupivacaine according to El-Boghdadly et al. [1]

This report, done according to the Declaration of Helsinki, was approved by the Ethical Committee of the Leskovac General Hospital (approval no. 2023/2).

DISCUSSION

QLB is the ultrasound-guided local anesthetic injection in the *quadratus lumborum* plane (Figure 1). It was described as a variant of the *transversus abdominis* plane (TAP) block by Dr. Rafael Blanco in 2007 [3]. Dr. Michaela Visoiu was the first to use it for pain management following colon surgery in pediatric patient in 2013 [5]. QLB was used as a part of a multimodal pain management technique in pediatric patients that underwent nephrectomy [6], pyeloplasty [7], orchidopexy and inguinal hernia repair [8–12], hip and femur surgery [13, 14], extracorporeal shock wave lithotripsy [15], and surgery for vesicoureteral reflux [16].

QLB can be learned relatively easily. It is a simple technique to perform due to clear sonographic markers [3] (Figure 1).

According to the results of many randomized controlled trials, QLB significantly decreases perioperative opioid use in adults and children, and subsequently opioid side effects such as nausea and vomiting [11, 13, 14, 17, 18, 19]. QLB prolongs time to the first request for rescue analgesic medication and speeds up ambulation and discharge from hospital [10, 11, 13, 14, 19]. QLB has found its place in the enhanced recovery after surgery (ERAS) protocols [20].

Regional analgesia techniques reduce opioid consumption during general anesthesia perioperatively, and provide better postoperative pain control compared to pain control provided by either general anesthesia alone or general anesthesia plus local anesthetic wound infiltration [13, 14, 21]. Until a few years ago, caudal block, TAP block, and ilioinguinal/iliohypogastric block were the most often used analgesic techniques for low abdominal surgery (inguinal hernia repair and orchidopexy) in pediatric patients. Caudal block provides postoperative analgesia as good as TAP block, and both of them provide better analgesia than ilioinguinal/iliohypogastric block according to the prospective randomized single-blinded study by Sahin et al. [22].

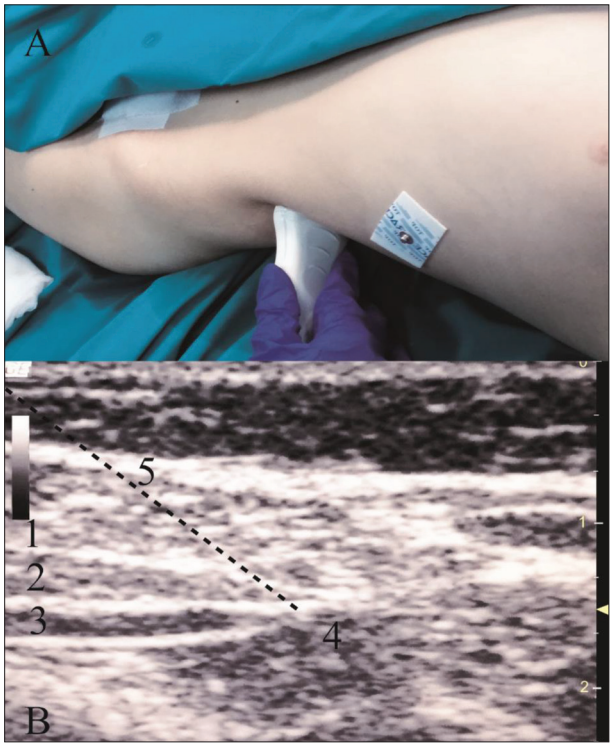

Figure 1. *Quadratus lumborum* block performance;
A: ultrasound probe position; B: ultrasound imaging; 1: external oblique muscle; 2: internal oblique muscle; 3: *transversus abdominis* muscle; 4: *quadratus lumborum* muscle; 5: needle direction

Kendall et al. [21] reached the same conclusion in their systematic review of 40 randomized controlled trials in 2018. Therefore, recently published data suggest that QLB provides significantly more effective and longer lasting analgesia than caudal block in pediatric patients undergoing inguinal hernia repair, orchidopexy, and ureteral reimplantation [10, 12, 16]. Also, patients with caudal blocks have significantly longer hospital stay [10]. Comparative studies show that QLB provides wider field of analgesia (T7–T12) than TAP block (T10–T12) [17, 23], more potent analgesia [8, 10, 24], and longer lasting analgesia (24–48 hours) than TAP block (8–12 hours) [8, 17, 23, 24]. Erector spinae plain block is a new interfascial plane block that provides similar postoperative analgesia to the QLB in pediatric patients undergoing lower abdominal surgery [25].

Complications with abdominal wall blocks are rare. There are no published cases of serious complications associated with QLB performance. Every regional block has some local anesthetic systemic toxicity (LAST) risk. Children are very sensitive to LAST, especially infants. Infants younger than six months are at a significantly greater risk of severe LAST than older children [26]. Caudal epidural block has the greatest risk of LAST [1]. Fluoroscopy guidance can decrease the risk from LAST, but is not used often because of radiation exposure and spatial requirements [27].

With regard to QLB, having the needle top on the screen during placement and local anesthetic injection under ultrasound control increases the safety level of the block technique. QLB has a significantly lower risk of LAST than TAP block [23]. There is no published case of LAST induced by QLB. However, we have to keep the risk in mind, and take measures to prevent LAST. It is suggested to calculate the maximal dose of the local anesthetic for each patient based on lean body weight. It is advisable to use local anesthetic as a fractionated injection in aliquots of less than 5 ml, with pauses of 30–45 seconds between injections, followed by gentle aspiration. It is suggested to use epinephrine at a dose of 15 μg/ml as a marker of intravascular local anesthetic injection. It will increase heart rate by ≥ 10 beats per minute or systolic blood pressure by ≥ 15 mmHg [1]. Epinephrine also delays local anesthetic resorption by inducing local vasoconstriction, and prolongs block duration. Patients should be monitored at least 30 minutes after block performance. According to the American Society of Regional Anesthesia and Pain Medicine recommendations, 20% lipid emulsion should be immediately available as a main treatment option in the case of LAST. The treatment of LAST should start with intravenous bolus of 1.5 ml/kg over a period of 2–3 minutes, followed by intravenous infusion of 0.25 ml/kg/minute up to the maximal dose of 12 ml/kg of 20% lipid emulsion [1].

Visoiu and Pan [28] published two cases of intramuscular hematoma in two patients who had full heparinization one hour after QLB performance. After several days the hematoma regressed without consequences.

There is a published case of unexpected motor weakness following QLB in an adult patient [29]. Local anesthetic concentration could influence the incidence of motor block development. Aksu and Gürkan [9] suggested QLB for postoperative pain management following ambulatory surgery. Their pediatric patients underwent inguinal hernia repair and had QLB for postoperative pain management. The patients left hospital 4–5 hours after surgery and had no QLB-associated complications. Careful ambulation is still advisable.

QLB has low risk of infection. It is advisable to use a clean technique for single shot and sterile technique if performed for a catheter for continuous infusion [20]. Walker et al. [26] stated that the risk of infection with regional anesthesia/analgesia techniques is likely associated with a longer duration of catheter use and a higher status according to the American Society of Anesthesiologists.

QLB as a part of multimodal pain management and ERAS protocol has been used in Leskovac General Hospital for almost three years and has been performed in more than 400 patients. We had no complications associated with QLB performance.

Conflict of interest: None declared.

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Quadratus lumborum блок код педијатријских болесника – прикази болесника

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САЖЕТАК

Увод *Quadratus lumborum* блок (*QLB*) први је интерфасцијални блок уведен у свакодневну клиничку праксу у Општој болници Лесковац. Његова примена почела је захваљујући међународном едукационом програму *Kybele Inc*. априла 2017. године.

Прикази болесника Од априла 2017. до децембра 2019. године код 22 педијатријска болесника подвргнута различитим хируршким захватима примењен је *QLB* у склопу мултимодалне периоперативне терапије бола. Једнострани блок примењен је код деце подвргнуте једностраној херниопластици, деторквацији, крипторхизму и отвореној апендектомији. Обострани *QLB* изведен је код деце за лапароскопску апендектомију и холецистектомију. Мања употреба фентанила и севофлурана примећена је код деце која су *QLB* добила преоперативно. Сви болесници су имали добру контролу бола.

Закључак *QLB* је једноставна и безбедна техника, а лако се изводи захваљујући прецизним ултразвучним маркерима који се лако идентификују. *QLB* има могућност да олакша и унапреди постоперативну терапију бола код деце.

Кључне речи: *QLB*; интерфасцијални блокови; педијатрија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Can multidisciplinary approach win the battle against metastatic rectal cancer?

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SUMMARY

Introduction Colorectal cancer is the third most common cancer and one of the leading causes of cancer-related deaths in men and women worldwide. The contemporary multidisciplinary approach has decreased rates of local recurrence and improved outcomes in metastatic colorectal cancer. We present a case of a primarily metastatic rectal cancer patient who underwent multidisciplinary planned treatment and showed complete response with now three years disease-free survival.

Case outline A 61-year-old female was diagnosed with a T4N2M1a rectal adenocarcinoma at the age of 58. She underwent six cycles of systemic chemotherapy capecitabine-oxaliplatin plus bevacizumab with partial response confirmed by diagnostic imaging procedures. According to multidisciplinary board decision, preoperative radiotherapy treatment was administered with concomitant capecitabine-based chemotherapy. A 50.4 Gy total dose was delivered with 1.8 Gy fraction dose. After concomitant chemoradiotherapy treatment, two more cycles of systemic chemotherapy capecitabine-oxaliplatin plus bevacizumab were administered. One month after completion of systemic chemotherapy, primary rectal cancer was operated with a complete response on histopathologic specimens. Six weeks following previous surgery, metastasectomy of lung deposits was performed; histopathology confirmed metastatic adenocarcinoma of colorectal origin. Three more cycles of postoperative chemotherapy capecitabine-oxaliplatin plus bevacizumab were administered.

Conclusion On regular follow-up, no evidence of disease was shown, with disease-free survival of three years. The treatment improved the patient's quality of life.

Keywords: chemotherapy; radiotherapy; rectal cancer; stage IV; surgical treatment

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and one of the leading causes of cancer-related deaths in men and women worldwide [1]. Approximately 30% of CRC refers to rectal cancer (RC), which is associated with poorer clinical outcomes. Metastases will occur in 20–50% of patients with RC [2, 3]. Contemporary multidisciplinary planned treatment has decreased rates of local recurrence in RC and improved outcomes in metastatic CRC (mCRC) [4]. It is important to evaluate characteristics of patients and of the disease, such as the extent of primary and metastatic disease, in order to select and deliver the appropriate treatment. The goal is personalized medicine, to individualize the treatment according to the patient and the disease [5].

We report a case of a primarily metastatic RC patient who underwent multidisciplinary planned treatment and showed a complete response with now three years disease-free survival.

CASE REPORT

The patient was diagnosed with stage IVa RC at the age of 58. She had been suffering from symptoms of hemorrhoid disease for several years. In December 2016, shortly after the onset of new symptoms indicative for CRC, such as rectorrhagia, changes in bowel habits, frequent tenesmus, the patient was diagnosed with metastatic RC. The patient's baseline Eastern Cooperative Oncology Group performance status (ECOG PS) was 1. Digital rectal examination revealed tumor mass related to RC. Serum levels of tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9) were within normal ranges. Colonoscopy performed in January 2017 showed a tumor mass in the rectum with the distal end located 7 cm from the anal verge. Histopathology (HP) examination revealed an exulcerated invasive rectal adenocarcinoma, G1. Magnetic resonance imaging (MRI) of the abdomen and the pelvis (Figure 1a) performed in January 2017 showed a 7-cm-long tumor mass in the rectum located within 8 cm of the anal verge, which occupied entire colon lumen in its caudal part, and predominantly

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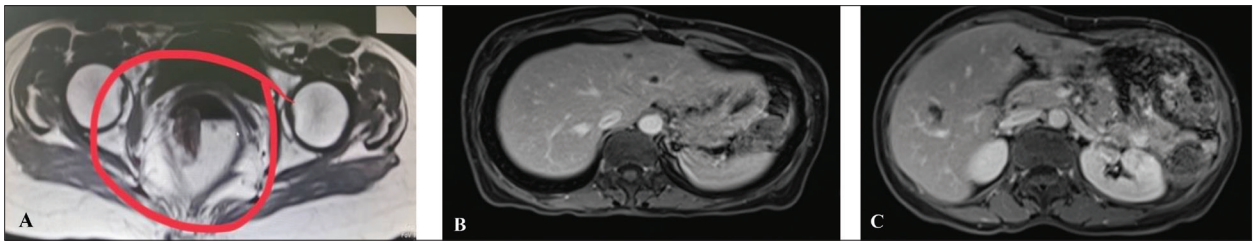

Figure 1. Initial magnetic resonance imaging of the abdomen and the pelvis in the axial plane: (A) on post-contrast T1w sequence, a tumor mass located in the rectum, penetrating all layers of the poster wall and infiltrating perirectal fat up to 30 mm, expanding to the mesorectal fascia bilaterally (mrT3d stage, MF+); (B) and (C) on post-contrast T1FSw sequence, cysts and hemangiomas in the liver (no metastatic lesions)

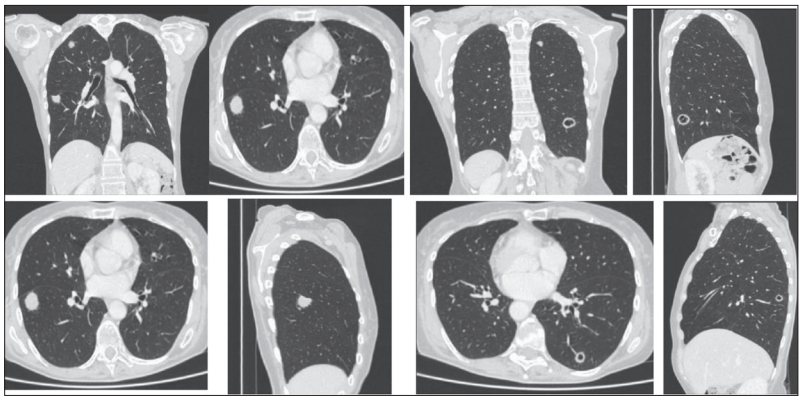

Figure 2. Initial contrast-enhanced chest computed tomography in the axial, coronal, and sagittal planes showing multiple nodular and excavated nodular lesions in both lungs: in the apical segment of the upper right lobe 12 mm, in the apicoposterior segment of the upper left lobe 11 mm, in the anterior segment of the upper left lobe 10 mm, in the superior segment of the upper right lobe 20 mm; bilaterally in basal segments one change on each side of the lung was described, measuring 12 mm in the right lung and 20 mm in the left lung

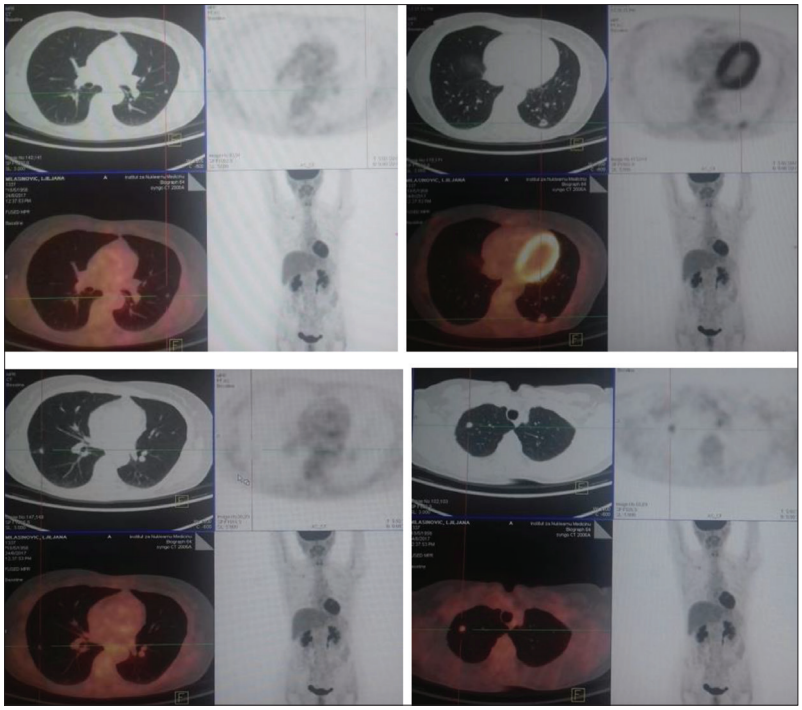

Figure 3. 18F-FDG positron emission computed tomography scans in the axial and coronal planes after systemic chemotherapy, demonstrating four nodular lung lesions with an increased uptake of the radiopharmaceutical

both lateral and posterior colon walls in its cranial part. The tumor penetrated all layers of the posterior and both lateral colon walls and infiltrated perirectal fat up to 30 mm, expanded to the mesorectal fascia bilaterally, reaching approximately 10 mm from the sacral bone. Lymph nodes in perirectal fat were enlarged, measuring 8 mm in diameter. The initial stage estimated according to the MRI was T3d, N2, circumferential resection margin +. In liver, two hemangiomas were shown in the third and the sixth segment, as well as four cysts in the second and the seventh segment (Figure 1b-c).

Chest computed tomography (CT) performed in January 2017 showed six nodular lung lesions, measuring ≤ 20 mm in the greatest diameter (Figure 2).

The pretreatment stage was determined as T4N2M1a (IVa) according to the American Joint Committee of cancer, seventh edition. According to the protocol, the treatment started with six cycles of systemic chemotherapy (CTx) including capecitabine-oxaliplatin (CAPOX) plus bevacizumab. Oxaliplatin (100 mg/m^2) and bevacizumab (400 mg) were administered as intravenous infusion on day 1 every three weeks. Capecitabine was given orally in an appropriate dose divided into two split doses for 14 days, followed by seven days' rest, repeated every three weeks. In May 2017, after completion of six cycles of systemic CTx, partial response of primary RC and lung deposits was confirmed in accordance with Response Evaluation Criteria in Solid Tumors guidelines. MRI of the abdomen and the pelvis showed a post-therapy altered tumor mass located within 8 cm of the anal verge, involving entire circumference and penetrating all layers of the colon, with its thickening up to 10 mm (previously it was 30 mm, then 14 mm). Chest CT was described as in regression with an unchanged number of lung lesions.

According to a multidisciplinary board decision, preoperative three-dimensional conformal radiotherapy (RT) treatment (6-MV photon posterior direct field, 15-MV photon opposed two lateral fields) was administered with

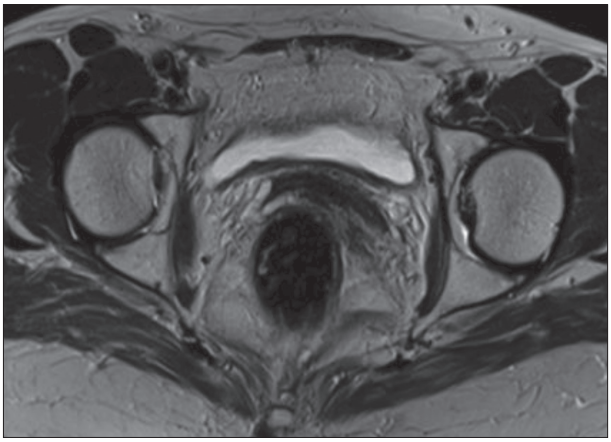

Figure 4. Magnetic resonance image of the pelvis after chemoradiotherapy of rectal cancer, in axial T2w sequence demonstrating complete regression of the rectal tumor

concomitant CTx. A 50.4 Gy total dose with 1.8 Gy in 28 fractions was given five times a week. Concomitant capecitabine-based CTx (825 mg/m^2) was administered twice daily, five days a week during RT. Treatment-related toxicity during chemoradiotherapy (CRT) included diarrheas and tenesmus. In July 2017, after CRT completion, two more cycles of systemic CTx CAPOX plus bevacizumab were administrated. Because of adverse events during CTx, such as sensory neuropathy, hand-foot syndrome, and neutropenia, doses of oxaliplatin and capecitabine were reduced.

In August 2017, fluoro-2-deoxy-D-glucose positron emission CT (^{18}F-FDG PET-CT) showed four lung lesions with an increased uptake of the radiopharmaceutical, while uptake of the pharmaceutical in the rectum was not detected (Figure 3). Complete regression of the primary tumor was described. Chest and abdomen CT from August 2017 showed stable disease. Pelvis MRI was also performed in August 2017 and revealed complete regression of the rectal tumor (Figure 4).

One month after systemic CTx completion, our patient underwent surgical treatment – low anterior resection of the rectum with coloanal anastomosis was performed; HP results showed no evidence of malignancy. Six weeks following previous surgery, metastasectomy of the lung deposits was performed; HP results confirmed metastatic adenocarcinoma of colorectal origin. From January to March 2018, three more cycles of postoperative CTx CAPOX plus bevacizumab were administrated with a total of 11 cycles of CTx. Treatment-related toxicity included oxaliplatin-induced allergic reaction, due to which premedication was prescribed. In March 2018, chest-abdomen-pelvis CT showed no signs of local recurrence (Figure 5).

Chest-abdomen-pelvis CT scans performed in March 2019 showed no evidence of disease. Further follow-up included serum tumor markers, which were within normal ranges, and ^{18}F-FDG PET-CT showed no signs of local recurrence, nor pathological lymph nodes. The patient is ECOG PS zero with a disease-free survival period of three years. The treatment has improved the patient's quality of life.

Informed consent was obtained from the patient for publication of this report and any accompanying images.

DISCUSSION

Previous studies reported that 20% of patients with CRC have distant metastasis at presentation and that 20–50% of patients with RC developed metastatic disease, mostly in the liver, lung, peritoneum, bone and extra-regional lymph nodes [2, 6–9]. These patients have a five-year survival of 13.1% compared to 90.1% for non-metastatic patients [9]. Due to the progress in personalized medicine, significant development has been reached in the treatment of patients with mCRC, which has encouraged a more developed collaboration between multidisciplinary teams and led to progress in survival rate and median survival duration [10, 11, 12]. According to the European Society for Medical Oncology consensus guidelines, a patient with mCRC may reach an overall survival of 30 months as a result of a treatment decision reached multidisciplinary [11, 13]. Nevertheless, the median overall survival in patients with mCRC has increased and it has been reaching over 40 months in molecularly selected patients [4]. A previously published randomized phase III study that evaluated the use of bevacizumab in combination with oxaliplatin-based CTx as the first-line therapy in mCRC, had shown

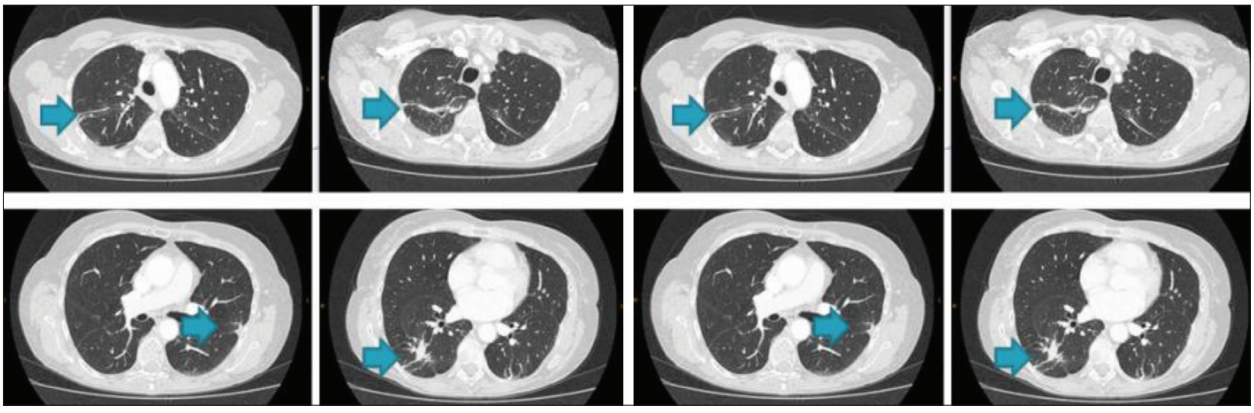

Figure 5. Chest computed tomography in axial planes after lung metastasectomy demonstrating no signs of metastatic recurrence; only fibrotic changes are visible

that the use of bevacizumab to oxaliplatin CTx improved progression-free survival, whereas overall survival differences and response rate were not improved by the addition of bevacizumab [14].

There are still some issues in the treatment of mCRC that need to be clarified, such as the best treatment modality, which regimens to administer in different patients and situations, when to start and when to finish treatment if a response is seen. According to Foubert et al. [15], patients with mCRC can be candidates for multiple lines of therapy. The decision should be based on characteristics of the patient and cancer including tumor biology, and it also depends on previously used therapies. In patients with unresectable mCRCs, multiple lines of therapy should be assessed. The never-used agent should be considered if the patient has not already been treated with all major CTx agents; also, a drug previously used with a good response could be reintroduced. Various options can be discussed, patients should be considered for inclusion in clinical trials [15].

A study by van Dijk et al. [16], which included 50 adult patients with primary metastasized RC, has shown that radical surgical treatment of all tumor sites conducted after short-course RT and bevacizumab plus CAPOX combination therapy may potentially enable the treatment of metastatic disease and good control of the primary RC.

For patients with metastatic RC and resectable primary tumor, as well as lung or liver metastases, the resection of both tumor sites is recommended [17]. Surgical treatment for liver and pulmonary metastases in selected mCRC patients may improve survival and prognosis. The five-year survival for mCRC patients with liver metastases who underwent surgical treatment reaches 58%, whereas the survival rate for mCRC patients with liver metastasis without surgical treatment ranges 20–24 months [18, 19]. Pulmonary resection for metastases from CRC may improve survival in selected patients. Thus, the outcome may vary due to the timing of surgical treatment [20]. Yamada et al. [21] showed that a follow-up of nine months from the date of pulmonary metastasis diagnosis to metastasectomy is associated with improved prognosis [21].

In our patient, the collaboration of multidisciplinary cancer management team supported by evidence-based guidelines made it possible to achieve better local control and longer survival followed by improved quality of life. With advances in cancer treatment modalities, comprising surgery, radiotherapy, and systemic treatment, we hope that the number of cancer survivors with metastatic disease will be significantly increased.

Conflict of interest: None declared.

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Да ли се мултидисциплинарним приступом у лечењу може победити метастатски карцином ректума?

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САЖЕТАК

Увод Колоректални карцином је трећи најчешћи карцином и један је од водећих узрока смрти повезаних са карциномима код жена и мушкараца широм света. Савременим, мултидисциплинарним приступом у лечењу смањена је учесталост појаве локалног рецидива и побољшани су исходи лечења код метастатског колоректалног карцинома. Приказали смо болесницу са примарно метастатским карциномом ректума која је лечена мултидисцилинарним приступом и код које је испољен комплетни одговор са периодом преживљавања без прогресије болести од три године.

Приказ болесника Код шездесетједногодишње болеснице постављена је дијагноза аденокарцинома ректума стажираног као *T4N2M1a* у 58. години живота. Болесница је примила шест циклуса системске хемотерапије капецитабином/оксалиплатином уз бевацизумаб, дијагностичким имиџинг процедурама процењена је парцијална регресија. Сходно одлуци мултидисциплинарног тима, ординирана је преоперативна радиотерапија уз конкомитантну хемотерапију капецитабином. Примењена је укупна доза од 50,4 *Gy* са појединачном дозом по фракцији од 1,8 *Gy*. После завршетка конкомитантне хеморадиотерапије ординирана су још два циклуса системске хемотерапије капецитабином/оксалиплатином уз бевацизумаб. Месец дана после завршетка примене системске хемотерапије оперисан је примарни тумор ректума са верификованом комплетном регресијом у хистопатолошком налазу. Шест недеља после претходно наведене операције учињена је метастазектомија депозита у плућима; хистопатолошки је потврђено присуство метастатског аденокарцинома колоректалног порекла. Ординирана су још три циклуса постоперативне хемотерапије капецитабином/оксалиплатином уз бевацизумаб.

Закључак При редовним контролним прегледима није доказано присуство болести, при чему је период преживљавања без прогресије болести три године. Лечење је поправило квалитет живота болеснице.

Кључне речи: карцином ректума; радиотерапија; хемотерапија; хируршко лечење; IV стадијум

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Upper extremity sensory training after stroke

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SUMMARY
Introduction Stroke is one of the leading causes for disability worldwide. After stroke, the majority of stroke survivors experience significant arm-hand impairments and a decreased use of the paretic arm and hand in daily life. Tactile sensibility of the hand is essential for identifying objects and for motor performance. Despite important sensory contributions to normal and abnormal movement, research has predominantly focused on motor aspects of stroke recovery. In this paper, we present the effect of sensory stimulation program on arm sensation and motor recovery in subacute stroke.
Case outline In a 65 years old woman the sensibility stimulation program was administered in subacute phase of post-stroke rehabilitation, six weeks after stroke, involving active and passive somatosensory intervention, motor control, coordination, strength and balance exercises. The rehabilitation protocol was applied for four weeks, five times a week. On discharge, the results of physiotherapy assessment showed full recovery of her right arm and hand.
Conclusion This case report shows that precise assessment, problems identification and problem oriented somatosensory interventions can improve, in a short time, functional motor performance of the arm involved in rehabilitation after stroke.
Keywords: sensory training; effectiveness; stroke; upper extremity; motor control

INTRODUCTION

Stroke is defined as the sudden onset of neurological signs and symptoms resulting from a disturbance of blood supply to the brain [1]. The number of people living with stroke is estimated to increase by 27% between 2017–2047 in the European Union, mainly because of population aging and improved survival rates [2]. Clinically, a variety of focal deficits are possible, including changes in the level of consciousness and impairments of sensory, motor, cognitive, perceptual and language functions. Proprioception, superficial touch and temperature sensation losses are common [3] and the sensory impairments may affect the patient's ability to control and coordinate movement [1]. The proprioceptive senses, including static position sense and movement sense or kinesthesia, are critical for accurate movement, but are often impaired following stroke [4, 5]. These deficits significantly contribute to the patient's motor disability and largely determine the degree of recovery [6, 7].

Deficits in somatic sensations (body senses such as touch, temperature, pain, and proprioception) after stroke are common with prevalence rates variously reported to be 11–85% [8]. Approximately 50% of stroke patients have hand sensory impairments, especially in tactile and proprioceptive discrimination [9, 10]. Sensation is essential for safety even if there is adequate motor recovery [11]. Findings particularly suggest the importance of somatosensory function after stroke for recovery of precision grip force control [12], safety and dexterity in the paretic hand [13] and functional independence in activities of daily living (ADL) [14, 15].

The current findings showed that active and passive sensory retraining may be an effective intervention for improving the light touch threshold of the hand, dexterity, upper extremity (UE) motor function [10, 16] to improve the ADL in stroke patients with impaired sensory motor abilities [17]. The quality of evidence is low to moderate [18, 19] so further research is required to determine the effectiveness of sensory training in stroke rehabilitation.

CASE REPORT

The patient, a 65-year-old right-handed English teacher, sustained a left ischemic stroke in 2019. She had received hospitalization service and was discharged from the hospital two weeks after the acute moment. Physical therapy treatment consisted of early verticalization and mobility exercise. She was able to walk on her own at the time of discharge from the hospital. Six weeks after the stroke, she was admitted to a rehabilitation facility as inpatient for a four-week rehabilitation program. At the moment of the treatment, she was taking antihypertensive therapy. At clinical examination she presented normal muscular tone and mild muscle weakness at her right side (4 on manual muscle testing or higher) and significant weakness of her right hand intrinsic and all thumb muscles (2 to 3 on manual muscle testing). Motricity index (MI) was used to evaluate arm motor ability (pinch grip, elbow flexion, shoulder abduction)

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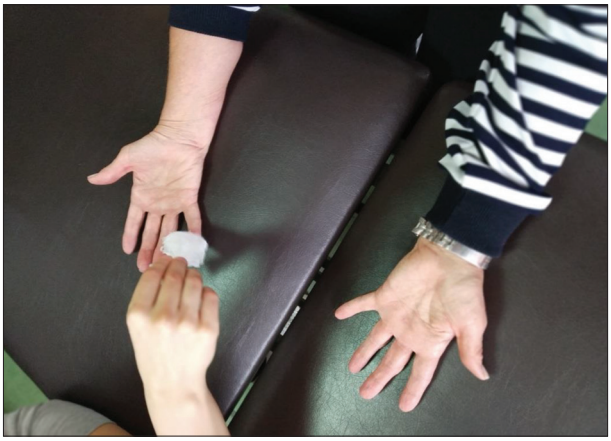

Figure 1. Light touch evaluation with a piece of cotton wool

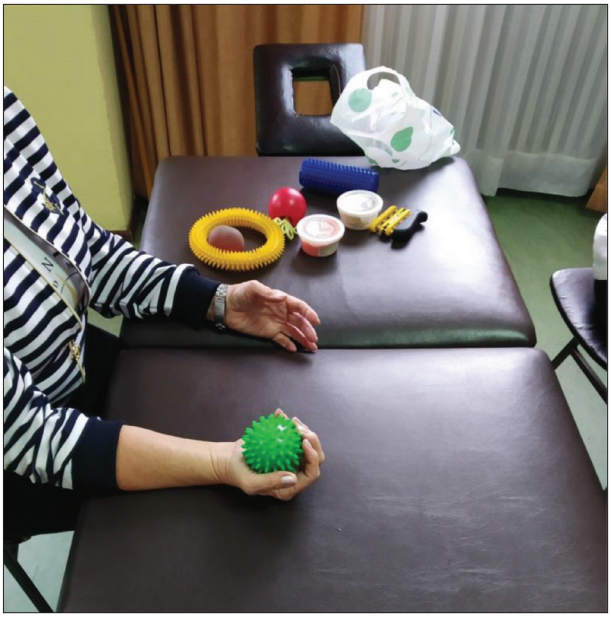

Figure 2. Spiky ball manipulation

[20, 21] and scored L: 100 R: 88/100. Despite satisfactory muscle strength, she was unable to perform functional movements. Tri-digital and pinch grips were impossible and hook and lumbrical grasp were incomplete. The opposition of the thumb to the other fingers was possible but the fingers were not well directed. It was difficult to pick-up small objects. No weakness over LE. The patient's body structure and function impairments include impaired proprioception, kinesthesia and light touch sensation of her right hand. The perception of light touch was preserved but diminished compared to the left hand and precise localization of stimulus was lost. Mislocalization of touch sensations was present in the entire right palm and forearm. Joint position and arm motion reproduction was impossible. The right LE sensibility was intact.

Passive range of motion was in functional range. During finger to nose test right hand dysmetria was noted. Dysdiadochokinesia of the right hand. Romberg test was negative. Tandem stance test: right leg back-positive at five seconds and left leg back-negative but shaky. Tandem walking test with eyes open: unstable. Single leg stance: right three seconds, left 10 seconds.

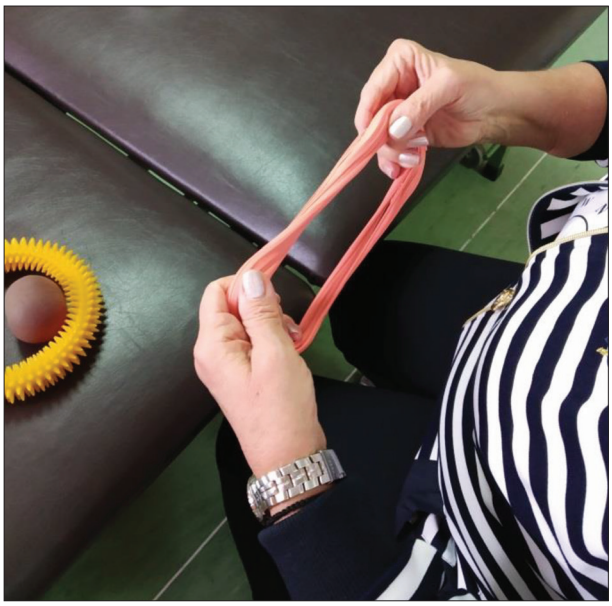

Figure 3. Strengthening exercises using red color putty

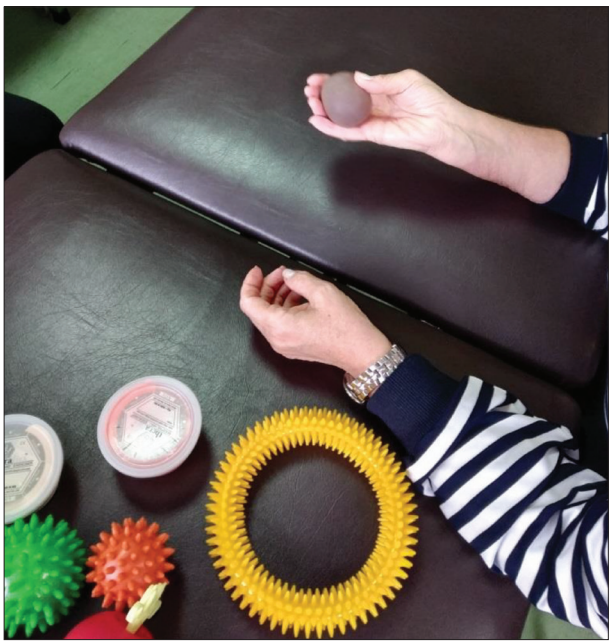

Figure 4. Opposition of thumb and fingers using silicone ball for resistance

The patient presented independent with ambulation and all basic ADLs. Physical function according to The Stroke Impact Scale 16 (SIS-16) was scored 68/80 [22]. The ability to use the right hand in bilateral activities was reduced. She mostly performed activities with her left UE. She could not take or hold a cup in her right hand. She could not hold a pen or sign. It was frustrating she could not hold a pen or sign because holding a pen and chalk was fundamental to her teaching profession. Reported participation restriction was regarding her paid work. There were no cognitive or speech impairments.

Short-term goals were to improve sensibility, to hold a cup of water in her right hand and to drink from it, to write short sentences and sign, to be stable in single leg stance.

Long-term goal was to return to work.

Physiotherapy treatment program consisted of sensory stimulation, motor control, strength and balance exercises. We placed different objects in her right hand while she was looking and then with her eyes closed. She tried to identify objects as they were placed in her hand again, one at a time. "Washing" and "dusting table" with a towel, wool socks and pieces of cloth of different textures. For texture identification, we made the patient recognize the difference in texture (cotton, velvet, cloth, paper towel, sponge, wool sock, sandpaper) by touch only. We applied stimulations with a cotton ball to both and then to her right forearm, wrist, hand and digits, volar and dorsal surfaces. She tried to identify and precisely localize the stimulus with her eyes closed. We also practiced hand movements into containers with rice, dry beans and corn. The patient had the task to feel an object (coin, eraser, paper clip) and then to try to find a matching object in the container. With her eyes closed and had someone else move her hand while holding a pencil, she tried to identify what letter, number or drawing was made.

Each exercise in a treatment session was chosen to target a specific functional skill such as reaching, grasping and manipulating an object (ring, balls, pen, key, roller, plastic glass, clothespins). Grasp stability and adequate grips force were practiced. For manipulation we used spiky massage balls, roller and ring. We instructed the patient to grasp plastic cup and to try to determine how much pressure she was putting on to hold it. We practiced that the patient takes a plastic cup, holds it in her right hand and brings it to her mouth as if she was going to drink from it, then we put first one and later two tangerines in a cup. The same task was performed with a cup half-filled with water. The patient was encouraged to count successful attempts. The tip-to-tip pinch, three-jaw chuck (digital) and the key (lateral) pinch were practiced. We taught her to hold a pen first, to monitor the pressure of holding it and to allow movements required for writing. Writing was practiced: first lines and shapes, then letters, signature, words and sentences. During the last week of rehabilitation, we practiced writing on the board: instead of blackboard we glued a sheet of paper to the wall and instead of chalk we used a thick felt pen.

Other exercises included bimanual alternative movements: clapping hands, playing the piano, thumb opposition and reposition.

The Romberg stance, tandem stance and single leg stance balance exercises were performed. Tandem walking and fast walk with a stop at command were practiced.

Isotonic strengthening exercises with mild resistance: manual, putty (beige, red) springs, silicone balls (red and green), 10–15 repetition, 1–2 series, in progression 2–3 series. Power (hook, fist, spherical, cylinder) and precision grips exercises using putty and silicone balls for resistance were administered. This exercise program (45 min) was applied once a day on weekdays for four weeks.

The final assessment: Subjectively, she reported a complete sensibility in her right hand. SIS-16 score: 77/80. Objectively, sensibility improved: she accurately recognized the location of applied stimuli. She could recognize and repeat position and movement in hand and finger joints. MI: L100, R 100. She could sign and write short sentences. She could write on a piece of paper taped to the wall. She could hold a glass it in her right hand and drink from it. She could drink coffee from a small cup. The tandem walking was stable. Single leg stance: 10 seconds bilateral.

Written consent for publication of this article has been obtained by the patient.

DISCUSSION

Even though the fact that patients often complain about somatosensory disturbances, true prevalence of somatosensory impairment in stroke patients can be underestimated in clinical practice because motor symptoms usually raise greater awareness in the therapists while accompanying somatosensory deficits may be overlooked [9, 23]. Despite the importance of sensory contributions to normal and abnormal movement, research has predominantly focused on motor aspects of stroke recovery. There is lack of evidence that UE somatosensory training improves somatosensory impairment, motor control, function and participation after stroke. Also, the poor quality of current evidences assessing the effectiveness of sensory training after stroke suggests the need for further research [18, 19]. Our patient's experience provided a unique opportunity to study the course and extent of UE motor recovery when sensibility disturbance is recognized and adequately treated. This case report points the importance of sensory information for motor function. Physiotherapy assessment revealed a somatosensory loss in right arm, a mild muscle weakness of right hand, thumb, fingers and right underarm, disturbance of motor control and fine coordination, difficulties in participating in instrumental ADLs and balance deficit. As she could not write, our patient could not do her job of a teacher. The decision that our rehabilitation protocol should involve sensory training was based on the results of physiotherapy assessment and current evidence. Precise assessment and identification of the problems were the first, and selection and application of adequate therapeutic interventions, the second step.

In similar study, findings showed that sensory retraining may be an effective adjunctive intervention for improving the light touch threshold of the hand, dexterity and upper limb motor function in chronic stroke survivors [16]. Serrada et al. [19] concluded in 2019. that the further high-quality research is required to determine the effectiveness of sensory retraining in stroke rehabilitation.

The rehabilitation protocol in our study mainly involved sensory and motor control training. Each evaluation test at discharge from rehabilitation unit showed quantitative and qualitative improvement. The level of manual ability of right arm in ADLs improved. This case report will provide an increased understanding of contributions of sensorimotor integration and sensorimotor learning to skilled hand movements post-stroke.

Conflict of interest: None declared.

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Стимулација сензибилитета руке после можданог удара

Весна Самарџић

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САЖЕТАК

Увод Мождани удар је водећи узрок онеспособљености у свету. После удара већина преживелих има значајна оштећења руке/шаке и редуковану употребу паретичног екстремитета у свакодневном животу. Очуван осећај у пределу шаке је основа за препознавање додиром и за покрет. Упркос значају сензибилитета за нормалан покрет, истраживања су претежно усмерена на моторни аспект опоравка после можданог удара.

У овом раду представљамо утицај програма сензорне стимулације на сензибилитет и моторику руке у субакутној фази рехабилитације после можданог удара.

Приказ болесника Код 65-годишње жене примењен је програм стимулације сензибилитета у субакутној фази опоравка, шест недеља после можданог удара. Програм се састојао из пасивних и активних интервенција стимулације сензибилитета, вежби моторне контроле, координације, јачања и баланса. Програм терапијских вежби се примењивао током четворонедељне рехабилитације, пет пута недељно. На отпусту су резултати физиотерапеутске процене показали потпун опоравак руке.

Закључак Резултати нашег истраживања су показали да прецизна процена, препознавање проблема и примена одговарајућих интервенција стимулације сензибилитета могу за кратко време унапредити моторну функцију паретичне руке после можданог удара.

Кључне речи: стимулација сензибилитета; учинковитост; рука; мождани удар; моторна контрола

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

The Fourth Industrial Revolution's impact on dentistry

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SUMMARY

Introduction Even the greatest visionaries could not have guessed at what speed the profession and science of dentistry would accept the concept of the Fourth Industrial Revolution. In terms of its scale and complexity, this transformation has been greater than any known before and it has been described in the literature as Dentistry 4.0. The digital revolution in dentistry has allowed for nearly all clinical and laboratory procedures to be supported by digital technologies. The aim of this paper is to understand the role of Industry 4.0 in the profession of dentistry and identify its research status today and in the future.

Methods An electronic search of Medline literature was performed via PubMed and Google Scholar databases with the terms "fourth industrial revolution," "digital dentistry," "dentistry 4.0," "CAD-CAM." The option "related articles" was also utilized as well as an additional manual search of review articles and the most relevant papers.

Results The paper describes the most frequently used diagnostic and therapeutic procedures supported by digital technologies.

Conclusion The sophisticated technologies of the Fourth Industrial Revolution have led to more rapid and precise diagnoses of oral diseases. Clinical procedures have become easier, more precise and predictable to the dentist, and more comfortable to the patient. The long-term benefits also include financial savings and environmental protection.

Keywords: digitalization; Fourth Industrial Revolution; digital dentistry; Dentistry 4.0

INTRODUCTION

Dentistry is a highly dynamic scientific field and the changes that occur in this field reflect the development of basic sciences technology [1]. Throughout history, there have been many examples of technological innovations that created new diagnostic and therapeutic procedures in clinical dentistry.

The profession of dentistry has experienced continuous growth, taking advantage of all the opportunities that resulted from the industrial revolutions. The Third Industrial Revolution that marked the transition from analogue electronic technology into a digital era (1980s) propelled a huge leap forward in clinical dentistry. This is when the term digital dentistry was coined, defined as "any digital or computer-aided technology or device in dentistry, as opposed to mechanically or electronically controlled tools" [2]. Digital dentistry opens completely new perspectives where communication, documentation, manufacturing and many other clinical procedures are brought under the umbrella of computer-based algorithms.

Quicker than was expected, another crucial advancement followed that led to automation and the use of robotics both in the industry and in the medical sciences. This shift was so profound that it became known as the Fourth Industrial Revolution – the term first used by Klaus Schwab, head of the World Economic Forum, in 2015. Unlike the three preceding revolutions, this one was not based on groundbreaking new technology but implied a transition to new systems developed using the infrastructure of the previous, digital revolution. Automation is facilitated by the cyber-physical systems enabled by the Internet of things and cloud computing [3].

Even the greatest visionaries could not have anticipated the speed at which both the profession and the science of dentistry, as well as the accompanying industry, would accept the new concept of digital transformation. In terms of volume and complexity, this transformation was greater than any known before. In dentistry, the digital revolution allowed for the possibility for almost all clinical and laboratory procedures to be supported by digital technologies (Figure 1). This new concept soon found its place and received the name Dentistry 4.0 [4, 5].

This paper aims to understand the role of Industry 4.0 in the profession of dentistry and to identify its research status both today and in the future. In dentistry, a truly wide array of diagnostic and therapeutic procedures exist that are based on the technological discoveries within Industry 4.0. Thus, here, only the most important ones will be briefly described.

An electronic search of Medline literature was performed via PubMed and Google

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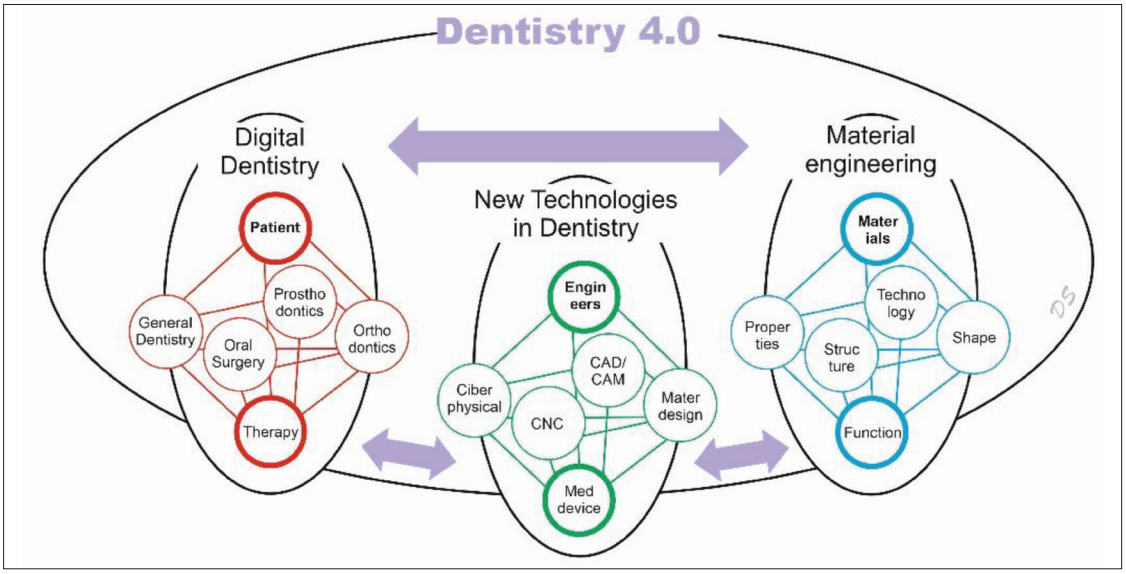

Figure 1. Dentistry 4.0 – synergy of dentists and engineers

Scholar databases with the terms "fourth industrial revolution," "digital dentistry," "dentistry 4.0," "CAD-CAM." The option "related articles" was also utilized, as well as an additional manual search of review articles and the most relevant papers.

MEDICAL IMAGING

Medical imaging is the visualization of anatomical structures using computerized recording techniques. The result of medical imaging is a digital image, which is the first step in digital dentistry. Many diagnostic and therapeutic procedures have been created by generating digital images [1]. Let us mention only those that are used today in routine practice.

Digital teeth impressions

These are virtual, computer-generated copies of the hard and soft tissues in the mouth. Engineers have developed a medical device for digital impressions that is comprised of an intraoral scanner (IOS – hardware), a computer and software. The IOS records a three-dimensional image of an object (a tooth or the surrounding structures) by using concentrated light beams to precisely "capture" the tooth and the surrounding tissue and generates an image in the Standard Tessellation Language (STL) format (Figure 2). More recent intraoral scanners also register the color and texture of the tissue in a Polygon File Format (PLY) file. Laboratory scanners work on a similar principle (Figure 3).

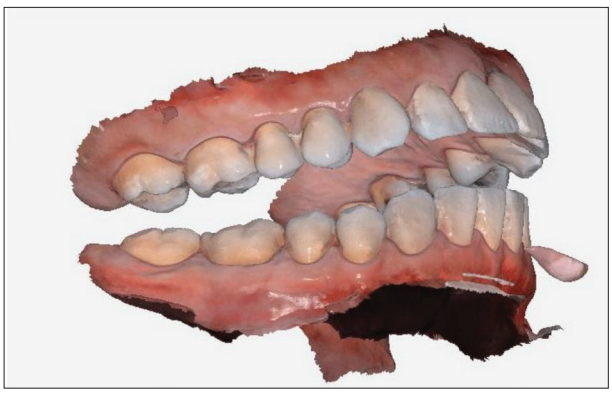

Figure 2. Image of the teeth of the upper and lower jaw obtained with an intraoral scanner

The digital tooth impression operates on a similar principle and, in comparison to the conventional impression, is more precise and easier for the dentist and less unpleasant for the patient. The digital impression is also the first step in prosthodontics, orthodontics, and dental implant treatment.

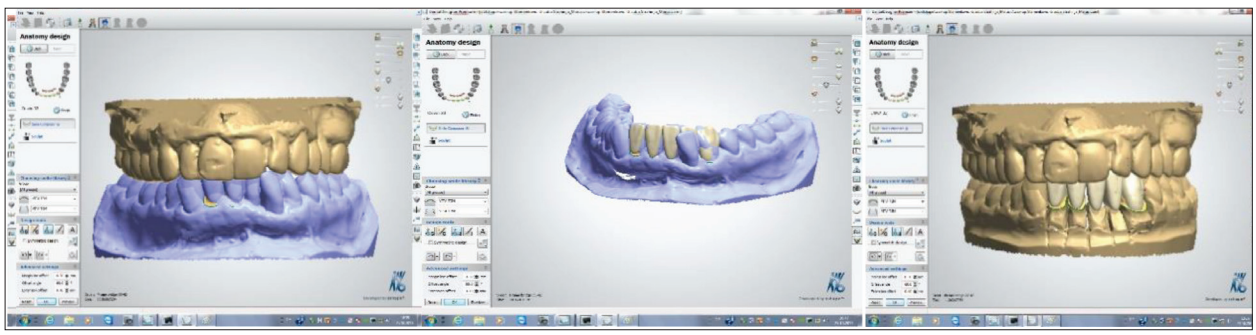

Figure 3. A – image of a cast model of the upper and lower jaw; B and C – computer animation in the Smile Design program in planning treatment for tooth anguish in the lower jaw

Cone-beam computed tomography

Three-dimensional diagnostics (computerized tomography, CT) has long been a superior diagnostic tool in nearly all branches of medicine. The conventional medical CT provides a good three-dimensional representation of the hard tissues and enables their easy visualization. Yet, with regard to our field of interest, this implies both a high dose of radiation and a costly price to pay. These were the basic reasons behind the development of cone-beam computed tomography (CBCT). CBCT uses cone-shaped X-radiation focused on the region of interest, which significantly reduces the effective dose of radiation in comparison to the conventional CT. Some 10 years after the first application of CBCT in angiography and mammography (1982, Mayo Clinic), CBCT-based devices were developed that were specifically intended for dentistry (Figure 4).

By representing the anatomical structure of the orofacial region in three planes, the CBCT technology brought significant advancement in the diagnostics and treatment used in oral and maxillofacial surgery, periodontics, endodontics and orthodontics. The three-dimensional representation of bone structures has enabled computer-aided surgical procedures that employ specially designed software.

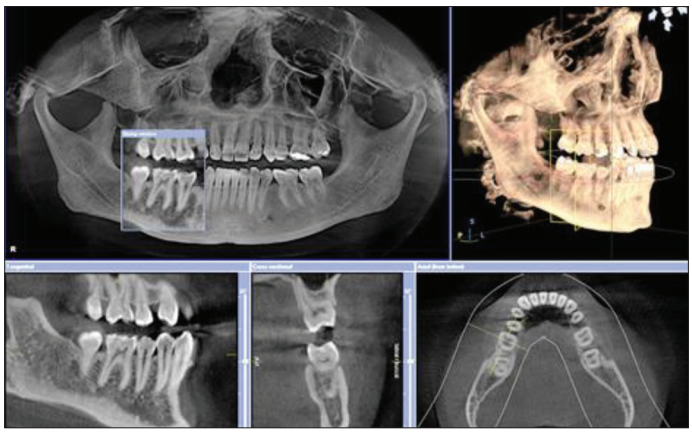

Figure 4. Cone-beam computed tomography screenshot with a small field of view – 6 × 6 cm

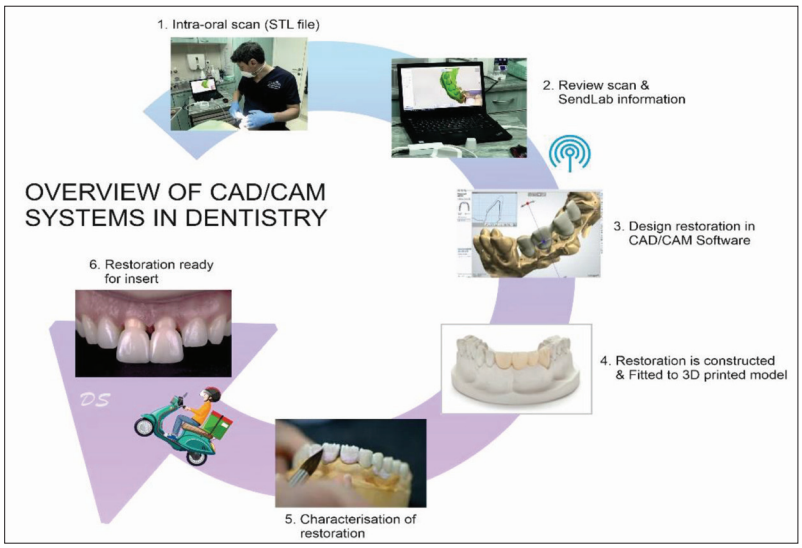

Figure 5. Overview of CAD/CAM systems in dentistry

Digital photography

In combination with the appropriate commercial software for image processing, digital photography allows virtual facial reconstruction, virtual occlusion (Real-Time 3D Reconstruction for Occlusion), smile designing (Digital Smile Design, Smile Creator), etc.

DATA PROCESSING

There is a large number of commercial software products for data processing available today that are designed to support the diagnostic procedures and therapeutic treatments in dentistry.

Computer-aided design and computer-aided manufacturing software

Commercial 3D computer-aided design (CAD) software has been developed that uses several standard data formats. The data files created when taking a digital impression (STL file) are transferred into CAD software to design a dental appliance. After the virtual dental appliance is formed, the files are transferred into the computer support software (computer-aided manufacturing/modeling/machining, CAM software). Based on the CAD model (virtual model), the CAM software then determines a tool path for the computer numerically controlled (CNC) machine (Figure 5). Data processing will depend on the type of machine that will be used for the final shaping of the appliance [6].

Digital facebows and virtual articulators

These are computer software tools that reproduce jaw relationships and simulate the movements of the lower jaw. In digital dentistry, digital facebows have replaced conventional facebows and facilitated their transfer to the space of an articulator. Digital images of three reference points (projections of centers of temporomandibular condyles and the infraorbital point) and an intraoral scan of the upper jaw are sufficient elements for fixating a virtual model of the upper jaw to the upper member of the articulator [7, 8].

Shade matching

Shade matching has resolved many doubts and issues that surface with regard to the visual determination of tooth shade. Machines used for the quantitative analysis of tooth color can determine the characteristics of the light reflected from the examined tooth

surface. Today, several well-rounded concepts are employed for instrumental tooth shade matching [red-green-blue (RGB) machines, spectrophotometers, colorimeters]. What all these concepts have in common is the integrated digital camera and image processing software [9].

Digital Smile Design

This is another computer tool that found an application in digital dentistry. Several digital images and a specially designed software package are enough to achieve the visualization of the existing state and the virtual simulation of different therapeutic plans in designing a smile (Figure 2). Besides visualization, the predictability of future treatment is the main advantage of this computer tool. Before the dental intervention, the patient can "see" or even create together with the physician the end-result of treatment [10].

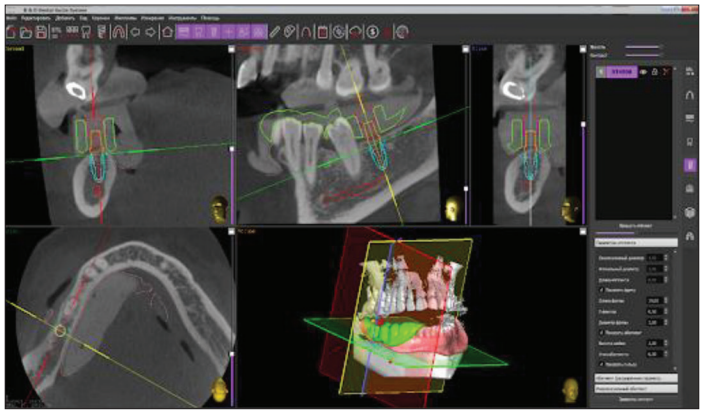

Figure 6. Cone-beam computed tomography screenshot in the preoperative treatment of implant insertion

Computer-guided implant surgery

This is a good example of the Fourth Industrial Revolution in dentistry. This concept involves a series of sophisticated procedures, from diagnosis to implant insertion, and indeed deserves to be called a generator of computerized dentistry. Advanced imaging methods such as CBCT and digital volume tomography supported by 3D software for the examination and analysis of radiograms allow three-dimensional reconstruction of the tissue into which an implant is to be inserted. In this way, the preoperative planning of the optimal implant position is achieved (Figure 6).

Today, the widely accepted technique for inserting implants involves using surgical splints that determine the direction and depth of implant insertion. This method is also known in the literature as "static navigation for implant placement" [11]. Computer-guided implant placement in its full capacity is the technique known as "dynamic navigation for dental implant surgery" or the navigation technique. As its name says, this technique "navigates" the handpiece in real-time during implant placement based on the dental global positioning system without the use of surgical splints or temporary appliances [11–14]. Further development of computer-guided implantology will likely derive from this navigation method. Even now, several commercial programs are present on the market (X-Guide Dynamic 3D Navigation System, Nobel Biocare Co, Kloten, Switzerland; Navident – dynamic navigation system, The Dental Imaging Company Ltd., Shoreham-by-Sea, UK, etc.).

Virtual diagnostics and treatment planning in orthodontics

The digitalization in orthodontics has a long tradition and includes three basic groups of programs: those for office management and patient files' management, those for designing and analyzing digital models, and those for cephalometric analysis (digital cephalometry). There are numerous software packages that support cephalometric analysis (Dolphin Imaging, Dolphin Imaging Systems LLC; OnyxCeph, Image Instruments GmbH, Chemnitz, Germany; AxCeph, Audax, Ljubljana, Slovenia, etc.). Invivo5 (Anatomage Co., Santa Clara, CA, usa) is certainly the most well-known software offering visualization of anatomical structures and other innovations of importance to orthodontics [15, 16].

COMPUTER-AIDED MANUFACTURING

CAM implies the application of software to control tool machines in the manufacturing of various 3D objects. A virtual model designed using CAD and if necessary verified by computer-aided engineering is introduced into the CAM software that controls the CNC machine during the manufacturing process. Essentially, this software allows for the automatization of the process, faster and more precise work and material savings. Machines used in dentistry include milling, sintering, rapid prototyping, and 3D printing machines.

Subtractive manufacturing

The first CAD/CAM systems appeared in dentistry in the 1980s, namely, CEREC (Sirona Dental Systems Inc., New York, NY, USA) and Procera (Nobel Biocare). CNC machines, guided by CAM software, utilize firm blocks of material (ceramic or metal alloys) for milling to form the required shapes [4, 17]. These systems have developed in two directions, which resulted in in-office and laboratory systems.

In-office systems (chairside CAD/CAM technique)

These systems are intended for manufacturing smaller fixed dental appliances in one patient visit. The prepared tooth is scanned and the 3D image is sent to the computer that creates a fixed dental appliance using the CAD/CAM software. The in-office CAD machine quickly mills the dental appliance that is also cemented during the same

Figure 7. Left – the action of milling a ceramic crown in an in-office CAD/CAM machine; right – a ceramic block from which the ceramic crown is milled

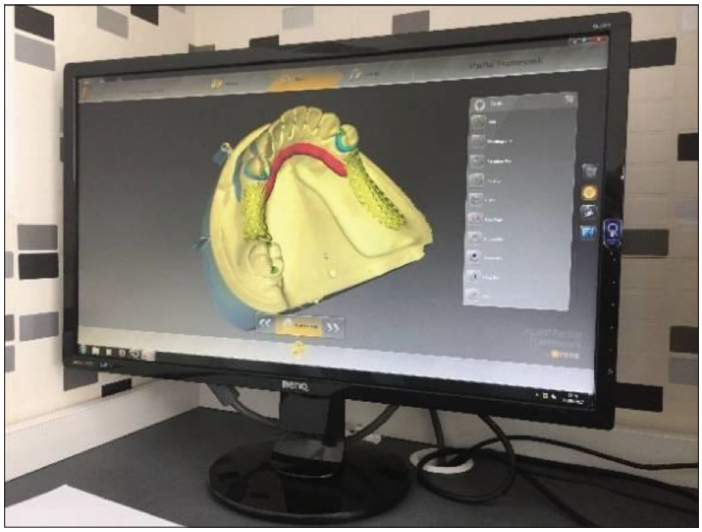

Figure 8. Screen of a monitor showing a virtual model and a model of the dental appliance designed in the 3Shape Partial Denture System (3Shape, Copenhagen, Denmark) program [20]

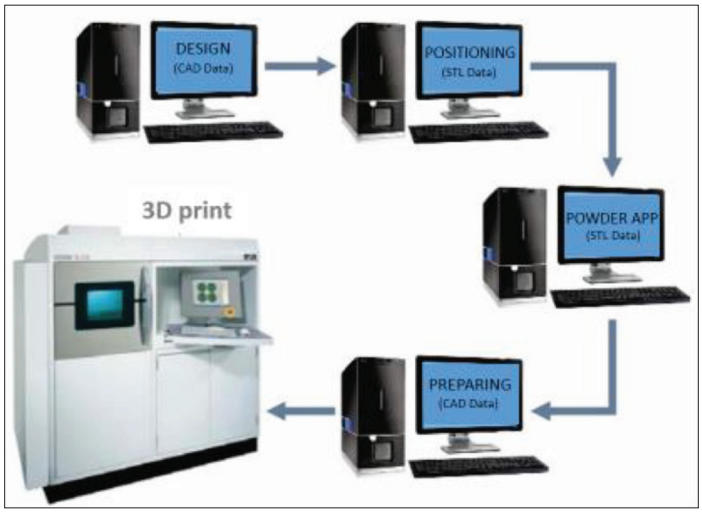

Figure 9. Schematic representation of the manufacturing of a frame using the selective laser melting technology [20]

patient visit. The advantages of this technique are the digital impression, no temporary crowns, and no laboratory costs. Insufficient precision of the gingival sulcus (soft tissue management) and the impossibility of individualizing the appliance are the basic shortcomings of this procedure (Figure 7).

In-lab systems (non-chairside CAD/CAM device)

An impression or model is sent to a laboratory that, after scanning the impression or model, designs and mills the frame (using a ceramic or a metal alloy) in the CNC machine and returns it to the dental laboratory for the application of veneering material and individualization of the appliance. These systems require two patient visits. Due to the fact that they connect the physical with the virtual world, the described systems share many common elements with the cyber-physical systems. The typical examples are Procera AllCeram all-ceramic system (Nobel Biocare), Lava CNC 500 Milling Machine (3M ESPE AG, St. Paul, MN, USA), KaVo Everest CAD/CAM System (KaVo Dental GMBH, Biberach, Germany), InLab (Sirona), etc.

Additive manufacturing technologies

These technologies are broadly applied in the dental industry. In the literature, they are described as additive technologies and rapid prototyping, 3D printing and the manufacturing of free forms. What all formative technologies have in common is that the 3D form is obtained by adding new layers of material. Additive technologies enable direct production of physical shapes (dental appliances, dental implants, obturators, teaching aids, etc.) by using a 3D digital geometric model as input. The geometric model is either designed in a CAD program or obtained by 3D scanning an existing object.

There are numerous examples of the manufacturing of 3D objects in oral and maxillofacial surgery, oral implantology, prosthodontics, and orthodontics. In prosthodontics, there is basically no appliance that cannot be manufactured using additive technology, either in ceramic or composite material, or a metal alloy. The framework of a removable denture is an example of the superiority of this technology over traditional methods. A digital impression of a partially edentulous patient is sent to the laboratory via the Internet and serves as a basis for the virtual model from which the framework is manufactured, in five steps, using the selective laser melting technology (Figures 8 and 9) [17–20]. In order to transfer the physical framework of the denture to a real model and send it to the dental office, a real working polymer model is made on a 3D printer (dental model resin).

BIOMATERIALS

Teeth can be restored, moved or upgraded using materials that in addition to good physical and mechanical

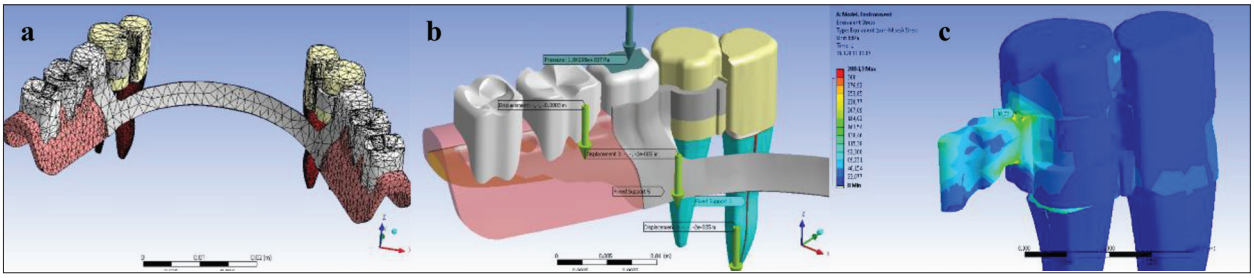

Figure 10. a – the mesh of finite elements of a partial complex denture: 110,970 elements and 213,931 nodes [21]; b – a virtual model of the free-end saddle of a complex partial denture with a point load of 700 N on the first molar [21]; c – stresses and deformations of a complex denture's fixed appliance with a point load of 700 N on the first molar [21]

characteristics also have to possess good biological properties, i.e., they have to be compatible with the oral tissues and the human organism as a whole. When inserted into the stomatognathic system, these materials most often exhibit predictive behavior. From time to time, however, inexplicable observations can be made that are the result of interaction between a material and the living organism. Hence, their name is justified – biomaterials. In the science of materials, in general, dental materials are classified as belonging to the group of advanced materials or materials of the future (nanomaterials and smart materials) [21]. With the accelerated development of the synthesis, shaping, and manufacturing of biomaterials with strictly controlled characteristics in terms of composition, structure, and physicochemical properties, new possibilities are being opened in bioengineering [21, 22, 23].

Dentistry uses a wide spectrum of materials. Most are the products of sophisticated technology. In nanodentistry, expectations are the same as in nanomedicine, except the field of action of the nanoparticles is limited to the stomatognathic system. In the field of dental materials, there are two strategic tasks: synthesis of new polymer and ceramic materials with specific characteristics and synthesis of new nanomaterials (scaffolds) as biological carriers [22].

Smart materials are already used in modern dentistry and they are often described as advanced materials. Some typical representatives include bio-shape-memory alloy and smart composites (these contain amorphous phosphates that act as calcium and phosphate depots) [22, 23, 24]. The widely applied glass-ionomer cements are known as smart materials because of their programmed release of fluoride in caries prevention.

VIRTUAL EDUCATION AND SCIENCE

This technological revolution in the form of virtual reality has fundamentally changed our way of living, working, and connecting. At all stages of education, from the elementary to the highest levels, there is an ongoing gradual transition from the analogue to the digital way of functioning.

In the education of students and residents, digital technologies have reached various degrees of application depending on the resources of particular schools. One of the greatest challenges in the digital education of future dentists is the need for continuous adjustment to technological advances [1, 25]. In dental schools, new courses have been introduced: Computerized Dentistry, Visualization Techniques, and the like. Most clinical courses (Oral Implantology, Prosthodontics, Orthodontics) utilize 3D images, video clips and simulation programs as teaching aids [26, 27, 28].

Continuing professional development (lifelong learning) is the product of this era and can be seen in all professional and scientific fields. In the medical sciences, it is known as continuing medical education (CME). Especially, the traditional CME has grown into eCME and this is one of the fastest rising trends in dental education both here and around the globe [1, 25]. The eCME allows for designing courses and webinars in an interactive form. Also, the comfort provided to users by the eCME is indeed substantial: every student can set his or her own tempo and time for education (the education is not bound by precise hours and locations). A mere glance at the work schedules of scientific and professional organizations will reveal numerous virtual events (webinars) that are conducted live online and enable the lecturers and attendees to connect in an interactive manner. In addition to a screen device and internet access, a software tool for webinars (Zoom, Skype, GoToWebinar, Google meet, Google Plus Hangouts) is needed that provides interactive participation via a chat box or the Q&A function. Webinars as a format of the eCME have given access to education to anyone interested, at any place and any time. During the pandemic (COVID-19) and social distancing, this format of eCME has gained even more significance.

The saying "without technology, medicine is powerless; without medicine, technology is blind" may best illustrate both the association and the inter-dependence between medicine and technology, or between physicians and engineers. Nearly all scientific and research projects in dentistry have engaged engineers to participate as researchers. In the study of dental sciences, the most frequently applied method of numerical analysis is the finite element method (FEM). In short, the FEM considers the physical domain (tooth, dental implant, denture or bridge, temporomandibular joint, etc.) as a real continuum where the points have infinitely many degrees of freedom of movement and reduces it to a discrete (virtual) model with a specific number of points (called nodes) with a finite number of degrees of freedom that can be described mathematically [21, 29].

The appearance of intraoral digital scanners and CBCT scanners allowed for the definition of a real physical model with complex geometry (teeth and the supporting structures of teeth, etc.). Specialized software translates the 3D images into a digital 3D model [20, 25, 29]. The following procedure is nowadays routine in the engineering world: a numerical model is produced by generating a mesh of nodes that comprise the so-called finite elements (Figure 10a). Doctors are expected to define the project assignment – in the case shown in the figures, this would be the loading and elastic deformations of the dental appliance, teeth and supporting structures of the teeth (Figures 10b and c). The physical characteristics of materials and tissues that should be considered to complete the calculation are Young's modulus, Poisson's ratio, and shear modulus [21, 29]. By using program packages for the finite element method analysis (such as the innovative platform ANSYS Workbench, ANSYS, Inc, Canonsburg, PA, USA), beside obtaining the values of stresses and elastic deformations, it is also possible to create animations of the movement of the free-end saddle of the denture and the carrier tooth in a three-axis Cartesian coordinate system (x-y-z) (in dentistry, the terms sagittal, frontal, and horizontal plane are traditionally used instead of the x-y-z system). A visual representation of the virtual movement of the free-end saddle of a complex denture and teeth in operation is a good example of digitalization in teaching dentistry students (Figure 10).

All research projects require the consent of the ethical committee, whose work is based on the principles of good clinical practice as the ethical and scientific standard of quality in designing, managing, monitoring, and reporting about studies done in humans. Sometimes, however, when it comes to investigating the behavior of tissues and organs of the orofacial region, dental appliances or implants under conditions of loading, it is impossible to obtain the ethical committee's consent. In such instances, the application of FEM is the method of choice. FEM should also be given advantage in cases when the proposed experiment is economically unsustainable. The results of FEM should not be taken as final but rather as preliminary findings that signal towards more valid methods, such as clinical studies.

PATIENT RECORD MANAGEMENT

Today, the complete healthcare system has been digitalized, which has made all the management activities simpler and quicker. Due to commercially available software, the management of patient records has become easier and permanently accessible. All patient documentation (dental chart, medical and dental patient history, treatment protocols, radiographies, photographs, digital models before and after the intervention, etc.) can be easily stored and made available in digital form. One of the software tools most often utilized for this purpose is the patient records management dental software [30]. The future holds a transition to web-based patient files, in which data are stored in centralized web servers instead of computers located in individual dental offices [30].

CONCLUSION

The increasingly sophisticated and integrated digital technologies in everyday dental practice (medical imaging, CBCT, digital photography) have led to a more rapid and precise diagnosis of oral diseases. Clinical procedures have become simpler, more precise and predictable for the doctor, and more comfortable to the patient (digital teeth impressions). A large number of commercial software products as CAD/CAM software for milling crowns and bridges, digital facebows and virtual articulators, shade matching, Digital Smile Design, computer-guided implant surgery and digital cephalometry have contributed the most to the progress of dentistry.

The benefits of new technologies in dentistry are enormous. Also, financial savings and environmental protection (less medical and communal waste) are no less important in the long run. At the same time, these technologies can be frustrating because they require great investments and a certain knowledge of informatics from all the members of a dental team. These would also be one of the main reasons behind the unequal level of application of digitalization in dental offices and dental laboratories.

Conflict of interest: None declared.

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Утицај четврте индустријске револуције на стоматологију

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САЖЕТАК

Увод И највећи визионари нису могли да претпоставе којом брзином ће стоматолошка струка и наука прихватити концепт четврте индустријске револуције. По обиму и сложености ова трансформација је већа од свих до сада познатих и у литератури је описана као *Dentistry* 4.0. Дигитална револуција је стоматологији омогућила да готово све клиничке и лабораторијске процедуре могу бити подржане дигиталним технологијама. Циљ овог рада је разумевање улоге четврте индустријске револуције у стоматологији.

Методе Претраживање базе *Medline* извршено је путем база података *PubMed* и *Google Scholar* за термине „четврта индустријска револуција", „дигитална стоматологија", „стоматологија 4.0", „*CAD-CAM*". Такође су коришћене опције „сродних чланака" уз додатно ручно претраживање прегледних чланака и релевантних текстова.

Резултати У раду су описане најчешће дијагностичке и терапијске процедуре које су подржане дигиталним технологијама.

Закључак Софистициране технологије четврте индустријске револуције довеле су до брже и прецизније дијагнозе оралних обољења. Клиничке процедуре постају једноставније, прецизније и предвидљивије за лекара, а комфорније за пацијента. Дугорочно, ту су и економске уштеде и очување животне средине.

Кључне речи: дигитализација; четврта индустријска револуција; дигитална стоматологија; стоматологија 4.0

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REGULATORY STANDARDS IN MEDICINE / РЕГУЛАТОРНИ СТАНДАРДИ У МЕДИЦИНИ

The SARS-COV-2 pandemic and the challenges of intellectual property rights

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SUMMARY
The COVID-19 virus pandemic had a drastic impact on the social lives of billions of people, hitting certain industries like a hurricane. What the answer will be to this and possible other occurrences of pandemics in the future will largely depend on the inventiveness of the researchers. Intellectual property is the first system to offer answers, opening patent bases to anyone developing new technologies to fight the COVID-19 pandemic. The need for the means of prevention, treatment, and care has caused thousands of different researches, which find inspiration and guidance for discovering new solutions in patents that already exist. Publication of scientific papers has never been so intense in any scientific field as in medicine since the fight against this virus began. The time since the beginning of the virus pandemic has shown that science and innovators are ready for such challenges, but the global health crisis has imposed a new challenge on the intellectual property system, which refers to the strict implementation of its rights at times when rapid and global effect is needed in order to avoid additional deterioration due to further circulation of the virus among the population, which inevitably leads to the emergence of new strains of the virus.
Keywords: pandemic; COVID-19; intellectual property; authorship; patents

INTRODUCTION

In the beginning of January 2020, the world started facing the biggest pandemic in the last 100 years. From the beginning of the SARS-CoV2 pandemic, the world has seen an unprecedented healthcare crisis.

From the moment when the patient zero believed to be an asymptomatic carrier was infected in the beginning of January in Wuhan, China, the impact of the outbreak of newly-identified coronavirus (COVID-19 virus SARS-COV-2) on the global population is unbelievable, and its consequences are being felt in all the industries [1, 2]. The world has faced an unprecedented crisis and medicine has been challenged with the task of helping all the sick and disadvantaged [3]. The virus, named by the World Health Organization as 2019-nCOV, has temporarily changed the manner of doing business, as well as the shape of global economy [4]. The coronavirus disease 2019 (COVID-19) pandemic has affected all aspects of public health, especially treatment processes that have never changed so quickly [5]. The objective of this paper is to point out the importance of research work through the prism of patents and copyrights in the fight against pandemic virus outbreaks.

COVID-19 PANDEMIC – AN ACCELERATOR OF INTELLECTUAL PROPERTY RIGHTS

Scientific work as a form of authorship holds great significance in such situations. Upon facing some new form of an illness that was inexistent until the given time, doctors, virologists, immunologists and other professions started closely following scientific journals, in waiting of new scientific works that would confirm or negate the existing stances and lead them towards finding a manner for treating the infected. The COVID-19 pandemic confirmed this. More than 500 scientific works were published world-wide during the first three months of the COVID-19 pandemic (Figure 1).

Thanks to the scientific work titled "Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding," published in the Lancet scientific journal, and which provided the characterization of the SARS-CoV-2 genome, the global effort for developing a vaccine for the prevention of COVID-19 has been greatly facilitated [6].

The significance of scientific work is also visible from the aspect of panic suppression, given that panic is being spread as a consequence of false of partly true information. According to data provided by the Sprinkle analytics platform as early as March 11, 2020, coronavirus had been mentioned on the Internet more that 19 million times. Such enormous interest is fertile ground for spreading different conspiracy theories, misinformation, and suspicious health recommendations [7].

The speed of publishing scientific work in such situations is very significant, but speed brings along mistakes. The results of laboratory and clinical trials are immediately published in

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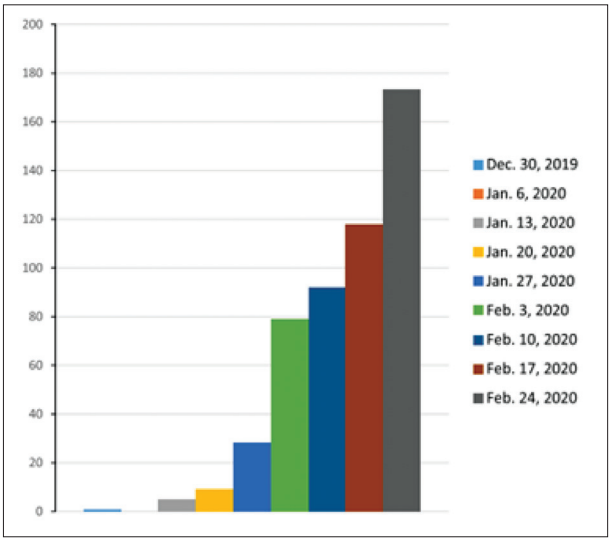

Figure 1. The number of scientific works referring to COVID-19 published over time (weeks) [7]

numerous scientific journals, so that their outcomes can be applied in clinical application as soon as possible [8]. As a response to the needs of the scientific community, many journals have sped up their publishing procedures, especially the ones dealing with COVID-19. Even though this is not the first time that an epidemic led to an increase in publishing authorship works, the change in practice and the lack of implementation of standards, have led towards the publication of papers that were not founded on valid clinical research [9]. In order to prevent a negative impact of false research results, certain journals, such as Royal Society Open Science, conducted study reviews before collecting data, with a special focus on methods and the analysis plan. In such a way, the authors were given an acceptance "in principle" – if they followed the previously determined research plan, their study would be accepted for publishing, no matter the results [10].

INTERFUNCTIONAL DEPENDENCE OF PATENTS AND MEDICINE

Coronaviruses were discovered in 1967, but only with the emergence of the new coronavirus SARS CoV in 2002 the new chapter in virology was opened, and the up-until-then "marginal" coronaviruses became a current topic worldwide. The SARS epidemic (which carries the same gene) also started in China and then spread to some 30 other countries, counting 8098 infected and 774 deceased individuals, and stirred up great interest world-wide, thus causing a need for the development of new diagnostic tests, vaccines, and anti-virus agents [11]. This resulted in current existence of dozens of different patents for diagnosing and treating coronavirus. A relatively small amount of infected has significantly impacted the fates of patents related to this virus. Inventing medicines, vaccines, and other pharmaceutical preparations demands vast material investments that are, for the time being, not cost-effective. Among registered patents related to the SARS virus, about 80% of them refer to therapy development, 35% relate to vaccines, while 28% relate to diagnostic means and methods [12].

Given that intellectual property results from innovations based on the previously existing knowledge, a great number of inventions is actually the result of creational improvements of previous work, or the result of new creative expressions of old ideas and constructs [13]. Due to this, the availability of information of the already existing solutions, the level of development of science and technique is of fundamental significance for researchers. In order to speed up the race and find the treatment modes and efficient therapeutic means and vaccines as soon as possible, the World Intellectual Property Organization (WIPO), within its already existing online platform PATENTSCOPE, set up a new functional search engine for examining information that could be of use to inventors. Given that this database includes 83 million patent documents, in order to facilitate easier overview of data to the interested innovators regarding the PATENTSCOPE WIPO COVID-19, the patents are grouped in accordance with the technical fields significant for detection, prevention and treatment of COVID-10 [14]. Patent lists are "a rich source of technological knowledge acquired by people throughout the centuries," and thus they must be made available to the interested public. By providing an insight in information on the previously existing technologies, the innovators might be inspired towards a further development of the already existing technologies in order to ease the suffering of thousands of patients, bend the death curves, and improve the quality of life for the non-infected individuals.

For faster and easier search of the patent database, the Strasbourg Accord introduced in 1971 the International Patent Classification, according to which patent applications and patents are being classified in accordance with their technical characteristics. Such classification determined eight technical fields (that are further divided into subclasses, groups, and subgroups) [15].

In order to enable easier and more functional search, the WIPO, through the PATENTSCOPE base, offered the inventors who work on easing the consequence of COVID-19 an opportunity to conduct research according to the following criteria: CPR; diagnostics; disinfection; computer science; medical equipment; medical facilities and transport; medical treatment / prophylactics; medical treatment / therapeutic; and personal protective gear. It is intended not only for inventors, but for the wider public as well, from creators of public policies to engineers, in order to find the resources necessary for easing the symptoms, prevention of the disease, and treatment of individuals infected with this virus, through mutual efforts and previously existing solutions.

The invention of a vaccine against COVID-19 is still seen by a majority of the community (with an active protest of one of its parts) as a public social interest, but it also has a huge potential within the economic interest. Global loss caused by the pandemic is measured in hundreds of billions, and the money that a vaccine could bring to pharmaceutical companies represents an enormous profit

and prestige. In the global race for the development of a vaccine, there are currently more than 90 vaccines against COVID-19 in different phases of testing.

The right to health is a fundamental human right; however it is often threatened by the high cost of treatment, cure, and prevention. The new medicines are the result of many years of clinical trials that require extremely high investments. From initial *in vitro* laboratory research, with sometimes *in silico* molecular modeling, through drug development with various phases of clinical trials, to approval by regulatory bodies, pharmaceutical companies invest huge funds, which condition the price of drugs [16]. Due to the high prices of medicines, especially when speaking of populations of the developing countries, the issue of generic medicine and compulsory licenses is often raised [17]. Legal protection by a patent implies a relation in which the protected innovation might be used, produced, sold or in any other form put on the market, with the approval of the carrier of the patent rights [12].

With regard to pandemic occurrences, the medicines used for treating or easing the impact of the virus must be on the list of fundamental medicines, whose availability and accessibility must be ensured for everyone. One study shows that, even though a patent lasts 20 years, an effective patent protection of pharmaceutical products in the European Union lasts only eight years, and the gamut of pharmaceutical preparations used in prevention and cure of SARS and MERS showed to be, on the off-chance of the humanity, unprofitable for the pharmaceutical industry, due to the small number of infected persons [18].

A justified question arises: if the progress in all fields, from culture to technology, is based on creations and innovations whose inventiveness is awarded by implementation of monopoly rights over a patent (patent protection), does this reduce the incentive for further improvement of the previously existing creations? It is hard to find the balance. Due to the crisis caused by AIDS and HIV virus, the Government of the Republic of South Africa passed a law that determined a reduction of prices of medicines used for the treatment of this illness in order to make them more accessible. Even though this action caused dissatisfaction among pharmaceutical companies and legal procedures, such restrictions in cases of pandemics seem like an adequate compromising solution [19].

A pandemic, unfortunately, causes a feeling of panic among numerous people when, due to a reduced ratio, numerous consumers become more prone to procuring counterfeit medicine. In accordance with the Law on Medicine and Medical Needs [Official Gazette of the RS, no. 30/2010, 107/2012, 113/2017 – State Law and 105/2017 – State Law], a counterfeit medicine is a medicine produced and/or placed on the market with an intent of deceiving the individuals that consume it, characterized by fake identification information (about the producer, place of production, etc.), or containing right or wrong contents in comparison to the declared content and/or does not contain or contains insufficient amounts of the active substance in question. In the times of the flu pandemic caused by the A (H1N1) virus, also known as the swine flu, the Internet was crowded with offers such as, "antivirus herbal product for the flu; natural prevention of swine/bird flu," "strong natural direction in the fight against swine flu and other viruses," etc., and numerous seizures of counterfeit medicine Tamiflu were conducted in the USA and in Europe (in the Netherlands and the UK) [20]. Deceiving sick people, as well as harmful consequences that counterfeit medicines can have on the health of individuals that consume it as a preventive measure, have unforeseeable consequences.

Even though vaccines and respirators are currently in the center of interest not only of scientific communities, but also the wider public, given that there is not a clearly determined model that would calculate the exact time of the end of this pandemic, numerous mathematicians are giving their contribution by attempting to find new models upon which it would be possible to foresee the end of the pandemic, as well as a possible new wave. Some have turned to the Gauss curve, while others search for the fundamentals in other theories.

In addition to pharmaceutical workers and mathematicians, thousands of new inventors give their contribution to the global fight against COVID-19 through innovations that refer to the means of personal protection, diagnostics, medical equipment and its transportation, respirators and medical preparations, bioinformatics and information technology in medicine.

ECONOMIC CONSEQUENCES OF PATENT REGISTRATION AND THEIR IMPACT ON HUMAN HEALTH IN A PANDEMIC

The pandemic has reduced economic activity in many economic sectors, reducing the incomes of citizens and the economy. As a response, many countries have provided financial assistance to citizens and the economy by increasing the public debt. In such a situation, the health sector is particularly burdened in less developed countries that find it difficult to meet the health needs of their citizens. The system of intellectual property that provides exclusive monopoly rights to patent holders further increases the cost of health care, which in extreme situations, such as a pandemic, raises the justified question of international exhaustion of patent rights [21].

Immunization in a number of developed countries progresses well, but there is great uncertainty about how developing countries and especially underdeveloped countries will overcome economic difficulties, not only in terms of vaccination, but also the necessary diagnostic testing, personal protective equipment, necessary logistics systems for vaccination and reporting on adverse events after vaccination. The development of medical and pharmaceutical inventions is also characterized by the fact that their development requires more time and money. Therefore, the monopoly right to an invention obtained through patent protection is especially important for this industry, in order to financially encourage further research. However, in situations such as a pandemic, the issue of social benefit

takes on another dimension, the social interest in advancing medicine and pharmacy is suppressed by ethical challenges. Intellectual property rights are limited temporally (20 years) and geographically. In order for vaccines to be available in a timely fashion in all countries, due to the huge demand, this can only be achieved by assigning rights to registered patents through licensing [22]. Although many important facts are still unknown regarding this virus (transmission, period of incubation, full clinical presentation, radiography, laboratory findings, immune response and specific treatment), the SARS-CoV-2 genome is fully sequenced and it is a cause for concern that the longer the virus circulates among the population, the number of mutations will increase and new pathogen variants will appear [23, 24]. That is why it is important to achieve global immunization as soon as possible.

Although some authors believe that Article 31 of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) can be interpreted as enabling the production of affordable vital pharmaceutical products in situations of global health crisis without violating the international intellectual property rights regime, India and South Africa, together with 57 member countries of the World Trade Organization, have launched an initiative to exempt certain provisions of TRIPS, due to the need for a temporary global waiver of patent protection for COVID-19 vaccines [25, 26]. This would enable the production of cheap generic vaccines, which would help enable more efficient vaccination of the population in poor countries. Local production of medicines is a far more affordable variant, because the prices of facilities used for their production are significantly lower with lower wages of workers, thus enabling a price that is acceptable for the markets of underdeveloped countries.

The alternative is the instrument of compulsory license issued in cases when the patent right holder refuses to assign to other persons the right of economic exploitation of the protected invention or imposes unjustified conditions for such an assignment. In such cases, a legislation such as ours stipulates that the state administration body responsible for affairs in the field in which the invention is to be applied may, at the request of the interested person, issue a compulsory license. The scope and duration of the compulsory license is limited by the purpose for which it was granted, and the holder of the compulsory license is obliged to pay the right holder a fee determined by both parties or determined by the competent court (in cases when no agreement on the amount and manner of payment was made).

CONCLUSION

COVID-19 has caused numerous changes in a very short period of time. Whether they are permanent or simply one-time changes will depend on numerous factors, but their effect has, without a doubt, a destructive impact on numerous economic branches and the society. Wishing to reach the solution for easing the consequences of the virus, researchers have sped up their studies by publishing a colossal amount of data, which led to certain wrong interpretations and explications. The activity of inventors who attempt to devise as efficient prevention, treatment and combat measures as possible, is extremely live. In order to provide researchers with access to already existing solutions and knowledge, access to many patent bases is eased. Whether the resulting changes are emergent will, to the greatest extent, depend on the virus itself, the length of its lifespan, its possible mutations, and the speed the science will need to combat it. The next step in that fight is the fair management of the system of intellectual property rights, especially in the part of assigning patent rights to states whose inhabitants are not able to pay for expensive medicines.

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Пандемија САРС-КОВ-2 и изазови права интелектуалне својине

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САЖЕТАК

Пандемија вируса корона драстично је утицала на друштвени живот милијарди људи, погађајући ураганском јачином поједине индустрије. Који ће одговор бити на ову и могуће друге појаве пандемија у будућности у великој мери ће зависити од инвентивности истраживача. Интелектуална својина је први систем који је понудио одговоре, отварајући патентне базе свима који развијају нове технологије за борбу против пандемије ковида 19. Потреба за средствима превенције, третманима и лечењем узроковала је на хиљаде истраживања која у већ постојећим патентима налазе инспирацију и пут ка новим решењима. Објављивање научних радова ни у једној научној области никада није било тако интензивно као што је у медицини од када је почела борба против овог вируса. Време од почетка пандемије вируса показало је да су наука и иноватори спремни за такве изазове, али глобална здравствена криза је пред систем интелектуалне својине наметнула нови изазов, који се односи на стриктно спровођење њених права у тренутку када је неопходан брз и глобалан ефекат, како не би дошло до даљих погоршања услед даљег циркулисања вируса међу становништвом, што неизоставно доводи до појаве нових сојева вируса.

Кључне речи: пандемија; ковид 19; интелектуална својина; ауторска права; патенти

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BOOK REVIEW / ПРИКАЗ КЊИГЕ

Review of the book titled "Great Women in the Great War"

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Author: Slavica Popović Filipović
Publisher: Mali Nemo, Pančevo, Serbia, 2020
Book volume: 761 pages, 21 chapters
ISBN: 978-86-7972-124-2

A new book entitled ***Great Women in the Great War*** written by Slavica Popović Filipović has recently been published by Mali Nemo (Pančevo). The editors are Milan Orlić, Duško Lopandić and Danica M. Savić, the reviewer is Dr. Veljko Todorović and the designer is Jelena Basta. The book is skillfully enriched with translations by Bob Filipovich.

This outstanding publication is a result of extended research not only in the history of Serbian medicine, but in the areas of the history of the Great War, international medical missions, remembrance, cultural diplomacy, history of the suffragette movement, humanitarian and philanthropic work as well. This book is the crowning achievement of many years of research and publishing works by Mrs. Popović Filipović, who had previously published scores of her scientific papers that encompassed the above topics.

Knowing that the place and role of women in the history of World War I have been traditionally marginalized, as pointed out by the author in the Introduction, this book gives a significant contribution to our understanding of these brave women who willingly risked their own lives in order to help others in need.

This research project involved reviewing extensive archived materials, many original documents, correspondence, hand-written diaries, and photographs in various archives around the world, as well as in private collections. The author, having crisscrossed the Mediterranean, the Atlantic and the Pacific, has gathered and presented valuable documentation about Serbian and foreign women doctors, British suffragettes, Scottish, American, Australian and Canadian women humanists, a French countess, a Russian noblewoman, writers, painters, journalists, titled Ladies, and heroines from faraway countries and continents.

These exceptional women shared wartime suffering with the Serbian people and its army in the midst of world war events: the typhoid epidemics in Serbia; the exodus through the Albanian mountains; the exile on the island of Corfu (Greece); the heroic battles at the Salonika front. Tunisia, Algeria, Corsica, Russian front, and Dobrudja (Romania) were blessed by their presence and immeasurable help as well. This book is, therefore, a remarkable evidence of the dedicated affection and strenuous work of over 2000 women doctors, nurses, orderlies, and humanists, who served in the hospitals of the Serbian Red Cross Society, the Scottish Women's Hospitals (SWH), the hospitals of the Serbian Relief Fund (SRF), the Allied Red Cross Units, and other voluntary humanitarian organizations in Serbia itself and in exile – during the Great War and afterwards, too. Mrs. Popović Filipović has carefully selected twenty-one of them as representatives and shaped their biographies into twenty-one memorable chapters.

Thus, the book provides the reader with new information about the translator and humanist Ljubica Luković, President of the Serbian

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Women's Society "Kolo srpskih sestara" in the Balkan Wars and World War I (Chapter 1); Dr. Anđelija Al. Jakšić, a woman doctor in the Balkan Wars (Šabac, Serbia) and the Great War (Kragujevac, Serbia) as well as in exile in Paris (France), who was awarded the Order of St. Sava and the French Gold Medal (Chapter 2); the Scottish surgeon and suffragette Dr. Elsie Maud Inglis, the founder and head of the Scottish Women's Hospitals (Chapter 3); Dr. Isabel Galloway Emslie, Lady Hutton, a Scottish doctor, who was awarded the Order of St. Sava and the Russian Order of St. Anna and who volunteered with SWH in France, Gevgelia (North Macedonia), Salonika (Greece), but also in Vranje (Serbia) after the liberation (Chapter 4). The sagas of extraordinary ladies continue with Honorable Evelina Haverfield, a Scottish baroness and a member of SWH in Serbia during the typhoid epidemic, who rests in peace in Serbia – Bajina Bašta (Chapter 5); Nadežda Petrović, a famous woman painter, humanist and an orderly in the Balkan Wars and the Great War (Chapter 6); Delfa Ivanić, a humanist, bearer of the International Charity Medal Florence Nightingale (Chapter 7); Rosalie Slaughter Morton, an American doctor at the Salonika Front and a generous philanthropist in war-torn Serbia after the war, who was awarded numerous Serbian and foreign state and church medals (Chapter 8); Dame Louise Margaret Leila Wemyss Paget – Lady Paget, a British volunteer nurse in Serbia, who headed the First Unit of the Serbian Relief Fund and was granted the First Grade of the Order of St. Sava (Chapter 9); Mrs. Gertrude Carrington Wilde, a member of the SRF Committee and a great friend of the Serbian people in war and peace (Chapter 10); Mrs. Hannah Hankin Hardy, the founder of the National League of Serbian Women (in Kragujevac, Serbia, Feb. 1915) and the holder of the Order of St. Sava (Chapter 11); Helen Losanitch Frothingham, a representative of the Serbian Red Cross Mission in America and Canada during the Great War, who, together with her husband John Frothingham, organized several homes for war orphans after the war (Chapter 12); Dr. Agnes Bennett, an Australian from Sydney, the head of the America Unit of SWH at the Salonika front and after the victorious battle of Kaymakchalan (Chapter 13); Lena Aleksandra Jovičić, a writer, translator and a humanist, who was following the story of her family (Chapter 14); Mabel Annie St. Clair Stobart, the head of the Third Unit of SRF in Kragujevac (Serbia) and the commander of the so-called "Flying Unit" during the Great Retreat (Chapter 15); Olive King, an Australian who wore medals instead of brooches and the Serbian national cap instead of a ladies' hat (Chapter 16); French countess Marie de Chabannes la Palice, who worked at the First Serbian Surgical Hospital at the Salonika Front (Chapter 17); Madam Mabel Gordon-Dunlop Grujić, an American – a great lady of grace, who remained with the Serbian people for years (Chapter 18); Aleksandra Pavlovna Hartvig, a Russian aristocrat in the humanitarian mission in Serbia in the Balkan Wars and the Great War (Chapter 19); Dr. Slavka Mihajlović Klisić, a woman doctor and a poet in the service of her homeland in war and peace (Chapter 20); and Dr. Harriet Macmillan Cockburn, a Canadian woman doctor in the Third Unit of SRF in Serbia, who took part in the retreat (Chapter 21).

Taking into account that the Introduction is written in English, that all chapters are followed by an extensive resume in English, that the quotations in the English language are retained in their original form and that there is also a bilingual Names Index, this reference book is readily available to a wide range of both domestic and foreign researchers. As it abounds in relevant details, it may serve as a valuable resource for many libraries and archives. A wider public and lovers of this genre will certainly embrace the opportunity to learn about the lives and deeds of the heroines from Mrs. Popović Filipović's book.

To write about the great women in the Great War is a limitless topic, and the moral obligation to save their names from oblivion should remain a constant. Their admirable energy, enthusiasm, professionalism, unselfishness, devotion and persistence can be most deeply felt by the ones who possess the same qualities. Hence, we highly recommend this book by Mrs. Popović Filipović and emphasize that nowadays and in the years to come, our gratitude to the heroines from the glorious past should always be accompanied by our gratitude to those who write about them in such a knowledgeable and warm manner.

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CONGRESS AND SCIENTIFIC MEETING REPORT /
ИЗВЕШТАЈ СА КОНГРЕСА И НАУЧНОГ СКУПА

Digest of the round table titled "Medicine and engineering: An inexhaustible source of challenges for cooperation between medical doctors and engineers"

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The Academy of Medical Sciences of the Serbian Medical Society (AMS-SMS) and the Academy of Engineering Sciences of Serbia (AESS) have successfully organized the first joint scientific meeting – the round table titled "Medicine and Engineering: An Inexhaustible Source of Challenges for the Cooperation of Doctors and Engineers" held in Belgrade, Serbia on June 24, 2021.

At the opening of the meeting (Figure 1), presidents of the academies greeted the audience and expressed their satisfaction that AMS-SMS and AESS have signed a protocol on cooperation in 2020. Prof. Ljubica Đukanović, the AMS-SMS president pointed out the goals of the meeting as to inform our scientific community about the established cooperation and to illustrate, by several lectures, how wide the cooperation field of engineers and doctors is. Prof. Branko Kovačević, the AESS president, added that the aim of the cooperation is not only to contribute to the multidisciplinary collaboration, but also to undertake activities that would lead to the realization of the appropriate place of national academies in the scientific community of Serbia.

The program of the meeting consisted of five lectures covering different fields of biomedical engineering.

Prof. Dr. Nenad Ignjatović (Institute of Technical Sciences of the Serbian Academy of Science and Arts; AESS) presented the lecture "A bridge over the great challenges in medicine: connecting doctors and engineers" showing the research on calcium phosphate-based nanoparticles designed at the molecular level for use in reconstructive, preventive, regenerative and cancer medicine. Joint teams composed of engineers and medical doctors participated in this scientific research. The synthesized nanoparticles have been successfully used as carriers of vitamins and antibiotics in bone tissue engineering; as a basis for contrast agents in multimodal imaging techniques; as scaffolds and carriers of stem cells and vehicles for delivery of steroid drugs as well as for targeting breast cancer cells.

Prof. Emeritus Miroljub Adžić (University of Belgrade, Faculty of Mechanical Engineering; AESS) aroused the interest of the audience with his lecture "Lesser-known connections between mechanical engineering and medicine". He presented research aimed to find a harmless liquid insecticide acting so to physically stop the flight of insects. The focus was on mosquitoes, the main vectors in transmitting vector-borne diseases, which have evolved into brilliant flying machines with exceptional sensors and behavior. The wings and body are hydrophobic due to the specific microstructure. Detailed calculations of flight dynamics, strength and wing deformation under the action of surface stresses depending on physical properties of the applied liquid were performed. Tying at least one drop 0.1 mm in diameter to the mosquito's wing would disrupt the dynamics of synchronous flapping of the wings and prevent flight, while several droplets attached to the insect's body block transpiration, with a possible lethal outcome. Based on this knowledge, a multicomponent liquid insecticide exceptionally efficient and safe for living beings was formed, which acts exclusively physically, preventing the flight of insects.

Vladimir Nešić, Senior Embedded Software Engineer at the Institute Mihailo Pupin, Belgrade, delivered the lecture "Application of automation in medicine" presenting the production program in the Institute and the current level of technology applied in power plants and traffic management. Various management segments of thermal and hydroelectric power plants, electrical power transmission, as well as in traffic management were introduced. Special attention was put on examples of development

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Figure 1. Opening of the round table titled "Medicine and Engineering: An Inexhaustible Source of Challenges for the Cooperation of Doctors and Engineers" – the first joint meeting of the Academy of Medical Sciences of the Serbian Medical Society and the Academy of Engineering Sciences of Serbia held on June 24, 2021 (Amphitheater of the Serbian Medical Society, Belgrade, Serbia).

of novel devices at the Institute such as Smart Blot, a device for automatic incubation of western blot membranes, and the first respirator designed and produced in Serbia. It was interesting to learn how the technology used in electricity industry was applied in the development of these devices, which indicated possible future directions in this area. The practice has shown that there are sufficient resources in knowledge and professional staff (medical and engineering) in Serbia for novel biomedical devices invention. However, the main problem is the placement of domestic medical equipment on the market, which is already profiled by the world's leading manufacturers.

Prof. Dr. Dragan Dankuc (University of Novi Sad, Faculty of Medicine; AMS-SMS) delivered the lecture "Artificial inner ear" presenting the results of cochlear implantation at the Center for Cochlear Implantation at the Clinic for Ear, Nose and Throat Diseases, Clinical Center of Vojvodina in which the first such successful implantation in Serbia was performed in November 2002. A cochlear implant is an electronic device, which bypasses damaged or destroyed receptor cells and transmits electrical stimulation directly to the fibers of the auditory nerve. Such an implant provides the opportunity for patients with severe-to-profound hearing impairments to hear again, for children to learn to speak and to involve in everyday life and regular schooling. Today, cochlear implantation is the standard treatment of severe-to-profound sensory-neural hearing loss but it would not have been possible without close collaboration between engineers, neurologists, otorhinolaryngologists, and speech and hearing health professionals.

Prof. Dr. Bojana Obradović (University of Belgrade, Faculty of Technology and Metallurgy; AESS) delivered the lecture "Biomimetic bioreactor systems for tissue and tumor engineering" presenting the main concept and purpose of biomimetic bioreactors, which aim to mimic conditions in tissues and organs *in vivo*. These bioreactors were initially developed for use in tissue engineering in order to stimulate the cells to regenerate functional tissues under *in vitro* conditions. Still, bioreactor cultivation of cells in a three-dimensional environment is also significant for cultures of cancer cells and tumor engineering that is, complex model systems which replicate certain features of the tumor microenvironment *in vivo* ultimately providing faster and more reliable anticancer drug testing and development of personalized medical therapies at reduced animal experimentation. Further, Prof. Obradović presented biomimetic bioreactors developed in her research group and the application of perfusion bioreactors in three-dimensional cultures of osteosarcoma and glioma cell lines in

alginate hydrogels performed in collaboration of engineers and molecular biologists.

Prof. Dr. Dragoslav Stamenković (University of Belgrade, Faculty of Dental Medicine, AMS-SMS) presented in his lecture "Biomedical engineering in dentistry" how the digital revolution in dentistry has enabled support to almost all clinical and laboratory procedures by digital technologies. The progress is evident in various fields of dentistry: medical imaging, data processing, computer-aided production, biomaterials, education and science, as well as in patient record management. Prof. Stamenković illustrated this progress by presenting the results of his scientific research and professional work. It is evident that the increasingly integrated digital technologies in everyday dental practice contributed to faster and more accurate diagnosis of oral diseases as well as more precise, efficient and for patients more comfortable clinical procedures. Just as significant are financial savings and environmental protection.

After the lectures, a discussion with the audience was dedicated to presented results and issues but also to some organizational problems in this area. It was concluded that regular joint meetings of experts in different fields of biomedical engineering are necessary. The emphasis was put on the fact that the sporadic development and placement of single medical devices on the market do not lead to sustainable economic development. Economic sustainability could only be achieved through the planned development of a complete range of products with the accompanying provision of services. Therefore, it is necessary for the two academies to define strategic development goals in the field of biomedical engineering in cooperation with the competent state institutions. It is also necessary to require recognition and inclusion of educational profiles in biomedical engineering, which have been introduced at several universities in Serbia, in the public sector jobs' catalogue.

The meeting confirmed the justification and importance of the established cooperation between AMS-SMS and AESS, which is expected to contribute better cooperation of doctors and engineers as well as experts in other fields to solve so far unresolved problems in the area of biomedical engineering.

Conflict of interest: None declared.

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:
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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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AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text. Authorship is based only on: crucial contribution to the article conception, obtaining of results or analysis and interpretation of results; design of manuscript or its critical review of significant intellectual value; final revision of the manuscript being prepared for publication.

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.

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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.

STRUCTURE OF THE MANUSCRIPT. All section headings should be in capital letters using boldface. Original articles and preliminary and short communications should have the following section headings: Introduction (objective is to be stated in the final paragraph of the Introduction), Methods, Results, Discussion, Conclusion, References. A review article and current topic include: Introduction, corresponding section headings, Conclusion, References. The firstly named author of a review article should cite at least five auto-citations (as the author or co-author of the paper) of papers published in peer-reviewed journals. Co-authors, if any, should cite at least one auto-citation of papers also published in peer-reviewed journals. A case report should consist of: Introduction (objective is to be stated in the final paragraph of the Introduction), Case Report, Discussion, References. No names of patients, initials or numbers of medical records, particularly in illustrations, should be mentioned. Case reports cannot have more than five authors. Letters to the editor need to refer to papers published in the *Serbian Archives of Medicine* within previous six months; their form is to be comment, critique, or stating own experiences. Publication of articles unrelated to previously published papers will be permitted only when the journal's Editorial Office finds it beneficial.

All enclosures (tables, graphs, photographs, etc.) should be placed at the end of the manuscript, while in the body of the text a particular enclosure should only be mentioned and its preferred place indicated. The final arrangement (position) of the enclosures will depend on page layout.

ABBREVIATIONS. To be used only if appropriate, for very long names of chemical compounds, or as well-known abbreviations (standard abbreviations such as DNA, AIDS, HIV, ATP, etc.). Full meaning of each abbreviation should be indicated when it is first mentioned in the text unless it is a standard unit of measure. No abbreviations are allowed in the title. Abbreviations in the summary should be avoided, but if they have to be used, each of them should be explained when first mentioned in the text of the paper.

DECIMAL NUMBERS. In papers written in English, including text of the manuscript and all enclosures, a decimal point should be used in decimal numbers (e.g. 12.5 ± 3.8), while in Serbian papers a decimal comma should be used (e.g. 12,5 ± 3,8). Wherever applicable, a number should be rounded up to one decimal place.

UNITS OF MEASURE. Length, height, weight and volume should be expressed in metric units (meter – m, kilogram – kg, gram – g, liter – l) or subunits. Temperature should be in Celsius degrees (°C), quantity of substance in moles (mol), and blood pressure in millimeters of mercury column (mm Hg). All results of hematological, clinical and biochemical measurements should be expressed in the metric system according to the International System of Units (SI units).

LENGTH OF PAPER. The entire text of the manuscript – title page, summary, the whole text, list of references, all

enclosures including captions and legends (tables, photographs, graphs, schemes, sketches), title page and summary in Serbian – must not exceed 5,000 words for original articles, review articles and articles on history of medicine, and 3,000 words for case reports, preliminary and short communications, current topics, articles for practitioners, educational articles and articles for "Language of medicine", congress and scientific meeting reports; for any other section maximum is 1,500 words.

Video-articles are to last 5–7 minutes and need to be submitted in the flv video format. The first shot of the video must contain the following: title of the journal in the heading (*Serbian Archives of Medicine*), title of the work, last names and initials of first and middle names of the paper's authors (not those of the creators of the video), year of creation. The second shot must show summary of the paper, up to 350 words long. The final shot of the video may list technical staff (director, cameraman, lighting, sound, photography, etc.). Video-articles need to be submitted along with a separate summary (up to 350 words), a single still/photograph as an illustration of the video, and a statement signed by the technical staff renouncing copyrights in favor of the paper's authors. To check the required number of words in the manuscript, please use the menu *Tools-Word Count*, or *File-Properties-Statistics*.

ARTICLE ENCLOSURES are tables, figures (photographs, schemes, sketches, graphs) and video-enclosures.

TABLES. Each table, with its legend, should be self-explanatory. The title should be typed above the table and any explanatory information under the table. Tables should be numbered in Arabic numerals in order of citation in the text. Use *MS Word*, the menu *Table-Insert-Table*, inserting the adequate number of rows and columns. By the right click of the mouse, use the options *Merge Cells* and *Split Cells*. Use *Times New Roman*, font size 12 pt, with single line spacing and no indent to draw tables. Abbreviations used in tables should be explained in the legend below each respective table.

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