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ЗА ЦЕЛОКУПНО ЛЕКАРСТВО Осн.1872

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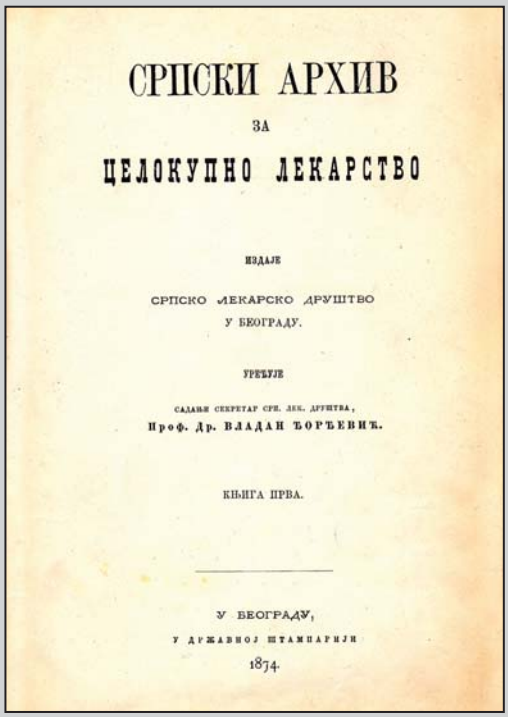

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ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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У БЕОГРАДУ.

УРЕЂУЈЕ

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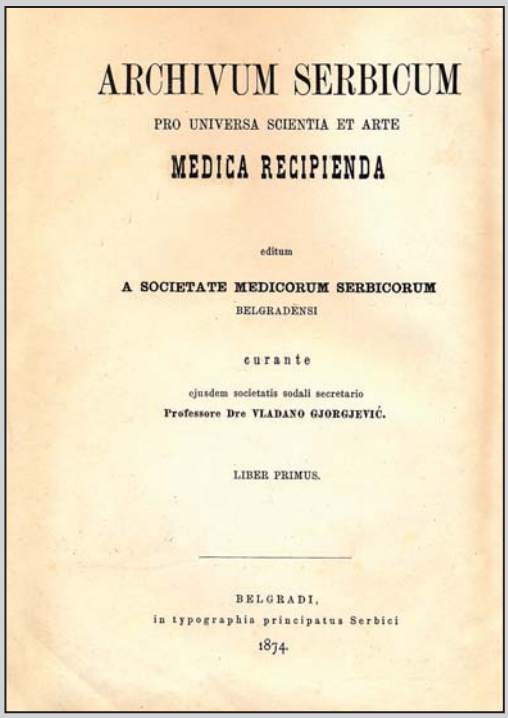

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ORIGINAL ARTICLES • ОРИГИНАЛНИ РАДОВИ

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Evaluation of permeability of root dentin after different irrigation protocols

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SUMMARY

Introduction/Objective This study was aimed at evaluating dentin permeability after irrigation with sodium hypochlorite (NaOCl) and final rinse with chlorhexidine (CHX), ethylenediamine tetraacetic acid (EDTA) + CHX, and new combination products: QMiX or MTAD.

Methods Roots of 60 maxillary incisors were randomly divided into five groups (n = 12) before instrumentation and irrigation with NaOCl according to the final irrigation regimen: CHX (2% CHX), EDTA + CHX (17% EDTA + 2% CHX), QMiX, MTAD, and control group (distilled water). After final irrigation, ten roots of each group were horizontally sectioned and dye penetration was evaluated in the coronal, middle, and apical thirds. Remaining samples were subjected to scanning electron microscopy. Data were analyzed with ANOVA/Tukey's test.

Results Less dye penetration was found in CHX group compared with control as well as with QMiX and MTAD group in all thirds ($p < 0.05$). A significant difference between the control and EDTA + CHX, QMiX or MTAD group was observed only in the apical root third ($p < 0.05$).

Conclusion Dentin permeability was significantly reduced after final irrigation with CHX, but not after use of other final irrigation solutions, except in the apical third of the root canal.

Keywords: dentinal tubule cleansing; intra-canal disinfectants, irrigants; chlorhexidine; EDTA; MTAD; sodium hypochlorite; QMiX

INTRODUCTION

Irrigation is essential for successful debridement of the root canals with mechanical procedures [1]. Sodium hypochlorite (NaOCl) is the most commonly used irrigation solution due to its antimicrobial action and tissue-dissolving potential [2, 3]. However, NaOCl is not sufficient for total cleaning of the root canal system from microorganisms, debris, tissue remnants, and the smear layer. For optimal irrigation, a combination of irrigation solutions has to be used. Therefore, NaOCl has been used in combination with demineralizing agents such ethylenediamine tetraacetic acid (EDTA), for effective removal of the smear layer. Chlorhexidine (CHX), a chemical substance with considerable antimicrobial properties has, been studied as a final irrigation solution after NaOCl and EDTA [2]. Recently, QMiX and MTAD, new combination products, have been aimed at removing the inorganic smear layer and disinfecting the root canal system following NaOCl irrigation [4, 5, 6]. QMiX and MTAD contain an antibacterial agent with known prolonged antimicrobial action (substantivity) (CHX and doxycycline, respectively), a demineralizing agent (EDTA and citric acid, respectively), and a detergent [7, 8].

Although a combination of irrigants may enhance its antimicrobial and cleaning effectiveness, a possible chemical reaction between them has to be considered. This is especially evident when CHX is combined with NaOCl. The chemical interaction between these two solutions results in the color change of mixture to brown and formation of precipitate [9]. When associated with EDTA, CHX produces white precipitate [10, 11]. In QMiX, this interaction is avoided by its chemical design [5]. The combination of QMiX with NaOCl produced inconsistent results. While some authors found orange-brown precipitation, others found visually detectable color change but without precipitate formation in the interaction of these two solutions [12, 13]. When MTAD was added to NaOCl, yellow precipitate formed [14].

The clinical significance of the precipitate formed in interaction with NaOCl and CHX is that it may contain substance harmful to the general health [15]. Concerns have been raised that color change could compromise esthetics [16]. Furthermore, it can act as a chemical layer occluding dentinal tubules and altering

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dentin permeability [17, 18]. Subsequently, diffusion of intracanal medicaments and sealing of root canal could be compromised [19]. The penetration of the precipitate into dentinal tubules formed in interaction between either NaOCl or CHX and other irrigation solutions has not yet been clarified.

Therefore, this study was aimed at evaluating dentin permeability after irrigation with NaOCl and final rinse with CHX, EDTA + CHX, QMiX or MTAD. The null hypothesis was that there would be no differences in permeability of root dentin between different final irrigation solutions.

METHODS

Sample selection and treatment

This study was conducted after approval form the Institutional Ethics Committee (No. 01-3-88/2015). Sixty intact human maxillary incisors with single straight and mature roots, and single canals extracted from 18–30-year-old subjects were included in the study. Teeth with caries, restorations, calcifications, intraradicular resorption or complicated root canal anatomy were excluded. Root canal anatomy was verified with radiographs. The root surface was cleaned with a scalpel, ultrasonic instruments, and brushes. The teeth were then stored in 0.9% saline with a 0.2% thymol solution at 4°C until use.

The crown of each tooth was cut to standardize the root lengths to 14 mm. Before chemomechanical preparation, the root canals were divided into five groups (n = 12) according to the final irrigant solution used: CHX (2% CHX solution, Consepsis, Dentsply Tulsa Dental, Tulsa, OK, USA), EDTA + CHX (17% EDTA, ENDO-SOLution, Cerkamed, PPH Cerkamed, Stalowa Wola, Poland, and 2% CHX solution, Consepsis, Dentsply Tulsa Dental), MTAD (Dentsply Tulsa Dental), QMiX (Dentsply Tulsa Dental) and distilled water (control group). The working length was established 1 mm short of the apical foramen by #15 K-file (Dentsply Maillefer, Ballaigues, Switzerland). After that, apical foramen of each root was sealed with wax. Root canal preparation was carried out with Pro-Taper rotary instruments (Dentsply Maillefer, Ballaigues, Switzerland) up to F4 file (40/0.06) as the master apical file. The canals were irrigated with 1 mL 5.25% NaOCl, after each instrument, except in the MTAD group, where canals were irrigated with 1 mL 1.3% NaOCl (recommended manufacturer's protocol). Irrigation was performed with 27 gauge stainless steel needles (Endo-Eze, Ultradent, South Jordan, UT, USA), whose tip was placed 1 mm from the working length and was then moved up and down during irrigation. At the end of preparation, 5 mL of 17% EDTA was used in the canals for five minutes for smear layer removal, followed by distilled water, to remove traces of EDTA. Then, 5 mL of 5.25% (CHX, EDTA + CHX, and QMiX groups) or 1.3% NaOCl (MTAD group) was delivered into the canals for two minutes, followed by 10 mL distilled water for two minutes to minimize the potential reaction between NaOCl and final irrigant solutions. Final rinse was performed with 5 mL of 2% CHX, 17% EDTA, followed by 2% CHX, QMiX, or MTAD for two minutes. In the EDTA + CHX group, canals received an intermediate flush between two solutions with 10 mL of distilled water for two minutes to prevent interaction. Finally, all canals were dried with paper points.

Dentin permeability analysis

Ten roots of each group were externally coated with fast polymerizing epoxy resin (Brascola Ltda, SP Santa Catarina, Brazil) leaving the root canals free and immersed in 0.2% Rhodamine B solution. After 24 hours, specimens were rinsed continuously under tap water over the next 24 hours. A sharp blade was used to remove resin coatings, and the teeth were embedded in polyester resin. Each root was horizontally sectioned using a slow-speed water-cooled cut machine (Extec Labcut 1010, Enfield, CT, USA) to obtain 1-mm-thick slices. All slices were polished with silicon carbide papers to obtain a flat surface. A slice from each third was randomly chosen, mostly from each third's middle portion, and scanned (Epson Perfection 1240U scanner; Epson Corp, Tokyo, Japan) with a resolution of 400 dpi, and analyzed with the software ImageLab 4.1 (Bio Red, Tokyo, Japan) to assess dye penetration. Dye penetration in dentin was expressed as percentage of the dye penetrated area in relation to the total root-third area.

Scanning electron microscopy analysis

Two roots of each group were prepared for scanning with an electron microscopy (SEM) analysis. The roots were transversely sectioned at 3 mm, 6 mm, and 9 mm from the apex using a diamond disc at slow-speed. The specimens were dehydrated using ascending grades of ethanol (25%, 50%, 75%, and 100%), mounted on an aluminum holder, sputter-coated with gold, and then examined with SEM (JEOL-JSM-6610LV, Tokyo, Japan). Specimens were examined at a magnification between 3,700× and 6,500× and 20 kV to detect precipitate formation on the root dentin surfaces and inside the dentin tubules.

Statistical analysis

The statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). The results obtained for dye penetration (Kolmogorov–Smirnov test $p > 0.05$) were submitted to the one-way analysis of variance (ANOVA) and Tukey's post hoc. The significance levels were set at 5%.

RESULTS

The results of percentage of dye penetration are shown in Table 1 and Figures 1, 2, and 3. The MTAD, QMiX and control group showed significantly higher dye penetration than the CHX group in the coronal third ($p < 0.05$). In the middle

Table 1. The mean ± SD of dye penetration (%) in dentinal tubule at the coronal, middle and apical third of root dentin; mean values represented with the same superscript uppercase (row) or lowercase (column) letters are not significantly different (p > 0.05)

Root level	CHX	EDTA + CHX	QMiX	MTAD	Distilled water
Coronal	61.61 ± 14.56^{Aa}	76.72 ± 10.71^{Aba}	81.33 ± 6.74^{Ba}	79.28 ± 7.81^{Ba}	83.77 ± 17.65^{Ba}
Middle	25.80 ± 9.03^{Ab}	52.95 ± 15.28^{Bb}	62.24 ± 15.37^{Bb}	58.52 ± 13.30^{Bb}	65.50 ± 18.28^{Bb}
Apical	14.43 ± 3.85^{Ac}	16.80 ± 4.91^{ABc}	24.57 ± 5.23^{Bc}	25.87 ± 6.56^{Bc}	36.01 ± 12.19^{Cc}

CHX – chlorhexidine; EDTA – ethylenediamine tetraacetic acid

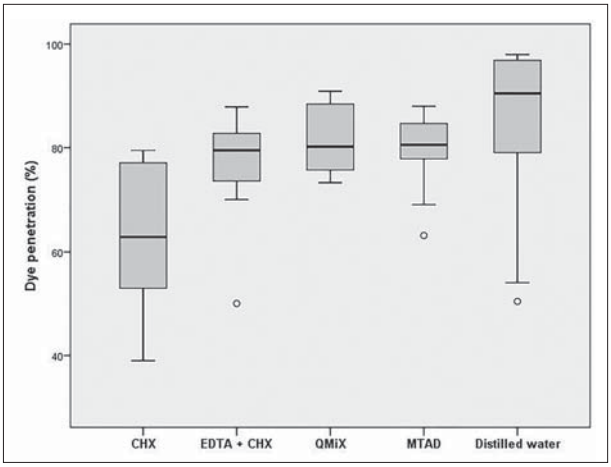

Figure 1. Box plots of dye penetration (%) in the coronal third; horizontal bars – medians; box-boundaries – the 25th and 75th percentiles; whiskers – maximum and minimum observed values; 0 – outliers

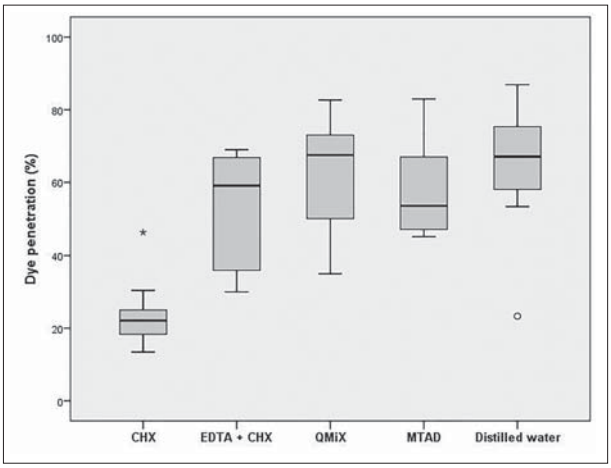

Figure 2. Box plots of dye penetration (%) in the middle third; horizontal bars – medians; box-boundaries – the 25th and 75th percentiles; whiskers – maximum and minimum observed values; 0 – outliers;

*extreme values

third, all groups showed more dye penetration compared to the CHX group ($p < 0.05$). Finally, in the apical third, the control group showed significantly more dye penetration than other groups ($p < 0.05$), while both MTAD and QMiX groups showed significantly greater dye penetration than the CHX group ($p < 0.05$). The highest dye penetration was recorded in the coronal thirds of all groups with significant differences between the thirds ($p < 0.05$) (Table 1).

Representative SEM images of samples irrigated with different final irrigation protocols are shown in Figure 4. Precipitate was found in the samples irrigated with CHX, EDTA + CHX, QMiX, and MTAD, while the control group revealed root canals without precipitate formation.

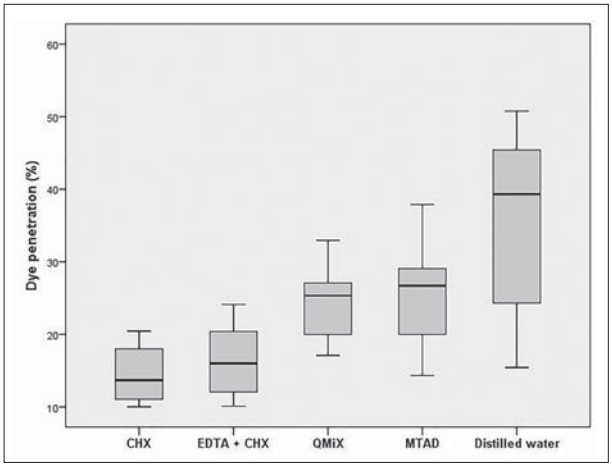

Figure 3. Box plots of dye penetration (%) in apical third; horizontal bars – medians; box-boundaries – the 25th and 75th percentiles; whiskers – maximum and minimum observed values

DISCUSSION

The present study evaluated the interaction between NaOCl and different final irrigants (CHX, EDTA + CHX, QMiX, and MTAD) and its effect on dentin permeability. Root canal irrigation with CHX significantly decreased dentin permeability, while other final irrigant solutions exert no significant effect, except in the apical third.

A closed-end canal model was used in the current study to mimic a clinical setting. Distilled water was used between NaOCl and final irrigation solution (CHX, EDTA + CHX, QMiX, and MTAD) as well as between EDTA and CHX in order to prevent precipitation, as it has been recommended in clinical conditions [4]. Moreover, the operational sequence used was aimed to exclude effect of smear layer on dentin permeability.

In the present study, irrigation with CHX after NaOCl significantly reduced dentin permeability in all thirds of root canals compared to the control group. This result indicates that the product formed in the interaction between NaOCl and CHX, characterized as brown precipitate, is present in dentinal tubules, as has been shown previously [9, 13]. This can be explained by the ability of both solutions to diffuse into tubules up to 500 μm, according to the results of studies that have used dyes or measured their antibacterial penetration [18, 20, 21, 22]. Akisue et al. [18], employing the same methodology for specimen analysis as in the present study, found that precipitate formed between 1% NaOCl and 2% CHX caused reduction of dentin permeability only in the apical third, when compared to no irrigation control group and group irrigated with 15% citric acid followed by 2% CHX. Discrepancy in the results between our study and the mentioned one could be

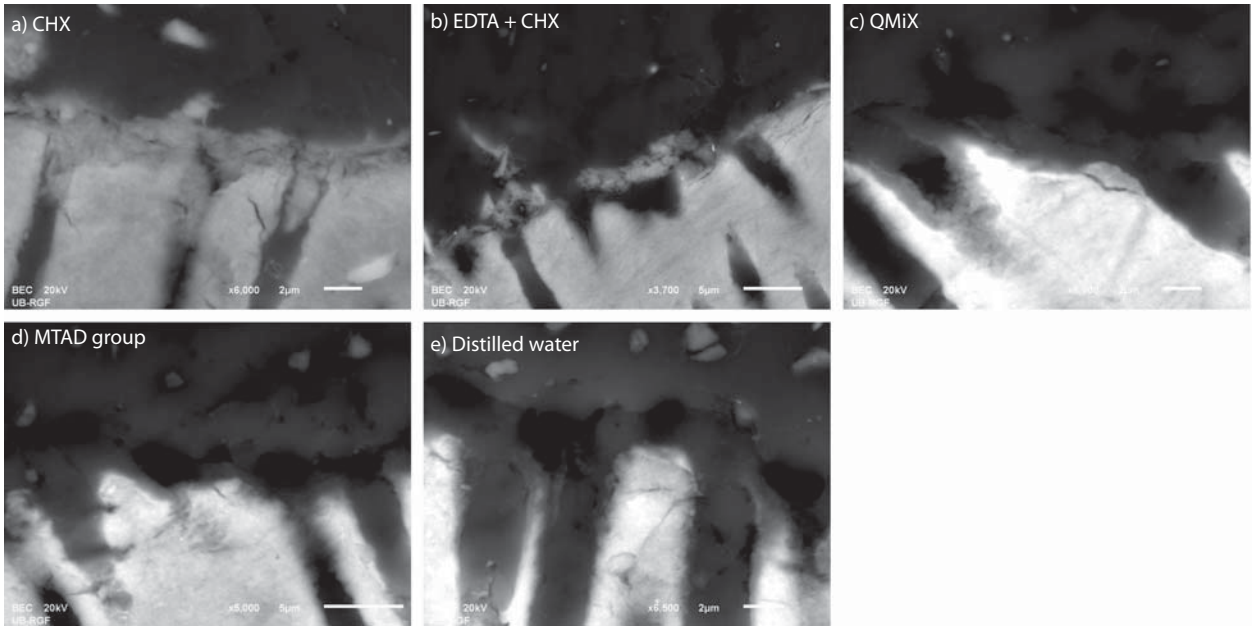

Figure 4. Scanning electron microscope images (magnification between 3,700× and 6,500×) of the sectioned specimens showing precipitate formation on the root dentin surfaces and inside the dentin tubules after final irrigation with CHX (a), EDTA + CHX (b), QMiX (c), and MTAD (d); in the control group (distilled water), precipitate was not found (e)

attributed to the concentration of NaOCl used (5.25 *vs.* 1%). Namely, it has been shown that precipitation is concentration-dependent [9]. The precipitate was formed in dentinal tubules, although an attempt was made to prevent its formation by introducing intermediate flush with distilled water in the main canal. This raised some concerns because this precipitate may act as a reservoir of a toxic and carcinogenic substance, known as para-chloranilin (PCA), even after removal of precipitate form main canal [23, 24]. In addition, this precipitate acting as a chemical smear layer may limit the effective disinfection of dentinal tubules by preventing intracanal medicaments from penetrating the dentinal tubules [17, 18]. Namely, in infected root canals, viable bacteria have been found deep within dentinal tubules (up to 375 μm) and their persistence after chemomechanical procedures may be responsible for root canal reinfection and treatment failure [25]. The precipitate may compromise adaptability of the root filling materials to the root canal walls and may reduce the sealer penetration into dentinal tubules as well [19]. The sealer penetration into dentinal tubules increases the surface contact between dentin walls and filling materials, which may improve retention of the filling material by mechanical locking and may exert antibacterial effect on bacteria remaining in dentinal tubules after canal preparation by isolating them from essential nutrient sources [26]. Moreover, the precipitate may provide a path through which leakage could take place between the root canal filling and the dentinal walls. Vivacqua-Gomes et al. [19] found that a combination of 1% NaOCl with 2% CHX favors coronal microleakage of root-filled teeth. Staining potential of this insoluble dark-brown precipitate is also of relevance [16].

In root canals irrigated with EDTA + CHX, QMiX, or MTAD after NaOCl, dentin permeability was reduced but did not significantly differ from the control group in the coronal and middle third. However, in the apical third, these groups showed significant less dye penetration than the control group.. Also, QMiX and MTAD exhibited more dye penetration than CHX in all root thirds. These results indicate that precipitation probably occurs in dentinal tubules, but not in the amount that could affect dentin permeability in coronal and middle thirds, in contrast to interaction between NaOCl and CHX. Stereomicroscope study showed that QMiX had significantly lower scores of precipitate associated with 2.5% NaOCl than 2% CHX in root canals, probably due to lower concentration of CHX in QMiX [12]. On the other hand, Kolosowski et al. [13] found no precipitation neither on dentin surfaces nor in dentinal tubules after immersion of dentin discs in 2.5% NaOCl followed by saline and QMiX, measured by time-of-flight secondary ion mass spectrometry (TOF-SIMS). Although direct comparisons could not be made due to differences in methodology, it can be argued that the intermediate flush with distilled water in our study prevented the interaction between QMiX and 5.25% NaOCl in dentine tubules, as did saline in the mentioned study [13]. Moreover, a lack of significant differences in dentin permeability of EDTA + CHX and MTAD group with control specimens also suggest that distilled water has a significant impact on precipitate prevention in dentinal tubules, except in the apical sections. Limitation of irrigation modality used and impaired delivery of irrigants into the apical third, including distilled water, constitute possible reasons that could explain lower apical dentin permeability in EDTA + CHX, QMiX, and MTAD group. In addition, the influence of anatomical factors on dentin permeability should also be considered. Namely, tubular sclerosis that starts in the third decade of life in the apical region interferes with the penetration of root canal irrigants [27]. Moreover, dye penetration into dentinal tubules

at the apical region is strongly dependent on the group of teeth [28]. In order to standardize dentin pattern among the specimens in the present study, only maxillary incisors of subjects under the age of 30 were included.

In agreement with the previous studies we found the highest dye penetration in the coronal third of the root canal and the lowest in the apical third in all the groups, including controls with significant differences between the thirds [18, 27, 29]. This may be due to the irregularity and lower size and density of dentinal tubules in the apical area [27]. Namely, the number of dentinal tubules decreases from 40,000 mm^{-2} from corona near the pulp to 14,400 mm^{-2} in the apex [30]. Moreover, lower efficacy of the irrigants in these portions of the root canal cleared out the dentinal tubules less thoroughly.

CONCLUSION

Final irrigation with CHX after initial NaOCl rinse significantly reduced dentin permeability at all root levels. Interactions between NaOCl and EDTA + CHX, QMiX or MTAD exert no significant effect on dentin permeability, except in the apical section of the root canal. Based on the current results, final irrigation with CHX after NaOCl should be avoided in order to prevent precipitate formation, which reduces dentin permeability, subsequently compromising sealing of the root canal system. On the other hand, EDTA + CHX, QMiX, or MTAD might be recommended as reasonable solutions for final irrigation. Further studies are necessary to better clarify the influence of different final irrigants on the dentin permeability.

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Испитивање пермеабилности коренског дентина после испирања различитим иригансима

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САЖЕТАК

Увод/Циљ Циљ овог истраживања је био да се испита пермеабилност коренског дентина после иригације натријум-хипохлоритом (*NaOCl*) и финалне иригације хлорхексидином (*CHX*), етилен-диамино-сирћетном киселином (*EDTA*) + *CHX* и нових комбинација: *QMiX* или *MTAD*.

Методе Корени 60 горњих централних секутића су, пре инструментације и иригације *NaOCl*, методом случајног узорка подељени у пет група ($n = 12$) на основу финалног протокола иригације: *CHX* (2% *CHX*), *EDTA* + *CHX* (17% *EDTA* + 2% *CHX*), *QMiX*, *MTAD* и контролна група (дестилована вода). После финалне иригације, десет коренова из сваке групе су хоризонтално пресечени и пенетрација боје је одређена у круничној, средњој и апексној трећини. Преостали узорци су испитивани методом електронске микроскопије. Подаци су анализирани применом *ANOVA/Tukey's* теста.

Резултати Пенетрација боје у *CHX* групи је била мања у свим трећинама у односу на контролну, као и у односу на *QMiX* и *MTAD* групу ($p < 0,05$). Значајна разлика између контролне и група *EDTA* + *CHX*, *QMiX* и *MTAD* је забележена само у апексној трећини корена ($p < 0,05$).

Закључак Пермеабилност дентина је значајно смањена после финалне иригације *CHX*, али не и после иригације другим растворима, осим у апексној трећини.

Кључне речи: чишћење зубних тубула; интраканални дезинфицијенси; хлорхексидин; *EDTA*; *MTAD*; натријум-хипохлорит; *QMiX*

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Strain visualization of supporting tissues rehabilitated using two different types of removable partial dentures

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SUMMARY

Introduction/Objective Current biomechanical analyses can provide full view of the strain induced by loading of various replacements to be used for prosthetic rehabilitation.
The aim of this study was to analyze strain distribution of supporting tissues beneath two different types of removable partial dentures, commonly indicated in the conventional rehabilitation of partially edentulous patients.

Methods This *in vitro* study included two groups of experimental models composed of the mandibles (Kenedy Class 1) and two types of removable partial dentures. These models were exposed to occlusal loading and the digital image correlation method was used for strain visualization and strain measurement.

Results The highest strain was measured beneath the removable partial dentures, on the surfaces of bone adjacent to distal abutments and in the anatomical structure called the retromolar area. Strain values in the experimental models with clasp removable partial dentures ranged 0–10%. Strain values in the experimental models with attachment – removable partial dentures ranged 0–2.3%.

Conclusion The findings showed that the attachment retaining removable partial dentures induced lower strain in the residual alveolar ridges. However, higher strain was detected in the marginal bone next to the abutment teeth.

Keywords: partially edentulous mandible; digital image correlation method; removable partial denture; bone strain

INTRODUCTION

The success or failure of the prosthetic treatment of patients rehabilitated with a removable partial denture (RPD) depends on the oral health state, the preparation designs on the available tooth structure, and the long-term prognosis of the remaining teeth [1]. Additionally, the RPD-framework design, the clasp morphology, and the extension of the RPD saddles, as well as adequately established guiding planes, properly prepared rest seats and perfectly designed milled crowns have a significant effect on ensuring a predictable and favorable prognosis for the treatment with RPDs [2, 3, 4]. Important factors like careful planning, designing, and preparation of remaining teeth are essential, since adequately prepared rest seats and precisely fitting rests will provide mutual assistance between teeth and the RPD in order to support each other [3, 4]. The design requirements must be especially considered in order to achieve proper and uniform occlusal load distribution. Properly balanced and transferred occlusal loads improve the longevity of the remaining teeth, bone, and prosthesis made to replace the missing oral structures. Therefore, a sophisticated RPD design manufactured in correlation with properly prepared abutments fulfils the functional, prophylactic, and aesthetic demands placed upon it.

Although significant explanations of biomechanical behavior of RPDs were proposed in the last few decades, our understanding of the ideal design is still lacking [2–6]. Some numerical and photoelastic models and *in vivo* analyses estimated and showed the RPD displacement under occlusal loading [3, 5–8]. Practical methods for biomechanical investigation of biomaterials and the jawbone are based on either contact or non-contact mechanisms for strain/displacement measurements [9–18].

The aim of the following study was to determine and evaluate biomechanical behaviour as the function of strain in the supporting tissues beneath two different types of RPDs most commonly used in the conventional rehabilitation of partially edentulous patients. The study employed the digital image correlation (DIC) technique for the strain determination. Following the aim of this study, the role of this study was to explain the effects of the strain produced by vertically loaded RPD replacements on supporting dental tissue. A region of interest was considered a surface that surrounded RPDs and distal retainers/abutments. In order to facilitate the interpretation of the results, we divided the region of interest into two locations

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(segments): the anterior segment (AS), corresponding the supporting bone tissue-adjacent abutment, and the posterior segment (PS), corresponds to the retromolar area.

Three sets of null hypotheses were established prior to statistical analysis:

1. Mean strain values are the same for all models;
2. Mean strain values are the same for both segments (AS, PS);
3. There is no interaction in effect between prostheses and segments of interest.

METHODS

Six dried, partially edentulous mandibles (two groups of three models) with bilaterally shortened dental arches (Kennedy Class 1) with first premolars remaining ($8 \leq n \leq 10$; n = number of the remaining teeth) were used in the experiment: three mandibles were restored with conventional clasp-retained removable partial dentures (cRPDs) and another three mandibles were restored with attachment-retained removable partial dentures (aRPDs). The mandibles were borrowed from the Laboratory for Anthropology of the Institute of Anatomy, Faculty of Medicine in Belgrade, Serbia. The donors were men, in their late sixties. The mandibles were checked to exclude any damage. The chosen mandibles were immersed in the 0.9% NaCl for eight hours to reach the volume and elasticity considered in *in vitro* experiments [12]. Following the drying procedure (27°C), the remaining teeth were prepared to receive metal ceramic restorations. Coarse and fine diamond burs were used during the preparation of the remaining teeth. The tooth preparation was done by grinding up to 2 mm of enamel, for all the axial walls and incisal and occlusal planes. The preparation procedure was followed by two impression procedures with elastomers in standard trays for obtaining two experimental models.

For the experimental models with cRPDs, the teeth were prepared to receive metal ceramic crowns and splinted in full arch reconstruction. The parallel guiding planes on proximal and lingual tooth surfaces on the crowned abutment retainers were established. The experimental model with the attachment-retained removable partial dentures (aRPDs) included units with full arch metal-ceramic crowns with ball attachments (bredent medical GmbH & Co.KG, Senden, Germany) positioned on distal surfaces of the abutment retainers. When the fixed restorations were finished, they were fitted to the models, verified, and impressions were taken for the definite RPD casts. The experimental models were restored with the following prosthetic restorations used for strain distribution evaluation: conventional RPDs with Roach clasp as the type of extra-coronal retainer that originates from the denture framework going over the buccal periodontium and reaches the tooth undercut area from a gingival direction (T-bar design) and full coverage metal-ceramic crowns on the remaining teeth and lingual rest positioned on distally milled retainers; complex RPDs with Bredent attachments (ball) positioned in the distal surfaces of the milled retainers with consideration that all the remaining teeth were splinted, as previously in cRPD models.

One peculiarity of the design of the RPDs employed in the experiment implied cutting of the buccal wings as parts of the denture-saddles in order to visualize strain during the simulated occlusal loading. The experimental models were then sprayed to enable the DIC method to perform surface-strain analysis. The distances between sprayed points were changed under vertical loading. This phenomenon was registered by cameras.

The experimental models were placed in the standard tensile testing machine (Tinius Olsen TMC, Horsham, PA, USA). The applied occlusal force was 300 N, in accordance with literature data about maximal willing force in humans and consideration that the mastication force intensity decreased by reducing the number of teeth [19]. The loading measurement was performed using the horizontal extension of the gnathodynamometer (Siemens, Munich, Germany). Occlusal (vertical) load was eccentric and it was directed at the cusps of artificial (acrylic) lower molars of the experimental models. The reason for performing only two-teeth loading was strictly experimental and was one of the inclusion criteria of the study. The acrylic teeth were loaded to visualize the strain below the partial dentures. The study included only the posterior mandible viewed from lateral aspect excluding the anterior mandible. The mandible was supported by two metallic plates within a tensile testing machine.

Strain measurement was conducted using the DIC method and the Aramis software (GOM-Optical Measuring Techniques, Braunschweig, Germany), in which stereophotogrammetric principles were used for analyzing model mobility. Generally, the system is based on two digital cameras (50 mm lenses with a 25 mm distance ring; Schneider Kreuznach, Bad Kreuznach, Germany), trigger box, PC, and the Aramis (software version 6.2.0, Braunschweig, Germany), and immediately after the calibration process, the photographing procedure was performed in accordance with the basic principles of the stereophotogrammetric measurements [15, 16]. The Aramis software used in this experiment detected three-dimensional (3D) changes on the surface of loaded objects and measured the strain automatically [12, 13].

This was experimental compressive static loading. Of the total number (n = 6) of the experimental models, four representative figures (virtual models) were selected following software-data processing and used to present the behavior of models under the load of 300 N.

Interpretation of the results was done using the following two statistical analyses for the six models (three in each group):

• Two-way ANOVA was used in order to examine the differences in effectiveness of the type of model, specific segments of interest (AS and PS) and their mutual interaction on the strain values in models. The strains in models with different kind of prostheses and strains within the specific segments of interest were compared using the two-way ANOVA. Significance level (α) was set to 0.05.

($p < 0.05$). All comparisons and calculations were made in package "stats" (Software R, Vienna, Austria).

• The post hoc t-test with Bonferroni correction; this test can compare only two values of strain at the time, and results for segments of interest and prostheses were obtained.

RESULTS

Certain differences were found between experimental models restored with two different types of RPDs under vertically loading conditions. The overall strain in the cRPD experimental models (Figures 1 and 2) was slightly higher than the strain generated in the aRPD experimental models (Figures 3 and 4). The average displacement value for the cRPD models was 0.54 mm, and 0.42 mm for the aRPD models during the loading of 300 N after software data processing. Tensile strain showed different strain propagation (Figures 1 and 3) compared to compressive strain, as seen in Figures 2 and 4. The highest tensile strain for the loading of the cRPD models was noticed just below the point of incidence in the retromolar area, and in the dried periodontium of the abutment teeth (7–10%), which is displayed showing colors determined by scales next to figures. Unlike tensile strain, the compressive strain was highly visualized along the entire zone of bone–denture contact within the upper part of the residual alveolar ridge, especially when cRPD mandible models were loaded (9–10%).

The vertical-section line, as seen in Figures 1–4, was set in software under the loading acting on acrylic lower molars. The section line changed its length before and after the experiment was performed. Obtained figures were efficient in visualizing the strain field under vertical loading. Strain values were computed by the software based on the experimental measurement. Major and minor strain values (%) were presented on the scale.

The cRPD experimental models showed higher strain values during loading (Figures 1 and 2). Major strain values in the line section of the mandibles ranged 0–10%. Major strain values for the entire section length are presented in Figure 5. The average major strain surrounding the upper part of mandibles was less than 1%. The highest strain values were noticed just below the cRPDs and in the retromolar area with the average major strain value between 6% and 7%. The buccal marginal periodontium of the distal abutments strained about 3–4%. The retentive clasps and occlusal rests strained as well (7%). The highest minor strain values (compressive strain) were especially detected in the "bone–denture" contact regions (9–10%).

For the aRPD experimental models, major and minor strain was computed under the same conditions presented in the previous cases (Figures 3 and 4). Strain values in the line section were 0–2.3%. The aRPD line-sections indicated continuity of its flow, which was quite opposite in the case of cRPD line-sections. Major strain values for the entire section length are shown in Figure 6. The average strain on the area surrounding the upper part of the mandibles was less than 1%. The highest strain values

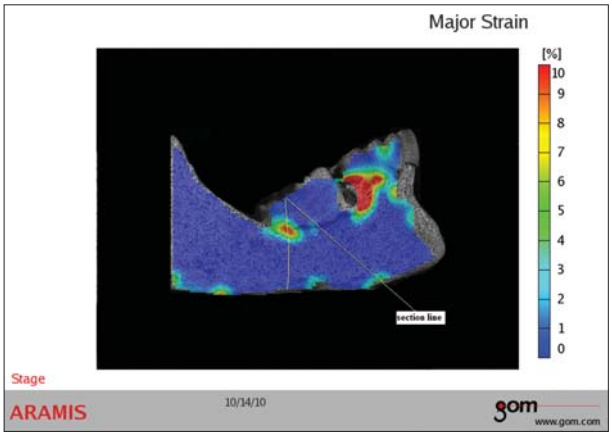

Figure 1. Major strain field of the clasp-retained removable partial dentures model showed high tensile strain up to 10% (red/yellow) around the clasp and in the retromolar area

Figure 2. Minor strain field of the clasp-retained removable partial dentures model showed high compressive strain with maximum reaching 10%, assigned to green and blue colors and negative values on the scale

Figure 3. Major strain field of the attachment-retained removable partial dentures model indicated maximum values of tensile strain in the marginal bone below the ball attachment; equal strain was found below the free-end saddle in the retromolar area

are noticed just below the RPD, with the average value of strain between 6% and 7%. The buccal marginal periodontium of the distal abutments strained 6–7%. Strain of the attachments was 2%. Minor strain showed similar direction of the strain propagation as the major strain, as seen in Figures 3 and 4.

Figure 4. Minor strain field of the attachment-retained removable partial dentures model indicated that high compressive strain corresponds to negative values on the scale assigned to yellow, green, and blue colors; in addition to the retromolar area strained due to offensive load located just above this region, strain was detected in the marginal and apical bone below the ball attachment

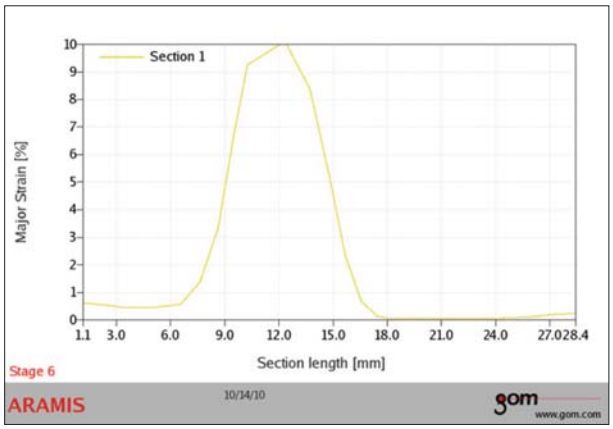

Figure 5. Clasp-retained removable partial dentures section line shows that the highest strain value in its middle segment corresponds to the upper part of the residual ridges and marginal periodontium

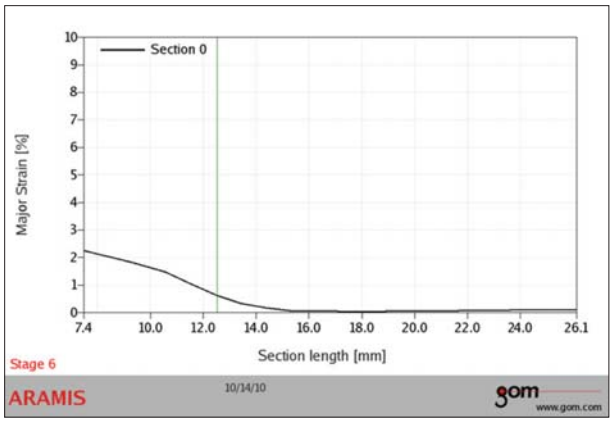

Figure 6. Attachment-retained removable partial dentures section line depicts slightly decreased values of strain along the section length unlike in the clasp-retained removable partial dentures models, which may be of high relevance for inducing uniform strain distribution

The relationship between types of the experimental models, segments of interest, and strain values is displayed in the interaction plot (Figure 7). It was noticed that cRPD models exhibited the highest strain in posterior segments of interest with the peak over 9%, while the peak strain for aRPD models was obtained in AS (6.8%). The minimum

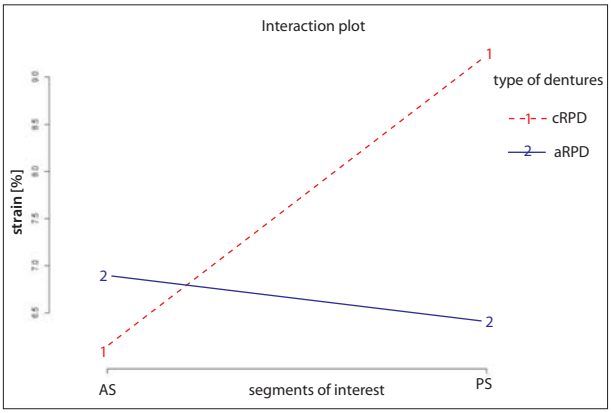

Figure 7. Attachment-retained removable partial dentures section line depicts slightly decreased values of strain along the section length unlike in the clasp-retained removable partial dentures models, which may be of high relevance for inducing uniform strain distribution

Table 1. Two-way Anova for prostheses types and segments of interest

Parameter	df	Sum of squares	Mean square	F	Pr (> F)
Prosthesis types	1	3.203	3.203	15.5	0.00431
Segments of interest	1	5.07	5.07	24.23	*0.00112
Prosthesis types: region	1	9.72	9.72	47.03	0.00013
Residuals	8	1.653	0.207		

*Probabilities for the segments of interest represent significant difference ($p < 0.001$)

strain in cRPD models was measured for AS (up to 6%). PS showed lower strain when considering aRPD models.

Significant differences in strain values between material groups ($F = 15.5$; $p = 0.00431$) were detected (Table 1). Furthermore, a statistically significant difference existed between region of interest with $F(2.18) = 24.23$, with $p = 0.00112$. Finally, there was an interaction between the type of the sample and the region of interest in the effect on strain values, with $F(4.18) = 47.03$; $p = 0.00013$.

A comparison between the two segments of interest showed a statistically significant difference in the experimental models restored with cRPDs ($p < 0.01$) and statistical insignificance for the experimental models restored with aRPDs ($p > 0.05$). Furthermore, both types of prostheses showed statistical significance for AS ($p < 0.05$) and PS ($p < 0.01$).

DISCUSSION

The study showed performances of the DIC method as a current technique employed to determine, visualize and measure the strain on mandible surfaces during the vertical loading of RPDs placed *in situ*. Full field, non-contact strain measuring was conducted using the Aramis software, which produced photos of real-time strains for every measurement stage from the pattern surface. Using two digital cameras, this optical system provided a synchronized stereo view of the specimen and sufficient data on the results showing the complete strain field during the tests. Several advantages of the DIC technique over other digital methods were established in the past: resistance

on the displacement of the observed model during the measurement process and full field of strain measurement, low sensibility to ambient vibrations, ability to register rigid body motion and to measure 3D displacements in a high dynamic range (microns to millimeters) of measuring capacity, and high reproducibility of the DIC measuring [10–14]. In dental biomechanics, DIC is often utilized for *in vitro* setups [11, 12, 13]. Whether it concerns the biomechanical behavior of the human jaw under static or dynamic load, biomechanical testing of biomaterials, or photogrammetric measurements of initial tooth displacement under tensile force, the DIC has been confirmed as a method especially suitable for 3D-strain measurements of dental materials and structures with complex geometry due to the ability to catch non-linear surface strain in the tested specimens [9, 11–18].

The study was conducted as a static, non-impact, *in vitro* loading of the experimental models with different designs of dentures positioned *in situ*. Two types of replacements were compared and the better one was determined with respect to biomechanics. Knowing of the biomechanical behaviour of hard tissues (bone and teeth) and their interaction with replacements is important for the investigation of biomaterials and designs of replacements, so this type of research can improve prognosis and treatment planning in partially edentulous subjects. The researchers used cadaveric mandibles without soft tissue coverage. This fact distinguishes the donor-related variability of the examined bone features as the key factor when performing the DIC experimental analysis. The absence of the elevator muscles and soft tissue as supportive structures, and thus the fixation of mandibles in contrast to the real (physiological) conditions, was another exclusion criteria addressed to the disadvantages of this study [20]. Nevertheless, this study investigated the upper part of the mandibles adjacent to prostheses; therefore, from the biomechanical standpoint, the results are adequate for arguing about the biomechanical behaviour of usually indicated RPDs. The study describes preparing all remaining teeth and restoring them with splinted porcelain fused to metal restorations. This was expensive, technically difficult, and required radical amounts of tooth structure removal. Nevertheless, we were guided by the fact that high percentage of partially edentulous subjects indicates signs and symptoms of periodontal disease and tooth wear of the tooth structure; thus, restoration of such teeth was considered an imperative. Additionally, treatment of the remaining teeth was done to achieve similar loading conditions of the supporting dental structure, for both types of RPD-restored experimental models, as much as possible. Following this criterion, experimental models restored with aRPDs included ball rather than slide attachment. Although both types of attachments, whether ball or slide, are indicated for rehabilitation of the Kennedy Class 1 partial edentulism, dimensions of the clinical crowns and length of the residual ridges/free-end saddles were the critical factors to opt for the ball attachments as more preferable.

In this experiment, results acquired from the Aramis system were sorted into two groups of experimental models and two groups of interest locations (segments). Dentures, as a part of the experimental models and locations of interest within the tested models, presented two factors that caused different values of strains of the loaded models. Their mutual effect on experimental models was presented in the interaction plot where the connection between experimental results was visualized.

Table 2. Comparison between prostheses types for different segments of interests (post hoc)

Segments	cRPD	aRPD	p-value	Bonferroni
AS	6.13 (0.21)	6.9 (0.4)	< 0.05	0.042
PS	9.23 (0.7)	6.4 (0.36)	< 0.01	0.0034

AS – anterior segment; PS – posterior segment; cRPD – clasp-retained removable partial dentures; aRPD – attachment-retained removable partial dentures

Table 3. Comparison between segments of interest for different prostheses types (post hoc)

Prostheses	AS	PS	p-value	Bonferroni
cRPD	6.13 (0.21)	9.23 (0.7)	< 0.01	0.0018
aRPD	6.9 (0.4)	6.4 (0.36)	> 0.05	0.18

AS – anterior segment; PS – posterior segment; cRPD – clasp-retained removable partial dentures; aRPD – attachment-retained removable partial dentures

Strains for different types of experimental models and different segments of interest were compared using two-way ANOVA. Two-way ANOVA was employed to determine whether there were statistically significant differences between the tested experimental groups. Prosthesis type and location of interest represented factors of influence. The strain was considered the dependent variable. Both factors such as prosthesis type and location of interest showed significant influence. Significant differences in the strain values existed between two groups of prostheses for both segments of interest ($p < 0.05$, $p < 0.01$; Table 2), as well as in two different locations of measured surface, but only for cRPD models ($p < 0.001$; Table 3). Although ANOVA revealed statistically significant differences between the type of the strained models, location of interest, and interaction of these two factors, this analysis could not determine between which groups of models and locations of interest these differences actually existed. Thus, additional post hoc t-test was introduced to reveal statistical significance between observed variables and to find out where these differences actually occurred. In order to provide a more valid comparison and to reduce type I error, the conservative Bonferroni correction was applied. Therefore, all three null hypotheses were rejected, and alternative ones were adopted, which state that strain was dependent from the prostheses used and from the locations within the region of interest. In addition, there was an interaction between prostheses and segments of interest in their effect on the strain values.

Although strain varied significantly between locations of interest, dentures' effect was also noticed. Namely, models with cRPDs showed highest strains for posterior locations of interest (PS) while loaded models restored with aRPDs induced the highest strain in the anterior locations of interest (AS). The cRPD models displayed the lowest

strain in the AS. Furthermore, cRPD models showed a statistically significant difference between strains in the AS and the PS, while aRPD models did not. Although anterior segments below aRPDs strained almost 1% higher than below cRPDs, PSs strained with higher statistical significance in regard to different types of prostheses.

The study investigated the impact of two types of bilaterally-distally-extended removable partial dentures on mandibles with shortened dental arches. Shortening of the buccal wings of the RPD saddles in the experimental models was done to obtain a wider field for optical observation of the upper part of the mandibles. Region of interest included upper part of mandible bone, the buccal cortical laminae below the abutments, and the retromolar area. Two different kinds of strain were presented in this study: the maximum value of minimum principal strain expressed as minor strain – compressive strain, and the maximum value of maximum principal strain, expressed as major strain – tensile strain. For a complete understanding of the biomechanical behavior of RPD-mandible models, it was necessary to take into account all major and minor strain values and not only strain within the section line.

Generally, compressive strain was generated by the compressive force (load) impact. This load affected the denture–saddle movement, which initially induced strain in the bone–denture contact area (compressive strain), and then through the entire residual alveolar ridge depending on the force intensity. Consequently, resulted tensile strain increased the mandible resistance, thus contributing to mandibles withstanding the compressive force load. The type of replacements and connection with the distal abutments may also influence the major and minor strain values. Practically, the study investigated two different modalities of RPDs through comparing the tensile and compressive strain between them.

When an RPD was considered to replace missing posterior teeth in the distal free-end edentulous ridges, careful planning of design was very important. Namely, in this situation we had to restore biologically two different tissues in order to achieve uniform distribution of the occlusal forces on the periodontal tissue of the remaining teeth and in the mucoperiosteum on the edentulous alveolar ridges. Most of the cases with bilateral shortened dental arch require specific management of the remaining teeth. Fixed restorations – full crowns – have been usually used for this purpose. In this research, the restorations of choice were full-arch metal-ceramic crowns. The milled guiding planes on the lingual and proximal surfaces of these restorations improved the retention and stability of dentures [4]. While the cast circumferential clasp causes some kind of elastic connection between the abutment and the RPD, when precision attachments were selected to retain an RPD, a removable prosthesis was "rigidly" connected to the abutment teeth.

The cRPD experimental models were fabricated to minimize the torque applied to the abutments by splinting all remaining teeth into one single unit composed of the full cast restoration prepared to receive clasp-retained RPDs. The RPDs made in this way provided displacement of the free-end saddles toward the edentulous ridge during vertical loading conditions. The displacement caused load transfer toward the mandibular edentulous ridge, which resulted in the appearance of a large amount of strain beneath the denture saddle, as seen in Figures 1 and 2. When the functional occlusal load is induced on this kind of distal extension RPD, rotary movement usually occurs around the fulcrum of the terminal abutments [5, 8]. This phenomenon not only decreases the denture function and causes the patient's discomfort, but also traumatizes the supporting tissues of dentures. A good design for a distal-extension RPD should prevent rotary movement in order to protect the supporting tissues.

In contrast to the cRPD models, the aRPD models had all the remaining teeth splinted in the full-arch metal-ceramics retained with attachments to RPDs. The RPDs retained in such a way fulfil a current demand for rehabilitation of the oral function and for protection of remaining teeth and residual ridges. These "rigid design dentures" with rigid precision ball attachments are considered to be less mobile/movable compared to dentures with resilient attachments [2]. As we know, rigid precision attachments have different mechanisms; nevertheless, the variation in the transfer of functional loads between conventional RPDs and complex RPDs has not been clarified yet.

The models were subjected to the vertical forces. Vertical displacement of the denture base presented in this study was a consequence of the compressive vertical load. Clinically, occlusal rests or attachments must resist multidirectional loads. Hence, the influence of the mentioned factors should be considered in future investigations before any conclusion is made.

The cRPD models showed a higher score of the overall strain than aRPD models, including especially the compressive (minor) strain. This means that the whole denture saddles compressed residual alveolar ridges because of the elastic properties of the cast clasps. This could be explained by different kinds of connections within two types of prostheses. In the case of aRPD models, higher tensile (major) strain was found in the bone adjacent to the distal abutments, especially concerning the marginal bone, than in cRPD models, as a consequence of the rigid connection. Nevertheless, residual alveolar ridges of cRPD models showed higher tensile strain than those in the aRPD models. Generally, the major strain (tensile strain) in the bone adjacent to the distal abutments showed lower values of intensity compared to strain of the alveolar ridges. This can be explained by the fact that splinted metal-ceramic crowns distributed lesser strain to the supporting structures, i.e. adjacent bone and abutments [13]. The idea of rigidly connected adjacent teeth was supported by a previous investigation, which confirmed the equitable distribution of strain to each single abutment and retainer in the block construction [21]. The effect of splinting adjacent teeth was limited locally, considering that the direction of strain was found in the upper part of all models.

Our findings confirm previous ones regarding the association between the rigidity of connection to the abutment and denture mobility [3]. Clasp-retained RPDs were supposed

to be more elastic than attachment RPDs, and therefore higher mobility of cRPDs was observed. Thus, higher rate of strain can be expected beneath cRPDs. In contrast, the flexibility of the attachment was lower and needed less amount of bone tissue support under the denture base.

Attachment RPDs may not be suitable therapy solutions in cases of periodontally weakened abutment teeth due to instability and therapeutic failure. These situations request splinting of periodontally compromised teeth into single unit followed by adequately designed and adjusted RPDs with consideration of the denture extension and the level of periodontal damage [12, 21].

CONCLUSION

Visualizing the biomechanical behaviour of RPDs placed *in situ* on supporting dental tissues can improve the design of RPDs and preserve abutment teeth and bone. This will avoid possible failures in current dental practice. Within limitations and based on the results of this study, it can be said that higher strain was observed below the clasp RPDs, particularly if we consider movement of the distal portion of the free-end saddles caused by the teeth and dentures' vertical displacement. The findings proved that attachment RPDs generated less strain in the residual alveolar ridges, and thus, from the biomechanical standpoint, can be considered a better choice for the rehabilitation of the Kennedy Class 1 partial edentulism compared to clasp RPDs. However, high strain was found in the bone adjacent to distal abutments. In accordance with the tasks provided by null hypothesis, the following conclusions were derived:

1. The mean strain was significantly different for all models, when its distribution and values are considered. This fact could be the reason for differences that exist between two types of RPDs with different types of connections with the adjacent teeth.
2. The mean strain values showed significant differences between mandibular AS and PS of cRPD models. However, the mean strain in AS and PS was similar in aRPD models probably due to the fact that aRPDs generated uniform strain distribution in mandibles compared to cRPDs.
3. The findings provide a noticeable difference in the effect induced by interactions between prostheses and segments of interest due to incremental movements of two types of RPDs toward the residual ridges.

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Визуелизација деформација у потпорним ткивима рехабилитованим са два различита типа парцијалних скелетираних протеза

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САЖЕТАК

Увод/Циљ Савремене биомеханичке анализе омогућавају комплетну визуелизацију деформација од оптерећивања различитих зубних надокнада у протетској рехабилитацији. Циљ ове студије је био да анализа дистрибуције деформација унутар потпорних ткива испод два различита типа најчешће коришћених парцијалних скелетираних протеза.

Методе *In vitro* студија је обухватила две групе експерименталних модела доњих вилица (Кенеди 1 класа крезубости) и два типа парцијалних скелетираних протеза. Модели су били изложени оклузалним силама, а за приказ и мерење деформација је коришћена метода дигиталне корелације слика.

Резултати Највећа деформација је измерена испод парцијалних протеза, на површинама кости која окружује дистално зубе носаче и у ретромоларној регији. Вредности деформација у експерименталним моделима са протезама ретинираним ливеним кукицама су биле 0–10%. Вредности деформација у експерименталним моделима са протезама ретинираним атечменима су биле 0–2,3%.

Закључак Парцијалне скелетиране протезе са атечменима индуковале су мање деформације резидуалног алвеоларног гребена. Веће деформације су уочене у маргиналној кости која је у непосредном контакту са зубима носачима.

Кључне речи: крезубе доње вилице; метода дигиталне корелације слика; парцијална скелетирана протеза; деформација кости

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Factors affecting patient satisfaction in the health care sector in Serbia

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SUMMARY
Introduction/Objective The aim of this paper was to highlight and understand factors that influence the quality of healthcare services in Serbia in private and public health institutions.
Methods The data was collected during May of 2017 and June of 2017 through an on-field questionnaire. Out of 500 questionnaires in total, 406 were completed and returned, resulting in a response rate of 81.2%.
Results The following four most influential factors for patient satisfaction in Serbia's healthcare sector were identified: admission process, doctor care, staff care, and technology tools.
Conclusion The model describes that 66.2 variance for the doctor care variable is based on three constructs: admission process, technology tools, and staff care. The hypothesis that technology tools will have a positive effect on staff care was not confirmed.
Keywords: patient satisfaction, factors; health care; Serbia

INTRODUCTION

Patient satisfaction is a way to measure the overall quality of delivered healthcare services. Understanding patients as clients and taking care of their needs is crucial for improvement of the healthcare sector in Serbia. A research study by Savić and Jakovljević [1] also confirms that a patient perspective is important for clinical decision making in Serbia. The main responsibility for defining and executing the patient satisfaction strategy is borne by health care managers. They constantly receive patient feedback about all aspects of health care, which affects customer retention and are in the position to adapt to dynamic market conditions. The healthcare sector in Serbia is comprised of the public and the private system for treating patients. The health system of Serbia employs some 130,000 workers. The largest number is employed in health institutions, primarily in the 70 state hospitals. There are approximately 1,200 private medical entities in Serbia, out of which 60 are hospitals. They employ over 3,700 doctors, accounting for about 10% of the total number of doctors in the health sector in Serbia [2]. In the past 30 years, the health system in Serbia has changed substantially. After the breakup of Yugoslavia in the 90s, all the weaknesses and strengths of the healthcare system of that time have become more visible. Knowledge of factors that influence patient satisfaction is of great importance for the system. The country has entered the period of transition, and the creators of healthcare policies have been forced to start reforming the healthcare system by addressing structural, human resources, financing, and organizational issues [3]. In a recent research study, health policy, socioeconomic transition, trends in healthcare resources, and outcomes were observed among three historical health-policy legacies in Southeastern Europe. Significant differences exist between Serbia as the representative of former Yugoslav countries, post-Semashko countries, and free market SEE economies [4].

In order to improve the healthcare system in Serbia, it is necessary to understand the opinion of patients as clients of healthcare services. However, previous research in this field has identified different factors for patient dissatisfaction. Authors from Brazil highlighted the main weaknesses as follows: lack of qualified professionals for exercising management activities, delay in implementing new information technologies and management and work organizational process deficiencies. The main reasons for dissatisfaction with the healthcare system in Serbia are similar to Brazil – unequal delivery of quality in different health services, waiting time for certain medical procedures and interventions, inefficient use of health technologies, and dissatisfaction of the healthcare system staff [5, 6]. Scholars point out that knowledge-based resource allocation still has to make roots in health policy traditions of BRICS and other emerging nations [7].

A recent study from Balkan countries including Macedonia, Bulgaria, and Serbia identified the top three indicators of patient satisfaction: trust, attention of doctors, and perceived outcome of the treatment. Long waiting time, huge administrative procedures and patient privacy protection are also issues for concern in all three countries [8].

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Patient quality perceptions have been shown to account for 17–27% of variation in a hospital's financial measures such as earnings, net revenue, and asset returns [9]. It is one of the most effective key performance indicators if healthcare institutions want to evaluate business success on the market. Today it is important to recognize the role of patient-centered care. According to Irwin and Richardson [10], patient-focused care can be thought of as a merging of patient education, self-care, and evidence-based models of medical practice: communication with patients, partnerships, health promotion, and physical care (medications and treatments). The main goal of each health care institution is to recognize the factors that will improve patient-centered care.

Various research studies, which investigated factors that affect patient satisfaction, were analyzed.

The first literature stream relevant for this study is general literature on patient satisfaction. Naidu [11] conducted a systematic review of factors determining health care quality and patient satisfaction with 24 articles from international journals. A comprehensive model was made to better understand healthcare services. Healthcare services are difficult to evaluate: some authors feel patient perceptions are valuable healthcare quality indicators, others contend that health service quality should be evaluated by experts. The SERVQUAL instrument is used in many patient satisfaction studies. Dimensions that determine patient satisfaction have been identified, including: reliability – the ability to perform the promised service, dependably and accurately; assurance – employee knowledge and courtesy and their ability to convey trust and confidence; responsiveness – willingness to help customers and provide prompt services; empathy – caring, individualized attention the firm provides to its customers; and tangibles – physical facilities, equipment and appearance of the personnel. Another study written by Batbaatar et al. [12] reviewed studies of patient satisfaction between 1980 and 2014. Socio-demographic and personal-related characteristics were analyzed in the review.

The second type of study investigated the use of technology in health care and its effect on patient satisfaction. A study from Bangladesh implies medical treatment of the hospital, service of the hospital staff, hospital facilities, and technology are factors that affect patient satisfaction [13]. The population aging trends in the Next-11 nations have led to increased health care expenditures [14]. On the other hand, the millennial generation for health providers is crucial for understanding what content needs to be available at patient portals on mobile devices.

However, a recent study concerning health service in Serbia suggested the most common determinants of citizen satisfaction with health care are age, health condition, income, type of service (state or private sector), communication, politeness of staff, and the overall hospital environment [15]. Student satisfaction with the quality of service provided by student polyclinics showed that personal relationships had the most tangible impact on student satisfaction while promptness of service was also important [16]. Additionally, health managers from Serbia focus their efforts on ensuring the competence of employees while managers from health care organizations from Slovenia are more external-oriented [17]. The analysis of previous literature revealed the need to develop a model for identifying the most important factors for patient satisfaction in Serbia and their relationships.

The aim of this study is to determine factors that influence patient satisfaction, as it is an indicator of quality health care in Serbia [18]. The findings should encourage a shift in the attitude and relations of hospital staff with patients towards a more client/consumer-oriented healthcare service. The main reason is that better customer satisfaction leads to better customer loyalty for healthcare institutions.

METHODS

The research framework

The research framework of this study was based on the study by Otani et al. [19], which includes five elements for defining the initial conceptual model: admission process, doctor care, staff care, food, and room in the hospital. This study's scope did not include food and room as the research aimed to evaluate patient perceptions before they have stayed in healthcare institutions. A research study of various large hospitals in the USA investigated the relationship of doctor care and doctor environment to overall patient satisfaction. The results showed that all attributes were statistically significant and positively related to overall satisfaction [20].

Several studies have already proved that courtesy and efficiency of admission processes in health provider institutions are significant for patient satisfaction and waiting times [21, 22, 23]. The admission processes in this study consist of three elements: promptness or efficiency of the admission or registration, courtesy and helpfulness of the admission or registration, and waiting time for medical treatment.

Staff care is another important factor for determination of patient satisfaction. It should be evaluated from two sides. Firstly, staff care is about the willingness to help patients if they have questions or concerns. Secondly, staff care is about providing clear and complete explanations about how patients should practice self-care at home. Again, the emphasis is about clear communication with patients.

In the health service sector, it is crucial to ensure availability of doctors when patients need them [24]. Communication with a doctor usually develops trust with the patient and promotes patients' desire to understand health treatment.

There are also some differences regarding patient satisfaction with healthcare providers based on age. Taking a look at the health habits of the millennial, baby-boomer, and X generations, health institutions can better understand how to provide personal relationships and integrate health IT tools into the care process to create the best

Table 1. Factors of the initial conceptual model

Construct	Construct type	Items (given on a 1 to 5 Likert scale)	Variable name
Admission process	Reflective	Promptness of the efficiency of the admission or registration	AP1
		Courtesy and helpfulness of the admission or registration	AP2
		Waiting time for medical treatment is short	AP3
Doctor (physician) care	Reflective	Availability of your doctor when needed	DC1
		Doctor ability to communicate with you	DC2
		Doctor ability to provide adequate instructions or explanation of your treatment or test	DC3
Staff care	Reflective	Staff willingness to help if you have question or concern	SC1
		Clear and complete explanation provided by the staff on how to care about yourself at home	SC2
Technology tools	Reflective	Healthcare institution ability to provide on line admission process	TT1
		Health care institution ability to provide online doctor advice	TT2
		Possibility to track health condition using mobile application	TT3

patient outcomes. A large portion of this study's sample were millennial patients (51%) and the main results from previous studies refer that they prefer a strong doctor connection, adequate time for discussion, and verbal communication of recommendations. Younger generations abroad have unique preferences when they discuss health technology (tele-health, mobile health applications). This is supported by a previous research study from Bangladesh, according to which technology in health care is one of the most important factors that affects patient satisfaction. Three items can describe construct technology including a connection with admission processes (healthcare institution's ability to provide online admission processes), a connection with doctors (healthcare institution's ability to provide online doctor advice), and tracking health conditions (the possibility to track health conditions using mobile applications), see Table 1.

The set of relationships is given in a form of hypotheses that our model is testing (Figure 1):

H1: The quality of the admission process will have a positive effect on doctor care;

H2: The technology tools will have a positive effect on the admission process;

H3: The staff care will have a positive effect on doctor care;

H4: The technology tools will have a positive effect on doctor care;

H5: The technology tools will have a positive effect on staff care.

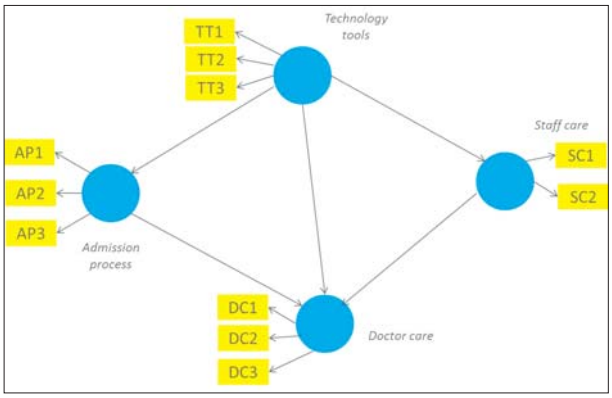

Figure 1. Initial theoretical research model

Data collection and sample size

Data were collected with a structured on-field questionnaire from different hospitals located in Serbia. We covered all regions in Serbia including Vojvodina (102), Belgrade (126), Šumadija and Western Serbia (94), and Southern and Eastern Serbia (84). The data was collected during May of 2017 and June of 2017. Out of 500 questionnaires in total, 406 were completed and returned, resulting in a response rate of 81.2%. Distribution of the background characteristics of the patients are regarding gender – 45.32% (184) were males, while 54.67% (222) were females. The majority of patients were young. The age groups of 18–29 years and 30–39 years comprised 51.23% (208) and 31.53% (128) of the total sample surveyed, respectively. Those 50 years old and above constituted only 17.24% (70) of the total sample. The responses for the patient satisfaction indicators were presented over the five-point Likert scale, ranging from highly unsatisfied to highly satisfied. After expiration of the surveying period and acquisition of the satisfactory number of completed surveys, the results were coded and entered into the IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY, USA). Following good practice, prior to data analysis, error screening and data cleaning were undertaken. After ensuring that there are no missing values or values that fall outside of defined ranges, data analysis proceeded. The following statistical tools were used: descriptive statistics (means, frequencies) for capturing average values on the examined issues, and factor analysis for analyzing patient perception of health care factors in choosing a healthcare institution.

Data analysis

The model was constructed and analyzed using the SmartPLS 3 (SmartPLS GmbH, Bönningstedt, Germany). SmartPLS 3 supports work with covariance-based structural equation models, and is particularly useful when working with small samples such as the sample evident in this study (n = 406). PLS analysis is a two-stage process [25].

Following the analytical procedures, the measurement model was examined first, followed by the structural model. The test of the measurement model includes an estimation of internal consistency (composite and indicator reliability), convergent validity, and discriminate validity. The second stage of PLS modelling is an assessment of the structural model. The rationale of this two-step approach is to ensure that the conclusion on structural relationships is drawn from a set of measurement instruments with suitable properties. PLS path modelling does not provide any global goodness-of-fit criterion.

RESULTS

The results of the final model based on the initial research model are presented in Figure 2. At the significant level of 5%, according to the results, the study found that the quality of the admission process was a significant factor and positively affects doctor care. In the second relationship, interaction with technological tools, patients report positively influenced admission process, and they want to book, track, and receive advice online about health care conditions. In the third relationship, the impacts of interaction with staff care, patients report that doctor care was statistically significant. Finally, in the fourth relationship, technology tools and doctor care, these significantly influenced patient satisfaction. The remaining hypothesis technology tools do not significantly affect staff care. The reason for this could align with age differences and the time to adapt to using technology in the healthcare system.

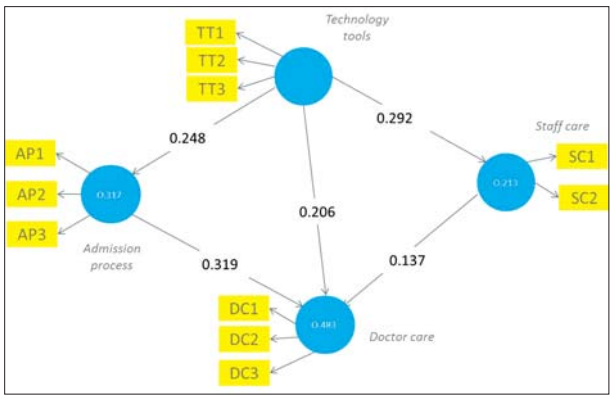

Figure 2. Model of factors affecting patient satisfaction

The model describes that 66.2 variance for the doctor care variable is based on three constructs: admission process (0.319), staff care (0.137), and technology tools (0.206). The first factor, admission process, emphasizes health process quality. It envelopes the following items: service is performed quickly; staff is willing to help patients with appointments; and staff tries to respond to patient requests. Score of latent variable doctor care is 4.20/5.00, which means that patients are mostly satisfied with doctor care.

In addition, the model explains that 42.9 variance for the staff care variable is based on two constructs: technology tools (0.292) and doctor care (0.137). Patients agree that using modern technology tools with staff care may increase patients' satisfaction. For the older population, it is crucial for hospital staff to provide clear instructions about health treatment at home.

Additionally, 56.7 variance for the admission process variable is based on only one construct: technology tools (0.248). It will be important in the future to investigate what other factors can explain the constructs in the model. This study found that health service from early stages is a service aimed at building relationships with patients. On the other hand, services provided after the transaction is a service that will always be remembered by the patient.

DISCUSSION

Given all indicators discussed, the model has good performance given its parsimony. The findings showed that the four hypotheses are confirmed (see Table 2).

Table 2. Hypotheses testing results

Hypotheses	Decision
H_1: The quality of the admission process will have a positive effect on the doctor care	Confirmed at 1% confidence level
H_2: Technology tools will have a positive effect on the admission process	Confirmed at 1% confidence level
H_3: Staff care will have a positive effect on the doctor care	Confirmed at 1% confidence level
H_4: Technology tools will have a positive effect on the doctor care	Confirmed at 1% confidence level
H_5: Technology tools will have a positive effect on the staff care	Not confirmed

The research hypotheses were tested using the questionnaire survey responses from 406 patients from Serbia from public and private health institutions. The main finding of this research is that patient satisfaction is determined by different factors – professional (doctor) care and staff care. Also, two important factors are the admission process and technology tools for healthcare institutions.

The first hypothesis confirmed the quality of the admission process would have a positive effect on doctor care. Promptness of the efficiency of the admission or registration, courtesy and helpfulness of the admission or registration, and short waiting time for medical treatment are important factors that affect patient opinion and have strong correlation with doctor care: ability to communicate with patients and provide adequate instructions or explanation of patients' treatment or test. Similar results are also confirmed in a similar study undertaken in Japan [26]. Items that described process quality – the service speed and the quality of the patient–provider interaction – seem to be greatly valued by Japanese patients.

The research model also explains that technological tools have a positive effect on the doctor, staff, and admission process. This finding is similar to results from other studies, which showed using mobile apps for patient health needs improved satisfaction [27, 28]. Mobile devices and the use of health-related applications is growing rapidly in the USA and provides many benefits for health providers

– increased access to point-of-care tools, which has been shown to support better clinical decision-making and improved patient outcomes [29]. Diagnosaurus is an example of a popular low-cost mobile differential diagnosis app for patients, presented on iPhone, iPad, and iTouch [30]. The influence of technology on a doctor's role is also an important relationship for future investigation. Regardless of doctors' technical competence, their ability to deal with patients and influence their behaviour will depend more on their personality and attitude [31]. Leadership skills are playing an important role in doctor care development. Our results highlight the importance of developing more technology tools in the healthcare sector in Serbia and providing education for patients, doctors, and staff for using these tools. Furthermore, resource constraints are influencing the quality of medical care in the Eastern European region and the Balkans. It is necessary to develop better healthcare planning practice for a more systematic policy approach in the future [32].

The third hypothesis that staff care would have a positive effect on doctor care is confirmed. It is important for the staff to be willing to help with patient questions and concerns such as doctor availability. Additionally, a professional approach is important for developing patient trust.

CONCLUSION

Public and private healthcare providers need well-planned marketing strategies to strengthen health service quality that improves patient perceptions. Findings suggest that healthcare providers in Serbia should encourage their doctors to assign more time to their patients if they wish to improve overall satisfaction of their patients with the delivered services. Another important remark is that a marketing strategy should be adapted to different target populations. For the older population in Serbia, doctors should focus more on developing a personal relationship while for the younger generation they should use technological tools along with personal relationships.

This study has certain limitations. Further research on Serbian health system satisfaction would require extending the research population, composed of health service specialists, so that it would be representative of the whole country, by consulting healthcare managers and including additional variables in the research. It would seem, therefore, that further empirical research is needed in order to determine an adequate marketing strategy for the millennial generation in order to find the right balance between the use of technology and personal relationship development.

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Фактори који утичу на задовољство болесника у здравственом сектору у Србији

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САЖЕТАК

Увод/Циљ Циљ овог рада је да истакне факторе који утичу на квалитет здравствених услуга у приватним и јавним здравственим установама у Србији.

Методе Подаци су прикупљени маја и јуна 2017. године путем анкетног упитника. Укупно је примљено 406 попуњених упитника од 500, што је 81,2% одговора.

Резултати Идентификована су четири важна фактора која највише утичу на задовољство болесника у здравственом сектору у Србији: процес пријема, лекар, особље и технолошки алати.

Закључак Модел описује да је варијабла брига лекара од 66,2 базирана на процесу пријема, технолошким алатима и нези особља. Хипотеза да ће технолошки алати имати позитиван ефекат на бригу о особљу није потврђена.

Кључне речи: задовољство болесника, фактори; здравствена заштита; Србија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Restless legs syndrome in patients with distal diabetic polyneuropathy

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SUMMARY
Introduction/Objective An association between restless legs syndrome (RLS) and etiologically different polyneuropathies is well established. However, the investigations about the prevalence of RLS in diabetic polyneuropathy (DP) have led to controversy.
Our study objective was to determine the frequency of RLS in patients with distal symmetrical polyneuropathy in patients with diabetes and identify possible risk factors for its occurrence in this group of patients.
Method We investigated 101 consecutive patients with distal DP. RLS was diagnosed according to the International RLS Study Group diagnostic criteria. The distal symmetrical polyneuropathy was confirmed by the electromyoneurographic study performed in each patient.
Results Overall RLS was present in 27 (26.73%) patients. The comparison between patients with and without RLS revealed that the RLS+ group included more women than men (14.85/9.90% *vs.* 35.64/37.62%, non-significant), patients were significantly younger (60.58 ± 10.54 *vs.* 65.57 ± 10.94 years, $p \leq 0.05$), sensory polyneuropathy was significantly more common (17/27 *vs.* 34/74, $p \leq 0.05$); the average level of the total serum calcium concentration was higher in the RLS + group than in non-RLS (2.43 ± 0.26 *vs.* 2.28 ± 0.39; $p \leq 0.05$). However, multivariate logistic regression analysis did not demonstrate these as significant independent risk factors for RLS in DP.
Conclusions RLS is common in DP and occurs in more than a quarter of these patients. Though sensory forms and higher total serum calcium concentration were associated with RLS, neither of these has been identified as a significant single risk factor for the development of RLS in DP.
Keywords: restless legs syndrome; diabetes mellitus; polyneuropathy

INTRODUCTION

Restless legs syndrome (RLS) causes an irresistible urge to move legs, usually accompanied by unpleasant sensations in them. The symptoms occur at rest, usually before sleep, and after an activity or stretching they subside [1]. Thus far, the assumption is that central dopaminergic dysfunction contributes to the disease pathogenesis [2]. The disorder can be primary and secondary. Forty to sixty percent of patients with primary RLS have a positive family history with autosomal dominant inheritance [3]. Secondary RLS can coincide with various conditions such as iron deficiency, low ferritin level, renal failure, and anemia, especially during pregnancy [4, 5, 6]. An association between RLS and etiologically different polyneuropathies, including diabetic neuropathy, has been suggested in previous studies [7, 8]. However, the investigations about a link between RLS and diabetic neuropathy has led to controversy; while some authors found a high prevalence of RLS in diabetic neuropathy, others did not [9, 10].

Our study objective was to determine the frequency of RLS in patients with distal symmetrical polyneuropathy in patients with diabetes mellitus and to identify possible risk factors for its occurrence in this group of patients.

METHODS

The study was conducted at the Clinical Department of Neurology of the University Medical Center Zvezdara. It included 101 consecutive patients with diabetes mellitus and confirmed diabetic polyneuropathy. Patients on dialysis, rapidly deteriorating patients, patients with other conditions that could cause RLS, as well as pregnant women, were excluded from the study. All patients voluntary participated in the study and signed written informed consent.

The original questionnaire (Table 1) was used to obtain demographic data and data about related conditions – diabetes, polyneuropathy, and RLS. Relevant essentials for each condition were the age at the time of the onset, the duration of the disease, its course, as well as a temporal relationship between them. Also, other concomitant illnesses and medications were registered.

One of the investigators performed clinical neurological examination of all the patients. The distal symmetrical polyneuropathy was diagnosed in patients with the clinical finding of the diffuse distal involvement of peripheral nerves on the extremities. The second investigator performed an electroneurophysiological study in all the patients and confirmed the diagnosis of polyneuropathy, using electromyoneurographic

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Table 1. Questionnaire

Name and surname
Gender M F
Age at observation (years)
Diabetes mellitus (DM)
Age at onset of DM (years)
Disease duration of DM (years)
DM type: I II
DM therapy
Duration of therapy for DM (years)
Age at onset of polyneuropathy (years)
Duration of polyneuropathy (years)
Concomitant illness
Blood donor: YES NO
No. of donations in the past 3 years
Blood transfusions: YES NO
No. of transfusions in the past 3 years
Habits
Coffee intake: YES NO
Duration of habit (years)
Cups of coffee No./day
Smoking: YES NO
Duration of habit (years)
Cigarettes No./day
Alcohol: YES NO
Duration of habits (years)
Restless legs syndrome (RLS): YES NO
Duration of symptoms (years)
Age at the onset of RLS (years)
Family history: YES NO

criteria [11]. Based on the symptoms, according to Wolf's criteria, polyneuropathy was classified as sensory, motor, or sensorimotor [12].

The third neurologist, blinded for the clinical and neurophysiological evaluation, established the diagnosis of RLS. The patients were diagnosed as RLS only if all four diagnostic criteria were present, defined by the International RLS Study Group: 1. an urge to move the legs, usually accompanied or caused by unpleasant and uncomfortable sensations in the legs; 2. the urge to move or unpleasant sensation begins or worsens during periods of rest or inactivity, such as lying down or sitting; 3. the urge to move or an unpleasant sensation are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; 4. the urge to move or unpleasant sensations are stronger in the evening or at night than during the day, or only occur in the evening or at night [1]. At the onset of the investigation, new criteria have not been defined [13].

A blood sample was taken from every patient and complete blood count, hematocrit, concentration of hemoglobin, ferritin, iron, electrolytes, blood urea nitrogen, cholesterol, cholesterol fractions, and triglycerides were determined.

Statistical analysis included methods of descriptive statistics, Student's t-test, and χ^2 test. Logistic regression analysis assessed the importance of the risk factors, and odds ratio measured the effect with a 95% confidence interval. A p-value of 0.05 or less was considered statistically significant.

RESULTS

The study involved 52 (52.5%) men and 49 (47.5%) women, with a mean age of 64.13 ± 11.02 years. One third of the patients had diabetes mellitus type I (34/101) and two thirds had diabetes mellitus type II (67/101), which persisted 12.64 ± 8.1 years on average. RLS was present in 27 (26.73%) patients, of whom 13 patients had diabetes mellitus type I and 14 patients had diabetes mellitus type II.

The comparison between patients with and without RLS was performed (RLS+ and RLS- group, respectively). There were more women than men in the RLS+ group (14.85/9.90% *vs.* 35.64/37.62%, non-significant), and this group of patients was significantly younger than patients without RLS (60.58 ± 10.54 *vs.* 65.57 ± 10.94 years, p ≤ 0.05).

No difference in the type of diabetes, duration of diabetes, or duration of diabetic polyneuropathy was found between the groups (Table 2). However, the type of distal

Table 2. Comparison of patients with and without restless legs syndrome in distal diabetic polyneuropathy

Parameter	RLS+ (n = 27)	RLS- (n = 74)	p
Sex M/F	10/15	38/36	ns
Current age (mean ± SD, years)	60.58 ± 10.54	65.57 ± 10.94	p ≤ 0.05
DM type I/II	13/14	21/53	ns
Duration DM (mean ± SD, years)	5.56 ± 5.74	12.84 ± 8.72	ns
Duration of polyneuropathy (mean ± SD, years)	4.47 ± 3.22	6.05 ± 5.64	ns
MCV (mean ± SD, cm)	36.38 ± 9.07	36.26 ± 8.14	ns
Latency (mean ± SD, cm)	5.16 ± 3.89	5.56 ± 4.72	ns
SCV (mean ± SD, cm)	29.62 ± 10.01	29.75 ± 9.90	ns
Er	4.21 ± 1.21	4.41 ± 0.74	ns
Hct	39.27 ± 4.09	39.14 ± 4.42	ns
Ferritin	173.93 ± 189.20	175.87 ± 143.66	ns
Na+	140.82 ± 3.49	138.10 ± 8.38	ns
K+	5.16 ± 4.14	5.36 ± 4.16	ns
Ca_2+	2.43 ± 0.26	2.28 ± 0.39	p ≤ 0.05
Mg	0.94 ± 0.46	0.79 ± 0.081	ns
Cholesterol	5.94 ± 1.50	5.82 ± 1.164	ns
Triglyceride	2.57 ± 1.87	2.39 ± 1.65	ns

RLS – restless legs syndrome; DM – diabetes mellitus; SD – standard deviation; ns – non-significant; MCV – motor nerve conduction velocities; SCV – sensitive nerve conduction velocities; Hct – hematocrit; Er – erythrocytes

peripheral neuropathy was different: sensory polyneuropathy was significantly more common in the RLS+ group (17/27 *vs.* 34/74, $p \leq 0.05$), while sensorimotor polyneuropathy was significantly more common in the RLS- patients (10/27 *vs.* 40/74, $p \leq 0.05$).

Comparing laboratory parameters, the only statistically significant difference was found in the average level of total serum calcium concentration: it was higher in the RLS+ group than in the non-RLS patients (2.43 ± 0.26 *vs.* 2.28 ± 0.39, $p \leq 0.05$). The complete blood count, iron and ferritin levels, electrolytes, and serum lipids concentrations were not different between the groups (Table 2).

Univariate logistic regression analysis revealed that total serum calcium concentrations ($p = 0.025$) and nerve conduction latency ($p = 0.048$) were associated with RLS. However, multivariate logistic regression analysis did not demonstrate these as significant independent risk factors for RLS in diabetic polyneuropathy.

DISCUSSION

Our results confirmed that RLS was common in patients with diabetic polyneuropathy: almost a quarter of them had RLS (26.73%), which was significantly more than in the general population (7–10%) [14]. According to other studies, the number of patients with polyneuropathy and RLS varies from 5.2% up to 36%, and this difference was the aftermath of diverse study designs [15, 16]. However, most studies have shown an alliance between RLS and neuropathy, despite whether they analyzed RLS frequency in patients with neuropathy or the frequency of neuropathy in patients with RLS [7, 16–19]. Our results were consistent with the results of Lopes et al. [19], who found RLS in 27 patients from the group of 100 patients with diabetes, and 25 of those 27 patients had neuropathy as well. Gemignani et al. [18] reported a somewhat higher frequency of RLS in patients with diabetic neuropathy (33.3%), especially in patients with distal diabetic polyneuropathy. Slightly lower prevalence of RLS in our group, compared with the results of Gemignani et al. [18], could be explained by the decision to include only patients with electrophysiologically confirmed neuropathy; consequently, the patients with small-fiber neuropathy could not qualify. Other authors, however, did not corroborate the frequency difference of RLS in diabetics and controls [10]. Since patients inform about similar symptoms in neuropathy and RLS, symptoms overlap and RLS could be overlooked in patients with neuropathy. Some authors suggested that in every patient with a suspected neuropathy, an interview focused on RLS criteria should be performed [20].

Results of this study showed that RLS is more common in patients with sensory polyneuropathy, the same as previously found by other authors [9], who particularly emphasized the association of RLS and sensory small-fiber neuropathy [18]. Further assumption was that abnormal inputs from the periphery activate spinal generators so that RLS is not exclusively associated with central dopaminergic dysfunction but possibly starts on a different level of the nervous system, either central or peripheral [18].

Our RLS patients were younger than those without RLS. The observation was interesting because, although children may have RLS, epidemiological studies have shown that it occurs most frequently in the middle-aged and that the incidence rises with age [4]. The results in the literature differ: while some authors concluded that patients with RLS are older than controls, others did not find this difference [8, 10, 16, 17, 18, 21].

In our RLS + group, women were slightly more represented, which was determined in the majority of trials, although there are papers where there is no difference between sexes [7, 16, 21]. Other female patients (without neuropathy) also have RLS more often, but the connection between RLS and anemia or pregnancy was established [4, 5].

We did not find the difference in serum iron and ferritin levels between patients with and without RLS. Numerous studies have suggested the association of iron metabolism and low serum ferritin with RLS, and several studies have shown that the severity of RLS correlates with the level of serum ferritin [4]. However, it appears that the RLS+ diabetic population is independent of serum iron and ferritin levels [8, 10, 21]. We recorded a significantly higher level of total serum calcium in those with RLS. The same was noted in hemodialysis patients and investigators suggested that high serum calcium was possibly connected to the pathophysiology of RLS [22]. The exact significance of this result in diabetic polyneuropathy is not clear and further tests are required to confirm and establish this result.

Though univariate logistic regression analysis has shown an association between serum calcium concentrations and nerve conduction latency with RLS, multivariate logistic regression analysis did not isolate any of the investigated factors as a significant single risk factor for the development of RLS in distal diabetic polyneuropathy. Investigation of possible risk factors for the occurrence of RLS in diabetics in some studies disclosed peripheral neuropathy to be the only risk factor for the occurrence of RLS, while others revealed none [10, 19, 21].

Our study had several limitations, including a relatively small sample and exclusion of patients with sensory small-fiber neuropathy. Nevertheless, we believe the research is important because only a few in our country deal with this problem.

CONCLUSION

The RLS is common in diabetic polyneuropathy and occurs in more than a quarter of these patients. Though sensory polyneuropathy and higher total serum calsium concentration have been associated with RLS, neither of these has been identified as a significant single risk factor for the development of RLS in diabetic polyneuropathy. Further studies are needed to clarify the real association between serum calsium concentration and RLS in diabetic polyneuropathy.

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Синдром немирних ногу код оболелих од дисталне дијабетичне полинеуропатије

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САЖЕТАК

Увод/Циљ Повезаност синдрома немирних ногу (СНН) са неуропатијама различите етиологије јасно је утврђена. Међутим, резултати истраживања о учесталости СНН код дијабетичне полинеуропатије (ДПН) су контроверзни. Циљ нашег рада је био да се утврди учесталост СНН код болесника са дисталном дијабетичном полинеуропатијом, као и да се установе могући фактори ризика за његову појаву у овој групи оболелих.

Метод Испитивање је обухватило 101 консекутивног оболелог с дисталном ДПН. Дијагноза СНН је постављена на основу критеријума Интернационалне групе за испитивање синдрома немирних ногу. Сваком болеснику урађено је електромионеурографско испитивање којим је потврђена дијагноза дисталне ДПН.

Резултати СНН је био присутан код 27 (26,73%) болесника у односу на целу групу. Поређење оболелих са СНН+ и без СНН- показало је да је у групи СНН+ било нешто више жена него мушкараца (14,85/9,90% тј. 35,64/37,62%), оболели су били значајно млађи (60,58 ± 10,54 тј. 65,57 ± 0,94 година; $p \leq 0,05$); значајно чешћа је била сензитивна полинеуропатија (17/27 тј. 34/74, $p \leq 0,05$) и имали су виши ниво *Ca* у крви у односу на оболеле без СНН- (2,43 ± 0,26 према 2,28 ± 0,39; $p \leq 0,05$). Међутим, мултиваријантна регресиона анализа није показала да је иједан од њих значајан фактор ризика за појаву СНН код дисталне ДПН.

Закључак СНН је чест код ДПН и јавља се код више од четвртине оболелих. Иако су сензорна форма и повишен ниво укупног *Ca* у серуму били удружени са СНН, ниједан од њих се није издвојио као значајан појединачни фактор ризика за настанак СНН код дисталне ДПН.

Кључне речи: синдром немирних ногу; дијабетес; полинеуропатија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

The influence of early antibiotic therapy on the clinical manifestations in patients with early Lyme disease

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SUMMARY

Introduction/Objective Lyme borreliosis is a multisystem infectious disease caused by Borrelia burgdorferi spirochetes transmitted by the bite of an infected tick. The disease manifestations are very different, with the skin, joints, heart, and nervous systems being most often affected.

The aim of this study was to find out whether there are significant differences in the appearance of symptoms and signs of the disease between the subjects who did / did not receive prophylactic, early antibiotic therapy, after the tick bite in patients diagnosed with the early phase of Lyme borreliosis.

Methods The study was carried out on 2,070 patients, who were treated or examined at the Clinic for Infectious and Tropical Diseases in the 1989–2004 period. The patients were divided into group A (n = 591), in which they were given early antibiotic therapy, and group B (n = 1,479), in which they were not. The antibiotic therapy was used within five days of a tick bite in patients with a probable infection, who, at the time, did not have any symptoms or signs. The applied antibiotics included cephalosporins, macrolides, tetracyclines, semisynthetic penicillins, repeatedly for seven or 14 days, or benzathine benzylpenicillin once only.

Results The disease developed in a statistically significantly larger number of patients who were not given early antibiotic therapy (537/1,479) than in those who received the therapy (10/951), i.e. the ratio was 36.3% *vs.* 1.7%. We concluded that only two antibiotics were sufficient for optimal prevention: doxycycline and ampicillin, administered for seven days. The applied antibiotics showed a high statistically significant efficacy, ranging from 93.7% (cephalosporins) to 99.4% (macrolides).

Conclusion The application of early antibiotic therapy after a tick bite was effective in preventing the early phase of Lyme borreliosis, while in the case of infection it prevented the development of extracutaneous manifestations.

Keywords: Lyme disease; tick; antibiotics; prophylaxis

INTRODUCTION

Lyme borreliosis (Lb) is a multisystem infectious zoonotic disease caused by the *Borrelia burgdorferi* (Bb) spirochetes transmitted by a bite of an infected tick of the genus *Ixodes*. The disease manifestations are very different, with the skin, joints, heart, and nervous systems being most often affected.

The tick bite is the primary mode of infection, and the infection can occur via the conjunctiva or micro trauma that occurs after the tick destruction and skin irritation by its contents [1].

Ixodes ricinus has been proved to be a vector in our country. The infection occurs after one to three days, and rarely within 24 hours, due to inappropriate tick removal [2, 3]. The risk of developing Lyme disease after the bite of an infected tick is 1–4%, while asymptomatic infections range up to 26% in the endemic area [4, 5]. There is a greater risk of the occurrence of manifest illness in children, as well as of the late stage development in people with an asymptomatic infection.

Depending on the stage and extent of the disease, the duration of antibiotic therapy for skin manifestations at the early stage is four to six weeks, while for extracutaneous manifestations the duration is about two months. At the late stage, antibiotic treatment lasts up to 16 weeks, i.e. until the loss of subjective symptoms and clinical signs of the disease [1, 6, 7, 8].

The fact that it affects multiple organs and systems, the development of the late stage of the disease with definite tissue and organ damage, the onset of autoimmune diseases, recurrence and disability, and a possible death outcome were the subject of research in many clinical studies in terms of disease prevention and recommendations for the use of antibiotic therapy after the tick bite, and before the manifestation of the disease [9, 10].

Most authors consider that neither the routine use of antibiotics nor serological testing is necessary just after the tick bite [11, 12]. However, the aforementioned therapy is justified in endemic areas in cases of repeated bites and of serious suspicion concerning the possibility of an infection [9, 13].

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One study involving 600 patients showed that the use of antibiotic therapy was unnecessary due to a small number of infected persons (1.4%) in patients who did not receive an antibiotic after the tick bite, but the same authors recommended carrying out additional studies concerning this subject [14].

Due to the early dissemination of the cause of the disease, the difficulty in diagnosis, and major problems in the treatment of infected patients, particularly in the late stage of the disease, there are opinions that, if there is a suspicion of an infection after the bite, it is justified to apply antibiotics for up to two weeks [6, 8].

The aim of this paper is to determine the effect of prophylactic, i.e. early application of antibiotic therapy on the clinical manifestations in the early phase of Lb. For the purpose of this study, prophylactic antibiotic therapy was defined as the use of antibiotics up to five days after the tick bite in individuals with suspected Bb infection who did not show clinical symptoms and signs of the disease at the time of the application of antibiotics.

METHODS

The study was designed as a retrospective-prospective cohort study. It initially included 2,470 patients who were treated at the Clinic for Infectious and Tropical Diseases of the Military Medical Academy (MMA), Belgrade, Serbia, or examined at the outpatient clinic in the period between January 1, 1989 and December 31, 2004; out of 400 excluded patients 207 did not show up for follow-up monitoring, and 193 received early antibiotic therapy. The study did not include patients who had a positive serological reaction to the Bb antigens at the first examination, i.e. those who had previously developed an infection.

All the patients were classified into two categories. The first category consisted of people who came to the Clinic because of a tick bite. The presence of probable Bb infection was based on the existence of at least one of the following criteria: the presence of Bb in the removed tick; the tick's presence in the skin for more than 48 hours; data on inappropriate tick removal; and the presence of the antibodies to Bb antigens in the serum after four to six weeks. In some patients, based on the clinician's assessment, early antibiotic therapy was applied, while in others it was not.

The second category included patients who came with some of the symptoms and were diagnosed with the early phase of Lyme disease. The diagnosis was based on a characteristic change in the skin, i.e. erythema migrans (EM), clinical picture and the course of the disease, an increase in antibody titer against Bb antigens in two consecutive serum samples within two to four weeks (IIF) or on the positive result after four to six weeks (ELISA), response to antibiotic therapy, exclusion of other related diseases, data concerning the tick bite, and stay in the endemic area.

A total of 2,070 patients were divided into group A, in which early antibiotic therapy was applied, and group B, in which it was not.

The disease symptoms included headaches, myalgia, arthralgia, loss of concentration, sleep and mood disorders, paresthesia, palpitations, and pruritus. The observed signs of the disease included high body temperature, EM and multiple EM (MEM), heart rhythm disorders, myocarditis, pericarditis, encephalopathy, meningitis, encephalitis, cranial neuritis, radiculoneuritis, arthritis, myositis, and lymphadenopathy.

Based on the type of antibiotic and duration of its application, all patients who received antibiotic therapy were divided into three groups: those who were given benzathine benzylpenicillin once parenterally, those who were given antibiotics for seven days orally and those who were given antibiotics for 14 days orally (macrolides, tetracyclines, cephalosporins, semisynthetic penicillins). In each of these groups, those who suffered and those who did not suffer from the early stage of Lyme disease were singled out.

Data sources and examinations included biographical data from medical and health records, tick bite data, physical, radiological, and electrophysiological examinations, serological tests concerning Bb antigens (reaction of indirect immunofluorescence IIF or ELISA tests done at the Institute of Microbiology of the MMA) and specialist examinations according to indications.

The tick was removed either appropriately by a surgeon or an epidemiologist at the MMA, or inappropriately by the patients themselves and/or other adults when a child had been bitten. Tick gut contents were tested for the presence of Bb by an epidemiologist at the MMA Epidemiology Institute, in a dark field, using phase-contrast microscopy. All the patients were monitored clinically, laboratorically, and serologically within the period of one to 15 years.

Antibiotics registered for administration in our country and recommended for the treatment of Lyme disease were applied in the early antibiotic therapy.

Continuous variables were summarized as means (M) and standard deviations (SD); the significance between the groups was determined by the Student's t-test for the validity of data distribution. All variables were presented as frequency of certain categories, while statistical significance of differences was tested by the χ^2 test. Statistical significance was accepted at a minimum level of $p < 0.05$.

Principles of ICH Good Clinical Practice were strictly followed and ethical approval from the Ethics Committee was obtained on September 15, 2017.

RESULTS

In total, there were 2,070 patients. Group A consisted of 591 patients who received early antibiotic therapy, while Group B comprised 1,479 patients who did not receive any antibiotic therapy. Comparing the number of patients in the groups, a statistically significant difference was found due to the fact that Group B was significantly larger (Table 1) than Group A since early antibiotic therapy was applied only to those with a probable infection, according to the assessment of the responsible physician.

In both groups, there were more male patients, a total of 1,572 (75.94%), while there were only 498 females (24.06%), and there was no statistically significant difference

in the distribution of sexes in the groups. The average age of patients in Group A was 35.2 ± 19.4 years, while in Group B it was 39.4 ± 20.7. The patients in Group B were statistically significantly older than those in Group A. The average age of women was 46.47 ± 20.26 years, while that of men was 33.89 ± 19.54 years, with women being statistically significantly older (p = 0.001).

When the presence of a tick during the examination is concerned, it was found that the distribution of the subjects was practically identical, as there was no statistically significant difference between these groups concerning the presence or absence of ticks, or the use of antibiotics (p = 0.99). The analysis of a large number of patients (2,041) with appropriately and inappropriately removed ticks showed a uniform ratio of these categories: 994:1047 (48.7%:51.3%) (Table 1).

The applied treatment was analyzed concerning the method of removing ticks. It was found that in Group B, which had not received early antibiotic therapy, the tick was removed appropriately in 652 patients (45%), inappropriately in 798 patients (55%), while 29 patients did not know about the tick bite and they came to the doctor's in the early phase of Lb. In Group A, the tick was removed appropriately in 342 patients (57.9%), and inappropriately in 249 patients (42.1%). There were statistically significantly more patients in the group that had received the antibiotic and in which the tick was previously appropriately removed (p < 0.001).

The duration of tick presence ranged from one hour to more than 48 hours. By analyzing the duration of tick presence in the skin we can conclude that there was no statistically significant difference between the groups (Table 1).

After the tick bite in infected patients, the signs of Lb were most frequently present on the skin (Table 2).

The results show that the clinical signs on the skin were found in 31.51% of patients who did not receive early antibiotic therapy, as opposed to those who did (1.52%) (p < 0.001).

The total number of signs of the disease was 679, and the number of patients was 537, which means that in some patients there were several affected systems. Table 2 shows the frequency of signs on a particular organ system in relation to the total number of recorded signs in Group B (679). We observed that the nervous system was affected in 5.34%, other organs were affected in 3.49%, locomotor system in 2.84%, and cardiovascular system in 2.77% of the patients.

The frequency of changes on the skin, in relation to the total number of patients (547), was 86.84%, the changes

Table 1. Basic demographic and relevant clinical data

Parameters	Groups				Probability
	Early antibiotic treatment A		Without antibiotic treatment B		
	n	%	n	%	
Age (years), x ± SD	35.2 ± 19.4		39.4 ± 20.7		t = 4.24; p < 0.001
Patient distribution (n = 2070)	591	24.06	1,479	75.94	χ^2 = 112.39; p < 0.001
Sex					
male	457	77.3	1,115	75.4	χ^2 = 0.76; p = 0.38
female	134	22.7	364	24.6	
Tick presence					
yes	260	44.0	652	44.1	χ^2 = 0.00; p = 0.99
no	331	56.0	827	55.9	
Tick removal					
appropriately	342	57.9	652	45.0	χ^2 = 27.34; p < 0.001
inappropriately	249	42.1	798	55.0	
Duration of tick presence (hours)*					
1–12	74	12.52	146	9.87	χ^2 = 2.31; p = 0.69
13–23	228	38.58	562	38.00	
24–48	111	18.78	245	16.57	
> 48	63	10.66	157	10.62	
unknown	115	19.79	369	24.95	

*Skin, based on anamnestic data

Table 2. Clinical signs due to *Borrelia burgdorferi* exposure

Systems	Groups				Probability
	Early antibiotic treatment A		Without antibiotic treatment B		
	n	%	n	%	
Skin	9	1.52	466	31.51	χ^2 = 213.03; p < 0.001
Nervous	0	0.00	79	5.34	Not shown due to extremely low frequencies in early antibiotic treatment group
Other	1	0.17	51	3.49	
Joints	0	0.00	42	2.84	
Heart	0	0.00	41	2.77	
Total	10	1.69	679	45.91	

Table 3. Efficacy of the early-applied antibiotic therapy

Antibiotics class	Lyme disease absent		Lyme disease present		Total	
	n	%	n	%	n	%
Macrolides	182	99.4	1	0.6	183	100
Semisynthetic penicillins	121	98.4	2	1.6	123	100
Benzathine benzylpenicillin	165	98.2	3	1.8	168	100
Tetracyclines	98	97	3	3	101	100
Cephalosporins	15	93.7*	1	6.3	16	100
Total	581	98.3	10	1.7	591	100

*significantly different ($p < 0.05$) from macrolides

Table 4. The frequency of the early phase of Lyme disease in patients regarding the type of treatment

Treatment	Lyme disease present		Lyme disease absent		Total	
	n	%	n	%	n	%
Early antibiotic treatment	10	1.7	581	98.3	591	100
Without antibiotic treatment	537	36.3	942	63.7	1479	100
Total	547		1523		2070	100
Probability	$\chi^2 = 258.40$; $p < 0.001$					

in the nervous system were registered in 14.44%, on other organs in 9.50%, on the locomotor system in 7.88%, and in the cardiovascular system in 7.49% of the patients.

At the same time, we observed that in patients who received early antibiotic therapy, there were no signs of disease in the nervous, cardiovascular, and bone-muscular systems.

After applying early antibiotic therapy in 591 patients, 581 (98.3%) of them did not develop the early phase of Lyme disease. Macrolides (99.4%) showed the highest efficacy, followed by semi-synthetic penicillins (98.4%), benzathine benzylpenicillin (98.2%), and tetracyclines (97%). Cephalosporins (93.7%) showed the lowest efficacy, which was statistically significantly lower in relation to other groups of antibiotics (Table 3).

In Group A, which had received early antibiotic treatment, only 10 (1.7%) out of 591 patients were infected, while 581 of them were not infected (98.3%). In contrast, in Group B, which had not received early antibiotic therapy, 537 (36.3%) out of 1,479 patients were infected, while 942 (63.7%) were not (Table 4). The difference found between these two groups of patients was highly statistically significant in favor of the group that had received early antibiotic therapy ($p < 0.001$).

DISCUSSION

Today, Lb is one of the greatest imitators in medicine, because it is a multisystem disorder involving many organs and systems, with the occurrence of a chronic disease form, the development of disabilities, autoimmune diseases, and sometimes lethal outcome [15].

The disease occurs in all parts of the world. In the United States, the incidence is 12–39 patients per 100,000, since the probable cases have also been reported since 2012 [16, 17]. In Europe, the incidence ranges from 35/100,000 patients in Germany to 206/100,000 patients in Slovenia [18].

In Serbia, the number of the infected is decreasing (6.83/100,000), since only 487 cases were reported in 2015 [19]. In the period from 1986 to 2000, Lb was represented in the zoonotic group with 16.34% in Belgrade, while 4,768 people developed the disease in Serbia from 1991 to 2000 [20].

In our study, there were significantly more males (75%), aged 11–30 years, as most of them were members of the army who had been outdoors in the field (younger ages were members of their families). In Europe, about 60% of women with a tick bite have been registered, which is similar to the findings in Serbia (57%), aged 20–60 years and over [19].

In the early 1990s, the infected ticks were frequent on the territory of Belgrade, ranging 20–67%, with a tendency to decrease. In 2007, this number amounted to 30% [2, 21].

The situation was similar everywhere. In Europe, the infection of *Ixodes ricinus* with Bb ranged 15–40%, in endemic areas of America up to 50%, while *Ixodes pacificus* was infected with Bb in 1–2% of cases [22]. The risk of the occurrence of manifest Lb after a bite by an infected tick in Europe ranges 1–4%, in hyperendemic areas 4.7–5%, but there are also data on a significantly higher risk (up to 27%) [4, 23, 24].

At the time of examination, 44% of our patients in both groups had a tick in the skin, while others came with a removed tick or not knowing about the bite. With the largest number of subjects, 48.31%, the tick stayed in the skin for up to 24 hours before the first examination.

In our study, there were 21 early-phase Lb patients with the tick staying in the skin for only 10 hours or up to one day who developed changes in the central and peripheral nervous systems, which is in agreement with some authors, but also in contradiction with some others [2, 3, 25, 26].

Given the large number of subjects in this study, i.e. 994 who had the tick removed appropriately (48.7%) and 1,047 who had it removed inappropriately (51.3%), it was possible to assess the significance of these two methods of tick removal for the occurrence of the disease. In the case of appropriate tick removal, the disease was reported in 22% of patients, while it was reported in 78% in the case of inappropriate removal, which was statistically significantly different. The ratio of patients with the tick inappropriately removed who were given early antibiotic therapy was 1.01% *vs.* 28.7% of patients in the group without antibiotic therapy. There was a significantly higher number of subjects in the group receiving the antibiotic and in whom the tick was previously appropriately removed ($p < 0.001$).

In patients with manifestations in the nervous and cardiovascular systems in our study, the tick was inappropriately removed in most cases, which is in line with the data given by Southern [27]. According to other authors' data concerning appropriate tick removal, the number of patients was statistically significantly lower in relation to the group where it was inappropriately removed (6% *vs.* 46%), but this study included a small number of subjects (52) [28]. According to the results of our authors, the early phase of Lb occurred in 0.61% of patients with appropriately removed tick, and in 2.5% of patients with inappropriately removed tick, while others claim that it occurred

in 0.2% of patients with appropriately removed tick and in 1.44% of patients with inappropriately removed tick [21, 29]. The aforementioned numerical indicators are lower in relation to the data from our research due to the longer monitoring of our patients and the timely started antibiotic therapy. The results of other studies suggest that 96% of patients with an appropriately removed tick did not suffer from Lb in a highly endemic region, thus emphasizing the importance of appropriate forceps tick removal even without the antibiotic prophylaxis [30, 31].

In our study, we observed the frequency of symptoms and signs of Lb and registered 12 different symptoms and 24 signs, which we grouped according to the affected organ systems. The disease was manifested on the skin in the form of EM and other skin changes in 86.84% of patients, in the nervous system in 14.44%, in other organs (lymphadenopathy, liver damage, high body temperature, hypothyroidism, multiple-systemic infectious disease syndrome – MSIDS) in 9.5%, on the locomotor system in 7.88%, and in the cardiovascular system in 7.49% of patients compared to the total number of patients (547). In patients who received early antibiotic therapy, there were no signs of disease in the nervous, cardiovascular, and musculoskeletal systems. In one patient (0.17%) who received early antibiotic therapy, we registered high body temperature without other signs of the early phase of Lb, as opposed to those who did not receive antibiotic therapy, in whom we registered the following: 3.49% MSIDS (in 29 patients), lymphadenopathy, liver, damage and hypothyroidism.

In patients who received early antibiotic therapy after a tick bite, Russian authors observed the infected (1.1%) without EM and with MSIDS, and in those without antibiotic therapy (12.3%) they noted those with MSIDS, sleep disorder, EM and MEM, lymphadenopathy, and cardiac disorders [32]. Other authors paid less attention to this category of patients and did not include them in the analysis when they evaluated the efficacy of prophylactic post-bite therapy [9, 14, 30, 33]. Our results show that in the group with antibiotic therapy only EM and MSIDS were observed, while all other signs were observed in the group without early antibiotic therapy. The difference between these two groups in relation to the number of signs was also statistically highly significant.

EM and MEM were significantly more frequently present (31.51%) in the group without early antibiotic therapy compared to patients with the treatment (1.52%). MEM was observed in 2.3% of patients without early antibiotic therapy, which was found in the United States in a higher percentage (20%) due to the early dissemination of Bb in that area [33]. Today, this can also be accounted for by new strains with high spirochetemia [34]. Compared to the total number of patients (547), the incidence of skin changes was 86.84%. Similar results were also reported worldwide, with 70–90% in the United States, and 48% in Slovenia [35]. Some patients with Lb without early antibiotic therapy had several organic systems affected, while 5.34% had changes in the nervous system, 2.47% in the locomotor system, and 2.77% in the cardiovascular system. Other studies state the same signs of disease with approximately equal frequency, which we also observed in our patients [31].

Unlike in our study, other authors followed their patients for a shorter period of time and observed fewer symptoms and signs. Among our patients, there were more neurological manifestations observed because we paid special attention to the damage of the peripheral nervous system due to Lb [36]. The incidence of cardiac manifestations in Lb was lower in relation to the data of other authors where they stated a frequency of up to 10% [37].

Opinions regarding the type and duration of antibiotic therapy in the treatment of Lb have not yet been harmonized. The general recommendation is that doxycycline, amoxicillin, and cefuroxime should be administered at an early phase for two to three weeks, while intravenous ceftriaxone, cefotaxime, or benzylpenicillin for two to four weeks in the case of extracutaneous manifestations [38, 39, 40]. The previous recommendation for treating the late phase was two to four weeks' therapy and even longer, until the disappearance of the symptoms [7]. New studies have not justified the extended, 12-week antibiotic treatment in late-stage patients with prolonged Lb symptoms [41]. Based on our experience, a longer four to six weeks' treatment prevents the dissemination of Bb and its affecting other organs and systems [1, 6, 8]. On the other hand, other authors consider that 10 days of doxycycline and amoxicillin therapy is efficient in the treatment of the early phase of Lb [42].

There is a significant difference in the recommendations for the treatment of the early phase of Lb, symptoms associated with Lb, and prophylaxis between the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society, which advocates extended antibiotic treatment in all categories [8]. IDSA, along with several other medical associations, is in the process of developing new guidelines for the prevention, diagnosis, and treatment of Lb [43].

There are two opposing standpoints in the world regarding prophylaxis after a tick bite. The authors who are against the early application of antibiotic therapy base their opinion on a small proportion of instances of infection after a tick bite (2–3%), costs, and possible side effects of antibiotics [11, 12, 31]. Other authors, including us, advocate the use of early antibiotic therapy, regardless of the small number of infected persons after a tick bite. Among the infected, there are often patients with a severe clinical picture with extracutaneous manifestations and a possible fatal outcome [15].

In the prophylaxis of Lyme disease, the most commonly used drugs were cefotaxime, ampicillin, doxycycline, and penicillin [22, 33]. The results of a multicenter study in Germany and Austria show that the local application of 10% azithromycin at the site of a bite of an infected tick reduces the occurrence of EM [44]. We consider that the recommendation for local therapy is not justified because EM does not occur in 20–30% of infected patients, and patients later develop extracutaneous manifestations. It was previously described in experimental studies that the damage to the hematoencephalic barrier occurs as soon as 12 hours after spirochete inoculation, which does not support the use of local antibiotic therapy at the tick bite site [45].

In our study, we administered four groups of antibiotics orally and benzathine benzylpenicillin once parenterally in

order to prevent the disease after the tick bite. The results of our study show that early antibiotic therapy after the tick bite was very effective in the prevention of Lb. This was documented by a statistically significant decrease in the number of patients who received early antibiotic therapy (1.7%) compared to the group that did not receive this treatment (36.3%). Moreover, the symptoms and signs of the disease were also significantly less pronounced in the group with early antibiotic therapy compared to the group without it. Extracutaneous manifestations as an indicator of the severity of the clinical picture, in the group that received early antibiotic therapy, were not present at all. In contrast, in the group that did not receive early antibiotic therapy, symptoms and signs were observed in cardiovascular, nervous, and musculoskeletal systems.

The high incidence of early phase of Lb during the conducted trial at the MMA Clinic for Infectious and Tropical Diseases correlates with the highest number of Lb cases reported in Serbia in the period from 1991 to 2000, which totaled 4,768, and a high percentage of infected ticks [10, 20]. The aforementioned findings coincided with the great migration of the population due to sanctions and wars on the territory of former Yugoslavia. In addition, in our patients we observed a greater number of symptoms and signs than had been observed in other studies, as we followed the patients for more than one year [10].

A study by Russian authors showed that the use of doxycycline reduces the occurrence of the early phase of Lb in patients with the infected tick bite, as 11 times more patients were found in the group without prophylactic antibiotic therapy [32].

Several studies showed, according to the results of the meta analysis, that the disease did not develop in people who received prophylaxis 72 hours after the tick bite, and that the risk of developing the infection was 11 times lower in the group that received antibiotics (doxycycline or amoxicillin), compared to the placebo group (0.2%:2.22%) [14, 30].

The administration of a single dose of 200 mg doxycycline after a tick bite showed that early antibiotic therapy was very effective in reducing morbidity of the early phase of Lb, as the disease developed in eight times fewer patients compared to those who did not receive antibiotics (0.4%:3.2%) [9]. In this study, subjects were monitored for six weeks and only EM was described, which is insufficient to evaluate the efficacy of the drug, because symptoms and signs of the disease can be subsequently exhibited up to one year after the bite. EM does not occur in 20–40% of patients with early phase of Lb. Following the publication of the results of this study, a single dose of 200 mg doxycycline after the tick bite was recommended in certain individuals within the given treatment criteria [33].

Contradictory opinions concerning the justification of the application of antibiotics have existed since the discovery of Lb and its treatment up to the present [11, 12, 31]. According to some authors, a small number of patients after a tick bite (on average 1.1–3.4%) do not require the use of prophylactic therapy [11, 12, 31, 39]. In hyperendemic areas in the United States, Lb was developed in 3% of patients with a tick bite without antibiotic therapy, so the use of prophylaxis in less endemic areas would have an even smaller effect [31]. In Europe, the tick infection rate is lower than in the United States, the risk of developing Lb is low (up to 4%), so prophylaxis is not recommended after the bite [4, 31].

This study showed that the early antibiotic therapy was extremely effective in preventing the disease compared to the control group (1.7%:36.3%). Our study followed the patients for 1–15 years, and therefore the percentage of patients who were infected at the early stage of Lb without early antibiotic therapy was greater [10]. Secondly, all five antibiotic groups were found to be clinically highly effective. The best results were achieved with roxithromycin (99.4%), followed by half-synthetic penicillins (98.4%), benzathine benzylpenicillin (98.2%), and doxycycline (97%), while cephalosporins (93.7%) showed the lowest statistically significant efficacy. As far as the efficacy of antibiotics and the duration of their use are concerned, (single-dose parenterally, seven or 14 days orally), there were no statistically significant differences.

Previously, the efficacy of short-term administration of amoxicillin as prophylaxis was not known and, therefore, was not recommended [33]. After a meta-analysis of four studies, it was concluded that the 10-day administration of amoxicillin may be as effective as 200 mg of doxycycline [30]. Our results showed that amoxicillin was very effective, even when given for only seven days. In addition, benzathine benzylpenicillin, not having been considered so far, also showed good efficacy.

Our study showed that, out of the 13 antibiotics we used, roxithromycin was the most effective one, but at the same time it was, by far, the most expensive drug. In previous studies, it was the second-line treatment for the early phase of Lb [33]. According to the principles of the World Health Organization that in the case of equal efficacy and good tolerance of more drugs, low-cost drugs should be used for treatment, in the past years we have decided to use ampicillin and doxycycline for a seven-day period. In case of need, i.e. in allergic patients (whom we did not register in our study), clarithromycin, azithromycin, (as suggested by British National Formulary [38]) or roxithromycin could be used.

In our study, we did not detect side effects of the applied drugs. There was no evidence of photosensitivity or gastrointestinal disturbances in soldiers who were exposed to the sun as part of their regular activities and diets that were not fully aligned with their usual family eating habits.

CONCLUSION

Taking into account our extensive experience in this field and results of the application of prophylactic therapies, we join the authors who are in favor of early antibiotic therapy after a tick bite. It is clinically justified, prevents the development of extracutaneous manifestations of Lb, is well tolerated, and the proposed antibiotics (doxycycline and ampicillin) are inexpensive.

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Утицај ране примене антибиотика на клиничке манифестације код оболелих у раној фази лајмске болести

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САЖЕТАК

Увод/Циљ Лајмска борелиоза (ЛБ) јесте мултисистемско инфективно обољење изазвано спирохетом *Borellia burgdorferi* (ББ) и настаје убодом инфицираног крпеља. Болест се испољава различито, а најчешће су захваћени кожа, зглобови, срце и нервни систем.

Циљ ове студије је био да се код особа код којих је дијагностикована рана фаза ЛБ утврди да ли постоје значајне разлике у испољавању симптома и знакова обољења између оболелих који су примили и оних који нису примили профилактичну, рану антибиотску терапију после убода крпеља.

Методе Испитивање је извршено на 2070 испитаника оба пола са убодом крпеља, лечених или прегледаних у Клиници у периоду 1989– 2004. године. Испитаници су подељени у две групе – групу А ($n = 591$), која је примала рану, профилактичну антибиотску терапију, и групу Б ($n = 1479$), која ту терапију није примала. Рана антибиотска терапија подразумева примену антибиотика код особа са насталом инфекцијом вероватно до пет дана по убоду крпеља, а које нису имале симптоме и знаке болести. Од антибиотика су примењивани цефалоспорини, макролиди, тетрациклини, полусинтетски пеницилини, понављано седам или четрнаест дана, или бензатин безилпеницилин једнократно.

Резултати Болест се развила код статистички значајно већег броја испитаника без профилаксе (537/1479) него код оних који су ту терапију примили (10/591), односно 36,3% : 1,7%. Применом пет група антибиотика закључено је да су за оптималну превенцију довољна само два: доксициклин и ампицилин у трајању од седам дана. Примењени антибиотици су испољили високу клиничку ефикасност, која се кретала од 93,7% (цефалоспорини) до 99,4% (макролиди) и била независна од дужине примене.

Закључак Примена ране антибиотске терапије после убода крпеља је ефикасна у превенцији ране фазе ЛБ, а када је болест била испољена, није било екстракутаних манифестација.

Кључне речи: лајмска болест; крпељ; антибиотици; профилакса

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Immunohistochemical evaluation of insulin-like growth factor receptor 1 in breast cancer

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SUMMARY

Introduction/Objective Activation of insulin-like growth factor receptor (IGF-1R) results in cell transition from growth phase to synthesis phase of cell cycle. Breast cancer is categorized into prognostic and therapeutic subtypes based upon hormone receptor, estrogen receptor (ER), and progesterone receptor (PR) expression and human epidermal growth factor receptor 2 (HER-2) expression.
The objective of this study was to examine the expression of IGF-1R in a specific subtype invasive breast cancer and its correlation with basic histopathological and immunohistochemical prognostic parameters.
Methods Formalin-fixed paraffin-embedded tumor samples were obtained from 129 female patients with invasive breast cancer (I–III disease stage) with the follow-up ranging 36–108 months (average 48 months). For immunohistochemical staining, we used monoclonal antibodies for ER, PR, IGF-1R, and polyclonal antibody for HER-2.
Results IGF-1R inversely correlated with tumor stage ($p = 0.017$), tumor grade ($p = 0.001$), HER-2 ($p = 0.003$), whereas significant positive correlation was found with multifocality/multicentricity of breast cancer ($p = 0.036$), ER ($p = 0.001$) and PR ($p = 0.0001$) expression. Cox-regression analysis for relapse-free survival (RFS) showed that disease stage ($p = 0.039$) and HER-2 ($p = 0.033$) were independent prognostic factors. IGF-1R did not predict clinical outcome in patients with breast cancer ($p = 0.488$, Kaplan–Meier test for RFS).
Conclusion Patients with low stage and grade hormone-dependent breast cancer had a significantly higher IGF-1R expression than patients with triple negative or HER-2 overexpressed cancer. The present findings also highlight that IGF-1R expression in multicentric/multifocal breast cancer supports the key roles in tumor initiation.
Keywords: insulin-like growth factor 1 receptor (IGF-1R); hormone-dependent breast cancer; HER-2

INTRODUCTION

Insulin receptor family represents an activator of class II tyrosine kinase with three members: insulin receptor (IR), insulin-like growth factor receptor 1 (IGF-1R), and insulin-like growth factor receptor 2 (IGF-2R). IR activation influences metabolic activity in vertebrates. IGF-1R activating results in proliferation and differentiation of cells. IGF-2R is structurally and functionally different from the IR and IGF-1R, it is a monomer without tyrosine kinase activity. IGF-1R is a dimmer made of α and β subunits and has the same structure as the IR with which it builds hybrid receptors (IR/IGF-1R) [1, 2, 3]. IRs can be activated by insulin and two insulin-like growth factors (IGFs): insulin-like growth factor 1 (IGF1) and insulin-like growth factor 2 (IGF2). Many cells have been identified as producing as well as responding to the IGFs, including fibroblasts, chondrocytes, osteoblasts, granulosa cells, and epithelial breast cells. In circulation, IGF1 and IGF2 are attached to six insulin-growth binding proteins (IGFBP 1–6) and protected from the action of proteases (Figure 1). IGF-1R together with the hormone receptors regulates the development of the epithelium of the normal glandular breast tissue [4, 5]. Breast cancers are categorized into subtypes based on immunohistochemical hormone receptors expression (ER and PR) and human epidermal growth factor 2 (HER-2) expression. There are two major groups: hormone-dependent/luminal breast cancer involves luminal A (ER+, PR+, HER-2/-, $Ki67^{low}$) and luminal B (ER+, PR+/-, HER-2+/-, $Ki67^{high}$); hormone-independent/basal-like breast cancer involves triple negative (TNBC) breast cancer (ER-, PR-, HER-2-) and HER-2 overexpressed (ER-, PR-, HER-2+). The TNBC subtype does not express therapeutically targetable ER, PR, or HER-2 receptors, making the aggressive subtype difficult to treat [6]. Nowadays, IGF-1R makes an attractive target for investigation for a different type of malignancy and anticancer therapy. The prognostic and predictive role of IGF-1R in breast cancer is still unknown. The optimal cut-point and standardized immunohistochemical expression of this receptor are subjects of discussion [7]. A few studies have examined the relationship of the IGF-1R expression according to the hormone and HER-2 and resistance to antiestrogen therapy [8, 9]. Some *in vitro* studies have

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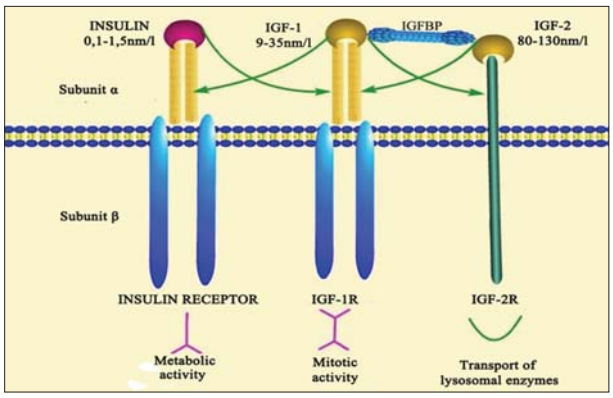

Figure 1. The structure of insulins receptors and concentrations of insulin-like growth factors (IGFs) in the blood; IGFs: insulin, insulin-like growth factor 1 (IGF-1), and insulin-like growth factor 2 (IGF-2); insulin-like growth factor-binding protein (IGPB); insulin receptor (IR); insulin-like growth factor 1 receptor (IGF-1R); insulin-like growth factor 2 receptor (IGF-2R); extracellular subunit of IGF-1R and IR (subunit α); intracellular subunit of IGF-1R and IR (subunit β)

given promising results, supporting the rationale for dual targeting of HER-2 and/or IGF-1R as an improved treatment regimen for advanced therapy tailored to different types of cancer [10].

METHODS

Patient selection

Biopsy specimens for 129 invasive breast cancer in stage I–III diagnosed at the Department of Pathology of the University Hospital Foča (Republic of Srpska) from January 2008 to January 2013 were taken for the study. We retrospectively analyzed the Clinical Centre medical data collected from the Department of Surgery, Department of Oncology, and records of family doctors. The prospective follow-up was 48 months (range 36–108) with last data obtained in November 2016. Subjects did not receive preoperative chemo-/radio- or hormone therapy. Minimum resection margin distance of invasive cancer or *in situ* component was 3 mm. Postoperative therapy for individual subtypes of breast cancer was determined following St Gallen consensus from 2008 [11]. The stage of breast cancer was determined following American Joint Committee on Cancer classification from 2010. Histologic grade of the tumor is determined by Elston–Ellis modification of the Scarff–Bloom–Richardson grading systems [12].

Immunohistochemical staining methods

Formalin-fixed, paraffin-embedded tissue samples were cut at 3–5 μm. Following standard procedure, they were dried (30 minutes in the air), "baked" (60 minutes at 65°C) in an oven, dewaxed in xylene (two changes of five minutes), underwent drop-down rehydration concentrations of ethyl alcohol (100%, 96%, 70%, five minutes for each change), and were rinsed in distilled water. Endogenous peroxidase activity was blocked by 3% H_2O_2 (10 minutes at ambient temperature), and the unmasking of antigens was derived by heat treatment of tissue in a microwave oven. Sections were incubated with primary antibodies: mouse monoclonal anti-IGF-1R (clone 24-31 ab4065, dilution 1:50; Abcam, Cambridge, UK); mouse monoclonal anti-ERα clone 1D5 (M7047, dilution 1:60; DAKO Corporation, Carpinteria, CA, USA); mouse monoclonal anti-PR clone 636 (M3569, dilution 1:100; DAKO Corporation); and polyclonal rabbit anti-HER-2 clone 340 (A0485, dilution 1:60; DAKO Corporation). After washing, primary antibodies were treated with streptavidin peroxidase for 15 minutes. DAB chromogen was added in the final procedure step to visualize a positive. During a short incubation period (± 51 minutes), a pre-formed complex was able to develop a brown colour in the interaction with the DAB chromogen. Following immunohistochemical staining (IHC) of the tissue sample, specimens were stained with Mayer's hematoxylin, dehydrated through a series of ethyl alcohols up to absolute alcohol (70%, 90%, and 100%), washed in xylene and mounted in Biomont. The IGF-1R protein was located at the plasma membrane (α subunit) and the cytoplasm (β subunit). Placental tissue was utilized as an adequate external control. Stainability was estimated semiquantitatively based on Allred scoring system. Summarizing of the percentage of positive tumor cells (< 1% = 1; 1–10% = 2; 11–33% = 3; 33–66% = 4; 67–100% = 5) and staining intensity (1 = weak staining can easily be observed at high-power field; 2 = moderate staining can easily be seen under moderate power objective magnification; and 3 = strong staining can easily be observed under low power objective magnification), the expression was scored as follows: negative (0–2), low 1+ (3–4), moderate 2+ (5–6), and strong 3+ (7–8). Scores of 0 and 1 were considered to be a negative finding, and scores of 2 and 3 a positive one. The same method was applied to ER and PR scoring. Hormone receptor positivity is defined as Allred score of > 2 [13, 14]. For the evaluation of HER-2, only staining of the tumor cell membranes was considered to be specific. Positive cases were defined as IHC-3+ and IHC-2+ FISH retested with amplification ratio C > 2.0 [15].

Statistical analysis

The association between the intensity of expression with tumor grade, lymph node status, and tumor size was studied with linear correlation method based on the Pearson correlation coefficient (r). For relapse-free survival (RFS) we used the Kaplan–Meier test, while the Cox proportional hazard regression model was used for multivariate analysis. Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was established at the $p < 0.05$ level.

RESULTS

Characteristics (clinical and histopathological data) of 129 patients with breast cancer are shown in Table 1. One hundred

Table 1. Clinical, histopathological, and immunohistochemical data of 129 patients with breast cancer

Variable	n (%)
Median age (range)	59 (33–84)
Menopausal status	
no	24 (18.6)
yes	105 (81.4)
Tumor stage	
I	10 (7.8)
II	56 (43.4)
III	63 (48.8)
Tumor type	
ductal	71 (55)
lobular	32 (24.8)
other	26 (20.2)
Tumor size	
< 2 cm	16 (12.4)
2–5 cm	75 (58.1)
> 5 cm and inflammatory carcinoma	38 (29.5)
Lymph node metastasis	
node negative	40 (31)
1–3 node positive	37 (28.7)
4–9	32 (24.8)
> 10	20 (15.5)
Postoperative therapy	
tamoxifen	97 (75)
chemotherapy	89 (69)
chemotherapy + Herceptin	33 (25.6)
radiotherapy	99 (76.8)
Estrogen receptor	
0	32 (24.8)
1	13 (10.1)
2	16 (12.4)
3	68 (52.7)
Progesterone receptor	
0	53 (41)
1	13 (10)
2	22 (17.2)
3	41 (31.8)
HER-2	
negative case*	96 (74.4)
positive case**	33 (25.6)

*Immunohistochemical expression 0, 1, and 2 with FISH retested negative; **immunohistochemical expression 3 and 2 with FISH retested positive (amplification ratio C > 2.0)

seventeen patients (90.7%) were alive without evidenced progression of the disease; 12 patients (9.3%) had a relapse of the disease. Bone metastases were registered in five (41.7%) patients, locoregional recurrence in two (16.7%), and one patient (8.3%) had metastases in lungs, liver, brain, remote lymph node and in two organ systems.

IGF-1R expression

Forty-seven of the 129 samples (37.2%) of breast cancer showed no or weak staining (scores of 0 and 1+), 41 (31.8%) moderate (score of 2+) and 42 (32.6%) strong immunohistochemical expression (score of 3+) (Figure 2).

Table 2. Multivariate Cox proportional hazards regression analysis for RFS in breast cancer patients

Variable	B	SE	HR	p-value	95% CI
Disease stage	4.8068	2.3302	122.344	0.0391	1.3008–11506.4
Lymph node stage (pN)	-0.1966	0.3923	0.8216	0.16164	0.3823–1.765
HER-2	1.3284	0.6259	3.7748	0.00338	1.1140–12.7915
IGF-1R	0.2511	0.2930	1.2854	0.3914	0.7260–2.2758

B – beta coefficient; SE – standard error; HR – hazard ratio; CI – confidence interval; HER-2 – human epidermal growth factor receptor 2; IGF-1R – insulin-like growth factor 1 receptor

Table 3. Correlation of insulin-like growth factor 1 receptor expression and prognostic parameters in breast cancer

n = 129	95% CI	r	p-value
Disease stage	-0.3671 to -0.0372	-0.2081	0.0175
Tumor size	0.1782 to 0.1661	-0.006221	0.9440
Lymph node stage (pN)	-0.319 to 0.162	-0.1564	0.075
Tumor grade	-0.492 to-0.189	-0.3501	0.0001
Lymphatic invasion (L1)	-0.249 to 0.092	-0.0812	0.3584
Venous invasion (V1)	-0.127 to 0.216	0.04615	0.602
Menopausal status	-0.211 to 0.132	-0.04105	0.642
Multifocal/multicentric cancer growth	0.011 to 0.344	0.1832	0.036
Age	-0.166 to 0.178	0.006337	0.943
ER	0.397 to 0.645	0.5328	0.0001
PR	0.331 to 0.598	0.4754	0.0001
HER-2	-0.410 to -0.088	-0.2567	0.003

r – Pearson correlation coefficient; ER – estrogen receptor; PR – progesterone receptor; HER-2 – human epidermal growth factor receptor 2

Neither IGF-1R, ER, nor PR were significant predictors of RFS (p = 0.48, p = 0.26, p = 0.28, respectively; Kaplan–Meier test). We confirmed the prognostic value of tumor stage, lymph node metastasis, and HER-2 expression (Figure 3) Disease stage and HER-2 expression were of prognostic significance on relapse-free survival (RFS) in the final Cox proportional hazard multivariate analysis (Table 2).

Correlation among expression of IGF-1R and ER, PR, and HER-2

IGF-1R was positively associated with ER (p = 0.001), PR (p = 0.001), and multifocality/multicentricity of breast cancer (p = 0.039). Inverse correlation existed between IGF-1R and disease stage (p = 0.017), tumor grade (p = 0.0001), and HER-2 (p = 0.003) expression. Other parameters did not show statistically significant correlation with IGF-1R (Table 3).

DISCUSSION

Up to now, the prognostic value of the IGF-1R expression on disease outcome has been controversial, with studies reporting both positive and negative findings [16, 17, 18]. In our study, IGF-1R expression did not independently predict on relapse-free survival and clinical outcome. Conflicting results may arise from discordant methodological

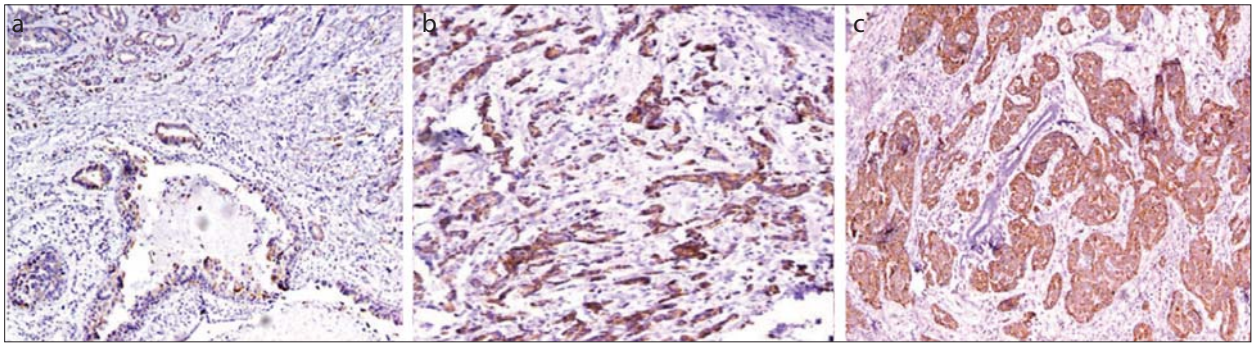

Figure 2. Immunohistochemical expression of insulin-like growth factor 1 receptor in breast cancer (formalin-fixed paraffin-embedded sections, ×40); the expression was scored according to area and intensity of membranous or citoplasmatic staining: a) score 1+; b) score 2+; c) score 3+

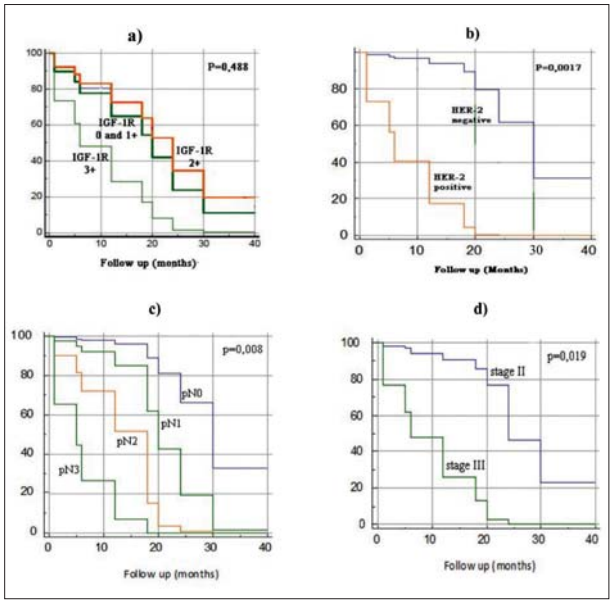

Figure 3. Relapse-free survival analysis (Kaplan–Meier test) prognostic value of a) insulin-like growth factor 1 receptor (IGF-1R), b) human epidermal growth factor receptor 2, c) lymph node metastases, and d) disease stage

approaches, distinct molecular subtypes studied, genetic differences between different populations, and tumor heterogeneity. Our study demonstrated high expression (score of 2+ or 3+) of IGF-1R in 64.4% of the samples. This is in line with some other studies [19]. Up to 50% of breast tumors express the activated form of IGF-1R. In our study, IGF-1R was predominantly expressed in well-differentiated and hormone-dependent breast cancers. IGF-1R and the ER are critical for mammary gland development. The ER and the IGF pathway show dynamic and intricate interference, resulting in bidirectional regulation of expression and activity. ER transcriptionally upregulates IGF-1R expression. Positive correlation exists between cyclin D1 and ER expression, which has already been explained in both experimental and clinical studies, because ER acts as the main mitogen stimulator in breast cancer [20]. The role of IGF-1R in mammary stem cell maintenance and a necessity for lineage differentiation suggest that aberrantly expressed IGF-1R may be capable of enhancing cell potential and changing cell fate in a tumor, perhaps even in tumors composed of fully differentiated cells. As discussed above, the IGF-1R expression is essential for driving luminal alveolar differentiation, linking IGF-1R to the luminal lineage [21, 22]. Furthermore, many studies indicate a down-regulation of IGF-1R upon cancer progression, whereas others report elevated levels in metastatic stages. Once cancer has been confirmed, the importance of IGF-1R for disease progression remains unclear. In our study, IGF-1R was highly expressed in patients with early breast cancer and overall positively associated with good prognostic variables. We have indicated the decrease of IGF-1R expression with disease progression. High-level IGF-1R expression had low stage breast cancer with multiple/multicentric unilateral or bilateral growth. We emphasize that IGF-1R could have effects in early phases of development of luminal breast cancer. Numerous in vitro studies demonstrate IGF-1R as a driver of self-renewal, stem cell surface markers, migration, and invasion in both normal and cancerous tissues and tumor initiation in hepatic, lung, prostate, and breast cancers [23]. Approximately 40–60% of ER-positive tumors express IGF-1R, while expression in ER-negative tumors is only 10–20%. Considering the correlation of IGF-1R with hormone-dependent tumor type and early stage, we assume that ER/IGF-1R axis might represent a distinct proliferative pathway during breast cancer development. Other studies report that IGF-1R is a receptor expressed in the basaloid type breast cancer and has a role in anti-HER-2 resistance (Herceptin) [24]. We found a negative correlation between IGF-1R-overexpressed and HER-2-positive breast cancer. In general, IGF-1R correlates with good prognostic markers, such as ER and PR-positivity and HER-2-negativity. However, the IGF-1R expression has differential effects in different breast cancer subtypes. For example, its expression has been shown to be positively correlated with improved breast cancer-specific survival among patients with ER-positive tumors, while its expression was associated with an inferior prognosis in patients with HER2-overexpressing or triple-negative tumors. In models of breast cancer cells that overexpress HER-2, anti-HER-2 activity is disrupted by increased expression of IGF-1R. Nowadays, antibody-based molecular therapies have been developed for HER-2. IGF-1R can form heterodimers with the HER-2 tyrosine kinase and contribute to the development of resistance to HER-2 inhibition with the monoclonal antibody. An association between IGF-1R and HER-2 in IGF-1R-dependent

tumor transformation has been reported in mammary luminal epithelial cells, indicating that the IGF-1/HER-2 cross-talk may occur via autocrine and paracrine signaling. A recent study concluded that neoadjuvant therapy can induce changes in the IGF-1R expression. Therefore, there are many studies with opposite results [25, 26]. It is possible that IGF-1R expression is dependent not only on the specific cell type and disease stage, but also it is dependent on specific therapy and another factor. In some other tumors, like lung cancer, the expression of IGF-1R correlated with a less favorable outcome [27]. This indicates that IGF-1R activities might be not only diverse but also tissue-specific. To test this hypothesis, we evaluated the protein expression of the most important components of the IGF-1R signaling pathway in hormone-dependent breast cancer and their significance according to the tumor subtypes. This clearly indicates other functions of IGF-1R that are not related to cell cycle progression and tumor aggressiveness, which may include cell differentiation and growth arrest.

CONCLUSION

IGF-1R is particularly important for the establishment and maintenance of the transformed phenotype and for the survival of tumor cells with anchorage-independent growth in breast carcinoma with luminal differentiation.

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Процена имунохистохемијске експресије рецептора инсулину-сличног фактора раста 1 у карциному дојке

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САЖЕТАК

Увод/Циљ Активација рецептора инсулину-сличног фактора раста 1 (*IGF-1R*) изазива покретање ћелијског циклуса из фазе раста (*G*1) у фазу синтезе (*S*). Оболели од карцинома дојке се деле на специфичне терапијске и прогностичке групе у зависности од експресије хормонских рецептора, естрогених (*ER*) и прогестеронских (*PR*), и експресије рецептора хуманог епидермалног фактора раста 2 (*HER*-2).

Циљ рада је откривање степена експресије *IGF-1R* у туморском ткиву код одређених терапијских група оболелих од карцинома дојке и његова корелација са важећим патохистолошким и имунохистохемијским прогностичким параметрима.

Методе Истраживање је спроведено на 129 укалупљених узорака инвазивног карцинома дојке код жена (у стадијуму болести I–III) уз постоперативно праћење тока болести 48 (36–108) месеци. За имунохистохемијско бојење коришћена су моноклонска антитела за визуализацију: *ER*, *PR*, *IGF-1R* и поликлонално антитело за *HER*-2.

Резултати Експресија *IGF-1R* је била у негативној корелацији са стадијумом болести ($p = 0,017$), степеном диферентованости тумора ($p = 0,001$) и експресијом *HER*-2 ($p = 0,003$). Позитивна корелација овог рецептора налазила се између мултифокалног/мултицентричног макроскопског начина раста карцинома дојке ($p = 0,036$) и експресије *ER* ($p = 0,001$) и *PR* ($p = 0,0001$). Коксова регресиона анализа времена без прогресије болести (*RFS*) показала је да стадијум болести ($p = 0,039$) и *HER*-2 ($p = 0,033$) представљају независне прогностичке варијабле. Експресија *IGF-1R* није имала утицај на клинички ток болести код особа са раком дојке ($p = 0,488$, Каплан–Мајер тест за *RFS*).

Закључак Болесници оперисани у почетном стадијуму болести са дијагностикованим добро диференцованим, хормонски зависним раком дојке имају већу *IGF-1R* експресију у односу на болеснике са троструко негативним и *HER*-2 амплификованим туморима дојке. Повећана *IGF-1R* експресија код карцинома са мултифокалним/мултицентричним макроскопским начином раста указује на значајну улогу овог рецептора у фази настанка тумора.

Кључне речи: рецептор инсулину-сличног фактора раста 1 (*IGF-1R*); хормонски зависни рак дојке; *HER*-2

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Pharmacological correction of retinal ischemia/ reperfusion by minoxidil

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SUMMARY
Introduction/Objective The objective of this paper was to increase the effectiveness of pharmacological correction of retinal ischemia-reperfusion by using minoxidil.
Methods The research was carried out on 180 Wistar rats. A modification of the retinal ischemia-reperfusion model was used, in which an increase in intraocular pressure is carried out by mechanical pressure (110 mmHg) to the front chamber of the eye for 30 minutes. Protective effects of minoxidil at a dose 0.5 mg/kg on the model of retinal ischemia-reperfusion were estimated by the changes in the level of retinal microcirculation (laser Doppler flowmetry), electroretinogram amplitude, morphometry of retinal layers after 1 hour and 72 hours of reperfusion.
Results Minoxidil at a dose 0.5 mg/kg of rat mass improves retinal microcirculation, its electrophysiological state after 1 hour and 72 hours of reperfusion, and prevents the development of degenerative changes in the retina caused by ischemic damage to a greater extent than recombinant erythropoietin at a dose of 50 IU/kg and sildenafil at a dose of 0.5 mg/kg in monotherapy. The protective effects of minoxidil were eliminated by the preliminary administration of glibenclamide at a dose of 5 mg/kg, which indicates the presence of the preconditioning effect of minoxidil, realized through adenosine triphosphate-dependent potassium channels.
Conclusion Minoxidil at a dose of 0.5 mg/kg of rat mass protects the retina from ischemic-reperfusion injury. Protective effects of minoxidil are carried out by a preconditioning action, as evidenced by the lack of positive effects with the administration of glibenclamide.
Keywords: ischemia-reperfusion; retina; minoxidil; erythropoietin; sildenafil; ATP-dependent potassium channels

INTRODUCTION

Local circulatory disorders in the branches of retinal artery are observed in diabetic retinopathy, hypertensive retinopathy, degenerative diseases of the retina, optic nerve atrophy vascular origin, traumatic eye injury, ischemic neuropathy [1, 2, 3].

Studying the way of how to improve tissue tolerance to ischemia is an actual problem of modern experimental and clinical pharmacology. Up to now, the treatment of ischemic retinal conditions was done by use of angioprotectors, antioxidants, fibrinolytics, anticoagulants and others. As the authors note, due to the instability and short-term effects after using these drugs in combination with other drugs and physiotherapy treatments is necessary to seek out a more effective way to improve blood circulation and increase resistance to ischemic retinal tissue having a specific orientation [4].

Thus, an important task is to find new, specific and highly effective means for correcting of retinal ischemia.

Therefore, the objective of the study is to increase the effectiveness of pharmacological correction of retinal ischemia-reperfusion by using minoxidil.

METHODS

Experiments were carried out on 180 Wistar rats weighing 250 ± 25 g. For the study, the rats were taken with no external signs of disease, passed quarantine regime.

Ethical principles of handling laboratory animals were observed in accordance with the European Convention for the Protection of Vertebral Animals Used for Experimental and Other Scientific Purposes, CETS No. 123.

Minoxidil, 0.5 mg/kg, was administered intragastrically (i/g) once 1 hour before ischemia-reperfusion modeling.

Recombinant erythropoietin (EPO) was administered intraperitoneally (i/p) once at a dose of 50 IU/kg 30 minutes before pathology modeling for the purpose of preconditioning as a reference drug [5].

Animals received i/p injection of sildenafil at a dose of 0.5 mg/kg once 30 minutes before pathology modeling.

Glibenclamide was administered at a dose of 5 mg/kg i/g once 1 hour before ischemia-reperfusion modeling.

Ischemia-reperfusion injury of the retina was simulated under anesthesia (chloral hydrate, 300 mg/kg of animal body weight, i.p.) by applying mechanical pressure (110 mmHg) to the anterior eye chamber for 30 minutes [4].

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The experiment included two series of animals (with an assessment of the parameters after 1 hour and 72 hours of reperfusion), nine groups in each series, 10 rats in each group.

The measuring of the level of retinal microcirculation of rats was carried out by laser Doppler flowmetry (LDF) after 1 hour and 72 hours of reperfusion [6]. Registration was carried out by MP150 data acquisition and analysis systems and the TSD144 needle-type sensor, with AcqKnowledge 4.2 software (BIOPAC Systems, Inc., Goleta, CA, USA). After animal anesthesia, assessment of microcirculation level was carried out at 10 points on the circumference of the eyeball; the recording duration of the microcirculation level readings at one point was 20 seconds. From the microcirculation level results at every point, the average value was calculated, which was taken as the indicator of the microcirculation level in the retina of the experimental animal. The value of microcirculation in the animal group was calculated as the average of the values obtained from each experimental animal in the group.

To perform electroretinography (ERG), after 1 hour and 72 hours of reperfusion, rats were kept in the dark for 30 minutes, then, anesthetized (chloral hydrate, 300 mg/kg, i/p), and fixed on the table isolated from electromagnetic radiation [7]. Strobe flash of white light that was connected to the STM200 stimulator (Biopac Systems, Inc.) and placed behind the animal; ERG registration was carried out in response to a single stimulation. Evoked biopotentials were run at a frequency of 1–1000 Hz, amplified, averaged, and presented graphically on the screen using the MP150 data acquisition and analysis system and the aforementioned software. The ERG recording was carried out for 0.5 seconds in each rat in the groups. To assess the degree of retinal ischemia, the ratio of the amplitudes of the a- and b-waves of ERG, the coefficient b/a was evaluated [7]. From 10 values received, the mean was derived for each group, which was introduced into the protocol.

After the LDF and ERG, eyes with surrounding tissues were subjected to enucleation in both series of experiments. Eyes with immediately adjacent tissues were fixed in 10% formalin solution for histological research. After fixation, the eyes were cut into two parts in the meridian direction strictly through the center, and both halves were poured into paraffin according to the standard procedure. Sections for the standard histological examination were stained with hematoxylin-eosin. A descriptive study of histological preparations was performed under a Axio Scope A1 microscope (Carl Zeiss Microscopy GMbH, Jena, Germany). The morphometric studies were performed on the Mikmed-5 microscope with the use of the Micro-Analysis View software (LOMO, JSC, Saint Petersburg, Russia) [8].

RESULTS

After the pathology modeling after 1 hour and 72 hours of reperfusion, microcirculation was measured in the retina by LDF, electrophysiological condition of the retina was determined by ERG, the extirpation of animals and enucleation of the eyes for morphological studies was carried out.

After the pathology modeling, microcirculation level measurement was performed after 1 hour and 72 hours of reperfusion by LDF. The results obtained after 1 hour of reperfusion are presented in Table 1.

Table 1. The level of retinal microcirculation after 1 h and 72 hour of reperfusion (M ± m), perfusion units

No.	Experimental groups	Level of microcirculation after 1 hour of reperfusion, PU (n = 10)	Level of microcirculation after 72 hours of reperfusion, PU (n = 10)
1	Intact	738.9 ± 37.6	743.9 ± 5.0
2	Control (ischemia)	1,155.0 ± 51.9*	353.3 ± 11.7*
3	Control + MIN	751.3 ± 21.8y	739.5 ± 14.1y
4	Control + EPO	798.5 ± 12.3y	724.0 ± 4.1y
5	Control + SIL	832.3 ± 20.1y	711.5 ± 15.3y
6	Control + Glib	1,135.8 ± 31.2*	359.4 ± 10.3*
7	Control + MIN + Glib	1,149.8 ± 18.6*	361.1 ± 10.9*
8	Control + EPO + Glib	1,148.3 ± 15.3*	372.3 ± 13.4*
9	Control + SIL + Glib	1,151.2 ± 31.9*	360.3 ± 12.1*

Glib – glibenclamide; SIL – sildenafil; PU – perfusion units; MIN – minoxidil; EPO – recombinant erythropoietin;
*p < 0.05 compared to intact rats;
yp < 0.05 compared to the control group

The level of microcirculation after ischemia modeling in the control group reached 1,155.0 ± 51.9 PU after 1 hour of reperfusion, which was significantly higher than the value in the group of intact animals ($p < 0.05$).

With the correction of pathology by minoxidil (MIN), microcirculation level in the retina after 1 hour of reperfusion decreased to 751.3 ± 21.8 PU, which was significantly different from the control group ($p < 0.05$).

With the correction of pathology by EPO, microcirculation level in the group was reduced to 798.5 ± 12.3 PU and was significantly different from the values in the control group ($p < 0.05$).

Introduction of glibenclamide, a blocker of adenosine triphosphate-sensitive (ATP-sensitive) potassium channels, prevented the reduction of microcirculation in groups with correction by MIN, EPO, sildenafil (SIL); this confirms the preconditioning action of these drugs in studied doses on retinal ischemia-reperfusion model on rats after 1 hour of reperfusion.

The level of microcirculation after the pathology modeling in the control group after 72 hours of reperfusion was 353.3 ± 11.7 PU, which was significantly lower than in the group of intact animals ($p < 0.05$). In the group with the correction by MIN, this rate increased to 739.5 ± 14.1 PU ($p < 0.05$), which was significantly different from the values in the control group.

Correction of the modeled pathology by EPO led to an increase of microcirculation level in the group to 724.0 ± 4.1 PU, which was significantly different from the values in the control group ($p < 0.05$).

Introduction of glibenclamide in groups with MIN-correction, EPO-correction, and SIL-correction prevented the improvement of the microcirculation level after 72 hours of reperfusion.

After the pathology modeling and measuring of microcirculation level in the retina, ERG on evoked potential was performed. The results obtained after 1 hour and 72 hours of reperfusion are shown in Table 2.

Table 2. Results of evaluation of electrophysiological retinal function after 1 hour and 72 hours of reperfusion (M ± m)

No.	Experimental groups	Ratio b/a after 1 hour of reperfusion (n = 10)	Ratio b/a after 72 hours of reperfusion (n = 10)
1	Intact	2.6 ± 0.09y	2.5 ± 0.10y
2	Control (ischemia)	2.0 ± 0.09*	1.2 ± 0.04*
3	Control + MIN	2.5 ± 0.06y	2.4 ± 0.09y
4	Control + EPO	2.5 ± 0.10y	2.3 ± 0.06y
5	Control + SIL	2.4 ± 0.09*y	2.3 ± 0.09y
6	Control + Glib	2.0 ± 0.08*	1.3 ± 0.04*
7	Control + MIN + Glib	2.1 ± 0.09*	1.3 ± 0.06*
8	Control + EPO + Glib	2.1 ± 0.09*	1.2 ± 0.07*
9	Control + SIL + Glib	2.0 ± 0.08*	1.2 ± 0.08*

MIN – minoxidil; EPO – recombinant erythropoietin; Glib – glibenclamide; SIL – sildenafil;
*p< 0.05 compared to intact rats; yp < 0.05 compared to the control group

The b/a ratio in the control group was 2.0 ± 0.09 after 1 hour of reperfusion, which was significantly different from the values in the group of intact animals ($p < 0.05$). In the group of animals with the correction by MIN, the b/a ratio was 2.5 ± 0.06 after 1 hour of reperfusion, which was significantly different from the group's ratio with retinal ischemia and approached the values in the group of intact animals ($p < 0.05$). An increase of this indicator in the group with the correction by EPO to 2.5 ± 0.10, by SIL up to 2.4 ± 0.09 after 1 hour of reperfusion, confirms the saving of retinal electrophysiological function after the pathology modeling.

The b/a coefficient in the control group after 72 hours of reperfusion was 1.2 ± 0.04, which was significantly different from that of the group of intact animals. In the group of animals with the correction by MIN, the b/a ratio was 2.4 ± 0.09, which was significantly different from that of the group with retinal ischemia ($p < 0.05$) and approached the values in the group of intact animals. The increase of this indicator in the group with the correction by EPO to 2.3 ± 0.06, SIL up to 2.3 ± 0.09 confirms the maintaining of electrophysiological retinal function after the pathology modeling.

Introduction of glibenclamide in groups with corrections by MIN, EPO, and SIL in monotherapy decreased the b/a ratio to values significantly different from the group of intact rats, indicating the blockade of the ATP-dependent potassium channels.

A decrease in the b/a ratio in animals with ischemia (control) due to inhibition of the positive b-wave of ERG indicates a violation of electrophysiological function of bipolar and Muller cells with the possible contribution of the horizontal and amacrine cells. Saving the electrophysiological function of the photoreceptor layer is confirmed by the absence of changes in the negative a-wave.

During the morphometric analysis of the thickness of the inner nuclear layer and a layer of photoreceptors, the increase of thickness of the inner nuclear layer was determined to amount to 25.9 ± 0.6 μm in the control group after 1 hour of reperfusion, which is significantly different from the values in the group of intact rats ($p < 0.05$) (Table 3).

In groups with the MIN-correction, the thickness of the inner nuclear layer was 23.7 ± 0.6 μm after 1 hour of reperfusion, which differs significantly from the values of the control group ($p < 0.05$). Prior administration of EPO reduced the thickness of the inner nuclear layer to 23.8 ± 0.6 μm, which was significantly different from the control group and approached the values in the group of intact animals ($p < 0.05$). In groups with the SIL-correction, the thickness of the inner nuclear layer was 24.0 ± 0.7 μm after 1 hour of reperfusion, which also differs significantly from the values of the control group ($p < 0.05$).

Prior administration of glibenclamide in groups with the MIN-correction, EPO-correction, and SIL-correction, after 1 hour of reperfusion, led to an increase of the thickness of the inner nuclear layer – group values were 25.7 ± 0.6 μm, 25.3 ± 0.4 μm, and 25.7 ± 0.5 μm, respectively.

The inner nuclear layer thickness was 20.3 ± 0.8 μm after 72 hours in the control group, which is significantly different from the group of intact animals ($p < 0.05$). In the group of animals with MIN and EPO, the inner nuclear layer thickness after 72 hours of reperfusion was 23.5 ± 0.5 μm and 23.3 ± 0.7 μm, respectively, which is significantly different from the values of the group with ischemia. In the group with SIL, the inner nuclear layer thickness was 22.7 ± 0.6 μm, which also differed significantly from the values of the control group ($p < 0.05$).

Table 3. Morphometric values of retinal layers of experimental animals after 1 hour and 72 hours of reperfusion (M ± m)

No.	Experimental groups	1 hour of reperfusion (n = 10)		72 hours of reperfusion (n = 10)	
		Thickness of the inner nuclear layer [μm]	Thickness of the photoreceptor layer [μm]	Thickness of the inner nuclear layer [μm]	Thickness of the photoreceptor layer [μm]
1	Intact	23.5 ± 0.8y	38.4 ± 0.8	23.8 ± 1.0y	38.1 ± 1.2
2	Control (ischemia)	25.9 ± 0.6*	39.1 ± 0.7	20.3 ± 0.8*	36.9 ± 0.9
3	Control + MIN	23.7 ± 0.6y	38.4 ± 0.9	23.5 ± 0.5y	37.9 ± 0.9
4	Control + EPO	23.8 ± 0.6y	38.6 ± 0.9	23.3 ± 0.7y	38.0 ± 1.0
5	Control + SIL	24.0 ± 0.7y	39.1 ± 0.6	22.7 ± 0.6y	37.3 ± 0.7
6	Control + Glib	25.8 ± 0.6*	39.2 ± 0.6	20.6 ± 0.6*	36.9 ± 0.9
7	Control + MIN + Glib	25.7 ± 0.6*	39.0 ± 0.5	20.3 ± 0.5*	37.2 ± 1.0
8	Control + EPO + Glib	25.3 ± 0.4*	38.6 ± 0.6	20.5 ± 0.5*	37.6 ± 1.1
9	Control + SIL + Glib	25.7 ± 0.5*	39.0 ± 0.7	20.5 ± 0.8*	38.0 ± 1.2

MIN – minoxidil; EPO – recombinant erythropoietin; Glib – glibenclamide; SIL – sildenafil;
*p < 0.05 compared to intact rats; yp < 0.05 compared to the control group

DISCUSSION

The search of new methods of retinoprotection for possible reduction of the damaging effect of ischemia, formed in various systemic diseases, is an urgent task of pharmacology and ophthalmology. Segment of drugs for the treatment of vascular diseases of the eye such as complication from hypertension, diabetes, and others, would be expedient to expand due to an increase in morbidity and lack of funds for targeted correction of ischemic lesions of the eye vessels.

Based on the fact that electrophysiological studies often have a decisive importance in the early and differential diagnosis of retinal disorders, to study the correction of functional changes in the retina, researcher must conduct a comprehensive analysis, including electroretinography and microcirculation research [9]. Analysis of the dynamics of retinal electrogenesis allows to evaluate the nature and topography of retinal disorders and to identify the most labile hypoxic retinal structure, as well as their reaction to the correction by the medications.

The most pronounced retinal protective action was observed in groups with pharmacological preconditioning by minoxidil at a dose of 0.5 mg/kg after 1 hour and 72 hours of reperfusion.

A single i/g injection of minoxidil at a dose of 0.5 mg/kg, 60 minutes before modeling of retinal ischemia-reperfusion, significantly reduced the level of retinal microcirculation after 1 hour of reperfusion, and saved the retinal electrophysiological activity, which was also confirmed by morphometrics of retinal layers. We found that minoxidil prevents the retinal layers' damages caused by ischemic injury to a greater extent than recombinant erythropoietin at a dose of 50 IU/kg and sildenafil at a dose of 0.5 mg/kg in monotherapy after 1 hour of reperfusion and degenerative changes of retinal layers after 72 hours of reperfusion.

Prior administration of glibenclamide at a dose of 5 mg/kg eliminated the positive effects of minoxidil, erythropoietin, and sildenafil, which confirms the implementation of retinal protection by preconditioning with the participation of ATP-dependent potassium channels.

CONCLUSION

Minoxidil at a dose of 0.5 mg/kg protects the retina from ischemic-reperfusion injury better than recombinant erythropoietin at a dose of 50 IU/kg and sildenafil at a dose of 0.5 mg/kg in monotherapy.

Protective effects of minoxidil are carried out by a preconditioning action as evidenced by the lack of positive effects with administration of glibenclamide.

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Фармаколошка корекција ретиналне исхемије/реперфузије миноксидалом

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САЖЕТАК

Увод/Циљ Циљ студије јесте да се побољша ефикасност фармаколошке корекције исхемије-реперфузије мрежњаче миноксидилом.

Методе Истраживање је спроведено на 180 пацова врсте вистар. Коришћена је модификација модела исхемије-реперфузије, при чему се повећање интраокуларног притиска вршило механичким притиском (110 *mmHg*) на предњу комору ока у трајању од 30 минута. Заштитни ефекти миноксидила у дози од 0,5 *mg/kg* процењене су на основу промена микроциркулације мрежњаче (ласерска доплер-флоуметрија), амплитуде електроретинограма, морфометрије слојева мрежњаче после једног и 72 сата од реперфузије.

Резултати Миноксидил у дози од 0,5 *mg/kg* масе пацова побољшава микроциркулацију мрежњаче, њено електрофизиолошко стање после једног и 72 сата реперфузије и спречава развој дегенеративних промена слојева мрежњаче изазваних исхемијом више него монотерапија рекомбинантним еритропоетином у дози од 50 *IU/kg* и силденафилом у дози од 0,5 *mg/kg*. Заштитно дејство миноксидила елиминише се давањем глибенкламида у дози од 5 *mg/kg*, што доказује прекондиционирани ефекат код миноксидила, који је остварен кроз АТП-зависне калијумове канале.

Закључци Миноксидил у дози од 0,5 *mg/kg* штити мрежњачу од исхемије / реперфузионе повреде. Заштитни ефекат миноксидила се реализује посредством прекондиционирања, што доказује недостатак позитивних ефеката на примену глибенкламида.

Кључне речи: исхемија-реперфузија; ретина; миноксидил; еритропоетин; силденафил; АТП-зависни канали калијума

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Reading performance of low vision children after using low vision aids

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SUMMARY

Introduction/Objective The objectives of the paper are to assess the causes of low vision (LV) in pediatric population in Montenegro and to evaluate the influence of low vision aids (LVA) on reading performance regarding the speed of reading and the understanding of the read text.

Methods A prospective study was conducted on 40 "treatable" LV children what represent all registered LV children in Montenegro. All participants read the same text before and after using LVA. Reading rate was calculated as the number of words read per minute. Functional speed of reading was calculated as the ratio of the rate of reading and the understanding of the read text multiplied by 100.

Results The study comprised 40 LV children with the mean age of 12.60 ± 4.06 years (20 boys and 20 girls). The most common cause of LV in children were premature retinopathy (10/40 or 25%), retinitis pigmentosa (8/40 or 20%), optic nerve anomaly (5/40 or 13%), degenerative myopia (4/40 or 10%), macular dysgenesis (4/40 or 10%), Stargardt disease (3/40 or 7%), optic nerve atrophy (2/40 or 5%), and albinism (2/40 or 5%). Nystagmus was found in 11 LV children or 28% of the group. LVA were prescribed to all of them. Reading speed before *vs.* after LVA use was 36.58 ± 35.60 *vs.* 73.83 ± 27.05 words/minute ($p < 0.001$), while functional reading was 26.00 ± 30.43 *vs.* 59.41 ± 29.34 ($p < 0.001$).

Conclusion LV children demonstrate a significant improvement in reading performance by using LVA.

Keywords: low vision aid; low vision children; reading performance

INTRODUCTION

According to the International Classification of Diseases 10, there are four levels of visual function: normal vision, moderate visual impairment (VI), severe VI, and blindness [1]. Moderate and severe VI are grouped under the term "low vision" (LV). "Functional" LV is defined as presenting best-corrected visual acuity (BCVA) in the better-seeing eye of less than 0.3 and more than 0.05 according to the World Health Organization (WHO) criteria, VA < 0.3 and VA ≥ 0.05 (or according to the United States (US) criteria VA < 0.5 and VA ≥ 0.1) and as blindness (WHO criteria VA < 0.05; US criteria VA < 0.1) [1]. LV cannot be improved or corrected with medical treatment, surgery, nor with conventional glasses or with contact lenses. Unlike total blindness, most individuals with LV have some degree of useful, residual sight even when vision loss is significant. The WHO estimated that 19 million children worldwide are visually impaired; of these, 1.4 million are irreversibly blind [2]. The International Classification of Functioning, Disability and Health adopted by the WHO can be used as a framework to comprehensively describe the problems of persons with VI and the environmental factors which influence their lives [3]. Surely, LV significantly interferes with the functioning of a person. Common subjective complains of LV persons include the loss of central and/or peripheral vision, constricted visual filed, abnormal color perception, generalized haze, blurred vision, extreme light sensitivity, and night blindness. LV patients represent unique challenge in ophthalmic and optometric care.

Very few LV clinics are available even in the most developed of countries. The Low Vision Service for pediatric patients at the Clinical Center of Podgorica, Montenegro (a referral tertiary health care center in Montenegro) has been established in 2013. The Service is a pioneer of LV service in the region, covering all the needs of LV children, including education, training, and sight rehabilitation. A team of trained specialists with comprehensive, multidisciplinary approach to LV children has the purpose to help them maximize the remaining functional vision and maintain their independence in daily living. Podgorica pediatric LV service meets the WHO recommendation for establishing LV centers to fight avoidable childhood blindness. Namely, since 2004, the WHO in partnership with Lions Clubs International has established a global network of 45 childhood blindness centers in 35 countries for the preservation, restoration, or rehabilitation of

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sight in children [2]. The LV center in Podgorica is exceptional since all registered LV children have the use of LV aids (LVA) at no cost to them.

According to the available data, there are approximately 1,000 blind and visually impaired persons of all ages registered in Montenegro. The exact number of blind LV children is unknown. There is no precise national register on the prevalence of childhood VI, but, according to available sources (referral associations, primary health care registers, etc.), it has been estimated that there are 200 VI children and 50–60 LV children in Montenegro at this moment. The assessment of the causes of VI is important to develop preventive and therapeutic strategies. The standardized protocol for reporting causes of blindness in children, with coding instructions and a database for statistical analysis developed by the International Centre for Eye Health, the WHO Collaborating Centre for Blindness Prevention, and the WHO, also serves as a mechanism to monitor changing pattern of childhood blindness [4].

The objectives of this paper are to assess the causes of LV in pediatric population in Montenegro and to evaluate the influence of using LV aids in reading performance regarding the speed of reading and the understanding of the read text.

METHODS

A prospective study was conducted on 40 "treatable" LV children, who represent all registered LV children in Montenegro. Including criteria were the BCVA ranging 0.05–0.3 in the better-seeing eye and age less than 17 years. The term 'treatable LV person' represents a person who has demonstrated an improvement in reading or in distance vision using LVA. Children were recruited from registers of Association of Blind and LV Persons (one association with eight local branches), followed by two schools for special education of blind and LV children (in Podgorica and Bijela) and primary eye care registers from all over the country. All amblyopic children (215 of them) underwent complete ophthalmological examination. In total, 40 children met the criteria of a 'treatable LV person'. The study was performed in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Review Board (decision number 03/01-12238/2). Written informed consent was obtained from all parents.

All the participants read the same text before and after using LVA. The words were printed in seven lines with 1.5-line spacing (0.8 cm), with black letters on white background to enhance contrast; the font used was Times New Roman, the letter size was N12. Reading rate was calculated as the number of read words per minute. Understanding of the read text was measured by a multiple-choice test with 20 questions related to the text. Scores were rated from 0 to 20 and presented as a percentage (for example, if an LV child had 12 correct answer, the score of understanding was 60%). Functional speed of reading was calculated as the ratio of the rate of reading and the understanding of the read text multiplied by 100.

Statistical analysis

All parameters were expressed as mean ± standard deviation (SD). Differences between pre- and post-LVA use were evaluated by the Wilcoxon signed-ranks test. The level of statistical significance was set at 0.05. All statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Forty LV children with the mean age of 12.60 ± 4.06 years (20 boys and 20 girls) underwent complete ophthalmological examination and socio-epidemiological assessment. The mean age of the girls was 10.95 ± 4.16 years, while that of the boys was 14.25 ± 3.28 years. All the LV children lived in families with both biological parents.

Regarding the educational profile of fathers of the LV children, 20 of them had completed primary school (50%), 19 had secondary degree (47.5%), and one (2.5%) had obtained higher education. Among mothers, none had finished higher education, 19 mothers had secondary school finished (47.5%), and 21 had completed primary school.

In the group of children with retinal dystrophy, eight children (20%) had retinopathy pigmentosa, in three cases (7%) was diagnosed Stargardt macular dystrophy. Development anomalies of the optic nerve had four children with optic hypoplasia and one with congenital coloboma of the optic disc. Associated macular and optic nerve anomalies were found in two cases, while four children had isolated macular hypoplasia. Causes of LV were presented in Table 1.

Table 1. Causes of low vision in children

Clinical finding	Number of patients	%
Retinal dystrophy	11	27
Premature retinopathy	10	25
Macular dysgenesis	4	10
Optic nerve anomaly	5	13
Associated macular and optic nerve anomalies	2	5
Central nervous tumor	2	5
Degenerative myopia	4	10
Albinism	2	5
Total	40	100

Optic atrophy in two cases was a consequence of intracranial tumor, but it was also found in two premature children and in one with albinism. Nystagmus was found in 11 cases (nine horizontal, one rotatory, and one vertical). Macular scars were diagnosed in two highly myopic cases and in three children with retinitis pigmentosa. Four children had esotropia, while two had exotropia.

BCVA concerning the better seeing eye was hand moving in eight children (20% of all); in 12 children (30% of all) the score was 0.1 while 20 children (50% of all) had a score of 0.2–0.4. In three children, fellow eye was blind, 16 children (40% of all) had BCVA described as hand movement only, while 21 children had less than 0.2 according to Snellen chart.

Regarding the refractive error, 27/40 children had myopia, 3/40 (7.5% of all) had hyperopia, 2/40 (5% of all) had astigmatism, while eight children had no possibility of being optically corrected.

All the children accepted LVA for reading distance. In Table 2 are listed devices which they had used.

Table 2. List of low vision aids for reading prescribed to low vision children

Low vision aid	Number of children	%
Electronic magnifier	17	42
Ready fit prism	21	53
Telescope	2	5
Total	40	100

The speed of reading and understanding of content was measured before and one month after using of LVA for reading. The results are presented in Table 3. As it has been shown, speed and functional speed of reading has been significantly improved.

Table 3. Speed of reading and functional reading results in low vision children before and after using low vision aids

Tested parameter		Before $\bar{x} \pm$ sd med. (min.–max.)	After $\bar{x} \pm$ sd med. (min.–max.)	p
Reading	speed	36.58 ± 35.60 21.5 (0–120)	73.83 ± 27.05 81 (31–121)	< 0.001[a]
	functional reading	26.00 ± 30.43 13.72 (0–108)	59.41 ± 29.34 62.65 (14.40–114.95)	< 0.001[a]

[a]Wilcoxon signed-ranks test

DISCUSSION

VI results in different degrees of difficulty in performing daily activities and tasks. Great progress has been made in the development and deployment of intraocular LVA, such as implantable monocular telescope, followed by the global positioning system-based navigation system, location-aware LVA. LV children have particular and additional tasks concerning education, and reading is one of the core activities of their studies. As it is well known, LV and VI affect their sensorial development, physical, psychological, and social well-being. Socio-epidemiological or so-called external factors (i.e. education/employment and parental influence) can either facilitate or hinder participation [3]. In our study, all the parents had completed primary and approximately half of them had completed secondary school. Finishing at least primary school is a legislative obligation that can explain a relatively high percentage of parents who had completed at least primary education level.

The commonest cause of LV among children and adolescents in Montenegro was retinal dystrophy – retinitis pigmentosa (20%), followed by Stargardt disease (7%). Also present are premature retinopathy (25%), macular dysgenesis (10%), and myopic degenerative changes (10%). The etiology of childhood VI in Montenegro includes 13% of those who had VI with coexisting neurological disability. In contrast, in Brazil, the most frequent finding was congenital glaucoma (21.1%), while in a Sao Paolo study congenital glaucoma (30.6%) was found to have higher prevalence, followed by macular retinochoroiditis due to congenital toxoplasmosis (16.7%), congenital cataract (12.8%), retinal and macular inherited disorders (11.7%), and optic atrophy (9.8%) [4, 5]. Furthermore, Haddad et al. [5] reported that only 2% of children with congenital glaucoma had normal visual acuity levels, while 29% had mild VI, 28% had moderate VI, 15% had severe VI, 11% had profound VI, and 15% had near blindness. Principal causes of blindness among VI children in New Zealand were cerebral VI in 61 children (42.4%), optic nerve atrophy in 18 children (12.5%), and retinal dystrophy in 13 children (9%). The main avoidable causes of blindness in 27 children (19%) were neonatal trauma, asphyxia in nine children (33%), and non-accidental injury in six children (22%) [6].

Causes of LV in childhood and adolescence in Africa and Asia differs from those in other parts of the world. In Nigeria, the most common causes were cataract (21%), followed by glaucoma (12.9%), but in as much as 43.6% of LV children, causes of blindness were found to be treatable [7], while Olusanya et al. [8] reported that the most common cause of LV in children was albinism (24.4%) and optic atrophy (24.4%). In Ekiti State Special Education School, Nigeria, in a study conducted in May–June 2008 it was reported that the most common causes of VI are cataract (26.7%), glaucoma (20%), retinitis pigmentosa (16.7%), and posttraumatic phthisis bulbi (6.7%); blindness was avoidable in as much as 61% of the cases[9]. In Ethiopia, the most common causes of childhood VI were corneal disease/phthisis (62.4%), followed by optic nerve lesions (9.8%), cataract/aphakia (9.2%), and lesions of the uvea (8.8%). The etiology was unknown in 45.1% of the cases, while 68% of the cases were considered to be potentially avoidable [10]. Cataract and corneal damage are the leading causes of LV in children in India as well. Even though the time difference between the studies is almost 20 years, the conclusions of both studies were that in prevention of avoidable blindness, it is very important to provide measles and rubella immunization and nutrition care [11].

Among LV children in Nepal, refractive error and amblyopia (20.1%), retinitis pigmentosa (14.9%), and macular dystrophy (13.4%) were the most common causes of pediatric VI. Nystagmus (50%) was the most common cause of LV in the one to five years age group, whereas refractive error and amblyopia were the major causes in the six to 10 and 11 to 16 years age group (17.6 and 22.9%, respectively) [12].

It is a widely accepted belief in clinical practice that children with VI can benefit from the use of an LVA [13]. To LV patients at the Instituto Brasileiro de Oftalmologia e Prevencao da Cegueira, telescopic system was the only optical aid indicated for distance (44%) and glasses were the most indicated aid for near vision (54.5%), which were prescribed as such [14]. In India, only 18% of LV children with coloboma, microcornea, and microphthalmos have been using telescopes, while a stand magnifier has been prescribed in 6% of children [15]. LV children from Montenegro have a special possibility to be treated with the

most diverse range of LVA for large distance, intermediate distance, and short distance, respectively.

CONCLUSION

According to the published data, this is the first study targeting the influence of LVA use in LV children on reading performance, as well as the first report on demographic data and causes of LV among LV children in Montenegro. Our results indicate that LVA for reading or short distances significantly improves reading performance in LV children and should be applied in everyday practice.

NOTE

This paper is a part of the doctoral thesis by Zorica Tončić, titled "The influence of visual rehabilitation on the quality of life using low vision aids in low vision children."

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Брзина читања код слабовиде деце после коришћења помагала за слабовиде

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САЖЕТАК

Увод/Циљ Циљ овог рада је био да се утврде разлози слабовидости деце у Црној Гори и утицај специјалних помагала на брзину и на функционално читање код ове деце.

Методе Проспективна студија спроведена је на 40 слабовиде деце која су користила специјална помагала. Сва деца су добила да прочитају исти текст пре и после кошћења помагала. Брзина читања је исказана као број прочиатних речи у минути, а функционално читање као однос између брзине читања и разумевања прочитаног × 100.

Резултати Средњи узраст слабовиде деце је био 12,60 ± 4,06 година (20 дечака и 20 девојчица). Најчешћи разлози слабовидости су били: прематурна ретинопатија (10/40; 25%), пигментни ретинитис (8/40; 20%), аномалије оптичког нерва (5/40; 13%), дегенеративна миопија (4/40; 10%), макуларне дизгенезије (4/40; 10%), Старгард дистрофија (3/40; 7%), атрофија оптичког нерва (2/40; 5%), албинизам (2/40; 5%). Нистагмус је дијагностикован код 11 деце (28%). Свој слабовидој деци су прописана помагала. Брзина читања пре у односу на брзину читања после коришћења помагала је била 36,58 ± 35,60, тј. 73,83 ± 27,05 речи/мин. ($p < 0,001$), док је функционално читање било 26,00 ± 30,43, тј. 59,41 ± 29,34 ($p < 0,001$).

Закључак Слабовида деца показују значајно побољшање читања после коришћења специјалних помагала.

Кључне речи: помагала за слабовиде; слабовида деца; брзина читања

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The impact of age, gender, acuteness, and etiology on short-term clinical outcome in patients with subdural hematomas – international dual-center study

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SUMMARY

Introduction/Objective Subdural hematoma is one of the most common intracranial types of bleeding with high risk of disability and mortality.

The aim of this study was to determine the influence of age, sex, acuteness, and etiology of subdural hematoma on short-term clinical outcome in these patients.

Methods We retrospectively studied 288 patients who were diagnosed and operated on for subdural hematomas (SDH) with different etiology (traumatic and spontaneous) and acuteness (acute, subacute, and chronic) for a period of five years. Patients scored ≤ 5 points on the Glasgow Coma Scale at hospital admission were not included in this study. Clinical outcome was assessed by the modified Rankin Scale (mRS) score at hospital discharge. Descriptive statistics and logistic regression analysis were used to determine the effect of the investigated factors on short-term clinical outcome.

Results Logistic regression analysis was conducted to predict degree of recovery (good = mRS ≤1 *vs.* poor = mRS ≥ 2 or death) using sex, age, acuteness, and etiology of SDH as predictive factors. It was established that the following three factors made a significant contribution to the outcome: age ($p = 0.004$), acuteness ($p < 0.001$), and etiology of a hematoma ($p = 0.023$), with acuteness being the strongest predictive factor. Sex was not a significant predictor, while age under 70 years and spontaneous origin of SDH were associated with lower mRS scores and had a positive effect on recovery chances.

Conclusion Age, acuteness, and etiology of hematoma are important predictive factors that influence the short-term clinical outcome in patients with SDH. These parameters should be taken into account when giving prognosis for recovery chances to a patient's family and relatives.

Keywords: subdural hematoma; outcome; predictive factors; recovery; surgery

INTRODUCTION

A subdural hematoma (SDH) is a common type of intracranial hemorrhage. The prevalence and total cost for a subdural hematoma has increased significantly in the last decade [1]. An acute intracranial subdural hematoma (ASDH) is commonly associated with high incidence of morbidity and mortality, despite its fatality rate has begun to decline with the developments in medicine and is currently around 14% [2, 3, 4]. On the other hand, some patients develop chronic SDH (CSDH) from causes other than head injury, such as brain surgery, neovascularization of the hematoma capsule, or coagulation factors. In addition, some factors, such as old age, alcoholism, coagulopathy, neurological status at admission, hematoma density, and irrigation, are reported to be correlated with the outcome [5]. However, these results are still controversial, and the influence of some important predictive factors on clinical outcome of SDH, regardless of its etiology and acuteness, has not yet been fully elucidated.

Therefore, the aim of this study was to determine the influence of age, sex, acuteness, and etiology on short-term clinical outcome in patients with subdural hematomas.

METHODS

Study design

This international study was performed in two neurosurgical centers – the Clinic for Neurosurgery, Clinical Center of Niš, Serbia, and the Clinic for Neurosurgery, St George University Hospital, Plovdiv, Bulgaria. It was approved by the institutional review boards, and informed consent was waived. Patient information was obtained via a retrospective review of medical records for the period between January 2011 and December 2015.

Patients

We identified and included a total of 288 patients diagnosed and operated on for SDHs,

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Table 1. Group comparisons of the investigated factors and their correlation with clinical outcome

Factors	No. of patents (%)	p-value	mRS			p-value
			mean	SE	median	
Age						
≤ 70	138 (47.9)	ns	1.40	0.14	1	0.002
> 70	150 (52.1)		1.99	0.16	1	
Sex						
male	198 (68.8)	< 0.001	1.63	0.12	1	ns
female	90 (31.3)		1.88	0.21	1	
Acuteness of SDH						
acute	44 (15.3)	< 0.001	3.16	0.30	3	< 0.001
subacute/chronic	244 (84.7)		1.45	0.11	1	
Etiology of SDH						
spontaneous	179 (62.2)	< 0.001	1.49	0.13	1	0.008
traumatic	109 (37.8)		2.06	0.19	1	
Total	288 (100)		1.71	0.11	1	

mRS – modified Rankin Scale; ns – non-significant; SDH – subdural hematoma

regardless of their acuteness (acute, subacute, or chronic), and etiology (traumatic or spontaneous). We collected data with relation to factors such as initial score on the Glasgow Coma Scale (GCS), length of hospital stay, age, sex, acuteness, and etiology of SDH. The short-term clinical outcome was assessed by the modified Rankin Scale (mRS) at hospital discharge. Thus, the follow-up period varied from seven to 35 days. Patients scored ≤ 5 points on the GCS at hospital admission were not included in the study because they usually have moribund prognosis.

In order to determine the influence of the investigated factors on the clinical outcome, the patients were grouped for comparisons as follows: patients aged ≤ 70 years *vs.* patients aged > 70 years; male patients *vs.* female patients; patients with acute SDH *vs.* patients with subacute/chronic SDH; patients with traumatic *vs.* patients with spontaneous (non-traumatic) SDH.

Statistics

Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). Distribution of the variables was tested using the Shapiro–Wilk test. We used the Mann–Whitney U-test to test for differences between groups and correlation analyses (Spearman's r). Logistic regression model was run to determine which variables were independently associated with functional recovery and mortality. All variables with $p < 0.05$ were considered statistically significant.

RESULTS

The mean age was 69.62 ± 0.79 years (range being 20–95 years), with 52.1% being over the age of 70 years. Male-to-female ratio was 2.2:1. The most common types of SDH were subacute/chronic (84.7%) and spontaneous (62.2%). The overall mortality rate was 10.4%. The average mRS score upon discharge was 1.71 ± 0.11. Sex was not significantly associated with differences in mRS score nor with the other factors ($p < 0.05$). Being above/below the age of 70 years was significantly associated with differences in the mRS score ($U = 8{,}307.5$, $p = 0.002$) and the outcome (independence, dependence or death) ($U = 9{,}124.5$, $p = 0.016$). Outcome (mRS score) was also associated with the acuteness ($U = 2{,}578$, $p < 0.001$) and etiology of SDH ($U = 8{,}014$, $p = 0.008$) (Table 1).

There was a moderate negative correlation between the acuteness and the mRS score (Spearman's $r = -0.339$, $p < 0.001$).

Clinical outcome and correlation between good recovery and investigated factors have been summarized in Tables 2 and 3.

A logistic regression analysis was conducted to predict degree of recovery (good = mRS ≤ 1 *vs.* poor = mRS ≥ 2 or death) using sex, age, acuteness, and etiology of SDH as predictors. A test of the full model against a constant only model was statistically significant, indicating that the predictors were reliably distinguished between acceptors and decliners of the offer ($\chi^2 = 49.535$, $p < 0.001$ with $df = 4$). Nagelkerke's R^2 of 0.218 indicated a relationship between prediction and grouping. Prediction success overall was 72.6% (94.1% for good and 32.7% for poor). The Wald criterion demonstrated that three factors made a significant contribution to prediction: age ($p = 0.004$), acuteness ($p < 0.001$) and etiology of SDH ($p = 0.023$), with acuteness being the strongest predictor. Sex was not a significant predictor, whereas age under 70 years and spontaneous origin of SDH were associated with lower mRS scores and had positive effect on recovery chances.

DISCUSSION

Many factors, including age, have been reported to influence the outcome in traumatic and non-traumatic SDH patients [6, 7, 8]. Age is considered as one of the major predictive factors for mortality in patients with traumatic

Table 2. Summary of clinical outcome and functional recovery of patients with a subdural hematoma at discharge

Clinical outcome	No. of patient (%)
mRS	
no symptoms	68 (23.6)
no significant disability	119 (41.3)
slight disability	38 (13.2)
moderate disability	17 (5.9)
moderate severe disability	14 (4.9)
severe disability	2 (0.7)
death	30 (10.4)
Outcome (based on mRS)	
independent (mRS = 0–2)	225 (78.1)
dependent (mRS = 3–5)	33 (11.5)
death	30 (10.4)
Recovery of surviving patients (n = 258)	
good/full recovery (mRS ≤ 1)	187 (72.5)
poor/disability (mRS = 2–5)	71 (27.5)

mRS – modified Rankin Scale

Table 3. Correlations between the investigated factors and good clinical outcome

Factors	Functional recovery (mRS ≤ 2) n (% within group)	p-value
Age		
≤ 70	116 (84.1)	0.016
> 70	109 (72.7)	
Sex		
male	156 (78.8)	ns
female	69 (76.7)	
Acuteness of SDH		
acute	21 (47.7)	< 0.001
subacute/chronic	204 (83.6)	
Etiology of SDH		
spontaneous	149 (83.2)	< 0.05
traumatic	76 (69.7)	
Total	225 (78.1)	

mRS – modified Rankin Scale; ns – non-significant; SDH – subdural hematoma

ASDH [9]. A recent study reported that the age of less or more than 77 years had been found to be an independent prognostic factor for the functional outcome in patients with CSDH [10]. Age is also indicated as a positive risk factor for a higher perioperative morbidity and mortality [11]. On the other hand, other authors shared that despite significantly higher complication rate in elderly patients with CSDH, the clinical outcome at one month after surgery in patients older than 85 years was significantly better in comparison to patients younger than 85 years [11]. On the contrary, in a large, prospective, multicenter, observational cohort study carried out in the United Kingdom by Brennan et al. [12], over 1,205 patients with CSDH, showed that increasing patient age had independently predicted unfavorable functional outcomes [12]. Another large study conducted by Toi et al. [13], which included 63,358 patients with newly diagnosed CSDH, also confirmed that the percentage of poor outcomes at discharge tended to be higher in elderly patients. Several publications demonstrated that clinical outcome of patients over 70 years old who have received surgical treatment for traumatic ASDH was significantly worse with the increase in age [14, 15, 16]. Our study found that patients with subdural bleeding older than 70 years had poorer short-term outcomes following surgery compared to those younger than 70 years. We identified the age less than 70 years as a significant predictor for better outcome in a mixed cohort of patients with SDH, regardless of its acuteness and etiology. Similar findings have been recently reported [17].

A recent study showed that premorbid impaired activities of daily living, consciousness disturbance, acute-to-chronic subdural hematoma, and death as outcomes at discharge were significantly more frequent in women than in men. Women had less frequent instances of good recovery. Female sex was also identified as a predictor of death at discharge [18]. In contrast, our study did not identify sex to be significantly associated with differences in outcome. Logistic regression analysis confirmed that sex was not a significant predictor of clinical outcome of patients with SDH, a fact also observed by other authors [9]. The prognosis for patients with ASDH remains poor, especially in elderly patients [19]. It has long been recognized that ASDH is often associated with intraparenchymal injuries and brain swelling. Hence, outcomes have historically been worse for patients with ASDH with mortality rates as high as 68% [20, 21]. Pathophysiology, patient populations, management strategies, and outcomes differ significantly between ASDH and CSDH [22]. As recently reported, patients with mixed acuteness or subacute/chronic SDH had significantly better three-month mRS with surgery compared to those with only ASDH [17]. In contrast, another study which investigated 45 patients over the age of 70 did not establish any change in the functional status from admission to follow-up in the groups of patients with ASDH and CSDH [23]. We also confirmed that acuteness of SDH was significantly correlated with functional recovery and outcome. Moreover, the acuteness was found to be the strongest predictor of clinical outcome. Our study suggested that patients with ASDH tend to have poorer outcome and lower chances for good recovery compared to patients with subacute/chronic SDH.

Patients with CSDH who reported a history of head injury are susceptible to poorer outcome [5]. However, SDH can develop spontaneously, without any history of sustained cranial trauma as a result of brain surgery, neovascularization of the hematoma capsule, or coagulation factors [5, 24, 25]. The etiology remains unknown in over 25% of cases because many patients have not experienced a prior traumatic event [26, 27]. We found significant correlation between etiology of SDH and clinical outcome. The etiology of SDH was also found to be a significant predictor of outcome. Our results indicated that patients with spontaneous (non-traumatic) SDH had better outcome and greater recovery chances after surgery than patients with traumatic SDH. One possible explanation is that traumatic SDH are often accompanied by a variety of diffuse parenchymal injuries and cerebral edema that increase brain damage and worsen prognosis.

We could not identify any other publication in the literature that discusses and compares clinical outcome in patients with spontaneous versus traumatic SDH with heterogeneous acuteness. Therefore, we consider this our original finding that could have social, economic and, chiefly, personal significance. Recovery of such patients and their ability to adequately participate in everyday life has a great impact on their quality of life.

CONCLUSION

In this study we documented that age, acuteness, and etiology of hematomas are important predictors of short-term clinical outcome in patients with SDH. Based on this, neurosurgeons can give a more accurate prognosis about the disease course and the outcome. Further studies are needed to elucidate the influence of these factors on long-term clinical outcome.

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Утицај старости, пола, динамике настанка и етилогије на краткорочни клинички исход код болесника са субдуралним хематомима – међународна двоцентрична студија

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САЖЕТАК

Увод/Циљ Субдурални хематоми су један од најчешћих видова интракранијалног крварења, са високим процентом морталитета и морбидитета.

Циљ нашег истраживања је био да утврдимо утицај старости, пола, динамике настанка и етиологије субдуралних хематома на краткорочни клинички исход код ових болесника.

Методе Ретроспективно смо анализирали 288 болесника који су оперисани од субдуралних хематома (СДХ) различите етиологије (трауматски или спонтани) и динамике настанка (акутни, субакутни и хронични) у периоду од пет година. У студију нису укључени сви болесници са Глазгов кома скалом ≤5. Клинички исход је утврђиван помоћу модификоване Ранкин скале (мРС) непосредно пре отпуста са клинике. Описна статистичка и логистичка регресиона анализа су коришћене за утврђивање ефекта испитиваних фактора на краткорочни клинички исход.

Резултати За предвиђање степена опоравака коришћена је метода логистичке регресионе анализе (добар = мРС ≤ 1 насупрот лошем мРС ≥ 2 или смрти), која је узимала у обзир старост, пол, динамику настанка и етилогију СДХ као факторе прогнозе. Утврђено је да су три фактора од статистичког значаја за степен опоравка: старост ($p = 0,004$), динамика настанка ($p < 0,001$) и етиологија хематома ($p = 0,023$). Пол болесника није био од прогностичког значаја, док су старост испод 70 година и нетрауматско порекло хематома удружени са ниским мРС имали позитиван ефект на опоравак.

Закључак Старост, динамика настанка и етилогија хематома су битни прогностички фактори који утичу на краткорочни клинички исход код болесника са СДХ. Ови параметри би требало да се узму у обзир када се даје прогноза опоравка.

Кључне речи: субдурални хематом; исход; прогностички фактори; опоравак; операција

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Operation time and intraoperative fluoroscopy time in different internal fixation methods for subtrochanteric fractures treatment

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SUMMARY

Introduction/Objective Subtrochanteric fractures are unstable, tending to a varus, antecurvatum, and shortening deformity.

The aim of this paper was to compare operation time and fluoroscopy time between different internal fixation methods in the treatment of subtrochanteric fractures.

Method The prospective study of the group of 27 patients with a subtrochanteric fracture treated by the SIF (selfdynamisable internal fixator with a trochanteric unit) method had been done. Operation time and fluoroscopy time values from this group were compared to the same parameters data from the literature for intramedullary (IM) nails, proximal femur locking plates (PF-LCP), dynamic condylar screws (DCS), and the 95°-angled blade plate.

Results In the SIF group, operation time was 62.2 (25–140) minutes and fluoroscopy time was 43 (20–95) s. Average operation time from the literature data was: 102.1 (43–181) minutes for IM nail, 94.2 (75–129) minutes for PF-LCP, 105.3 (70–166) minutes for DCS and 221.5 (171–272) minutes for blade plate. Average fluoroscopy time from the literature data was: 109.6 (34–250) seconds for IM nail, 102.3 (47–180) seconds for PF-LCP, 238 seconds for DCS. Operation time and intraoperative fluoroscopy time were higher in IM nail, PF-LCP, DCS and blade plate comparing to SIF method ($p < 0.05$).

Conclusion The above mentioned difference could be explained by a degree of required accuracy in the initial operative technique maneuvers, by used number of screws and by the type of the fracture reduction performance in different fixation methods. Operation time during IM nailing of subtrochanteric fractures sometimes can be shorter than average operation time in SIF method, what could be explained by the skill of the surgeon to perform as fast closed reduction for insertion of guide wire.

Keywords: selfdynamisable internal fixator; subtrochanteric fractures; dynamisation

INTRODUCTION

Subtrochanteric fractures occur in 3.2/100,000 population per year and are often pathological in nature [1]. They are more common in females and in patients who have been taking bisphosphonates. They are defined as extending from the lesser trochanter to 3–5 cm distally although there are other definitions [1, 2, 3]. Subtrochanteric fractures are almost always displaced, being in antecurvatum, varus, and external rotation position by the effect of muscles attached to the fractured area. That is the reason for a frequent occurrence of malunion with hip contracture in non-operative treatment of these fractures, thus giving poor functional results. External fixation can provide good final results after proper postoperative treatment. Disadvantages of external fixation are postoperative discomfort for the patient and a risk of infection around the pins; hence, this fixation method is used predominately when the operative intervention is considered a big life risk factor or for the treatment of open subtrochanteric fractures. Internal fixation is the most used treatment method for subtrochanteric fractures today [4].

These fractures are commonly managed with intramedullary (IM) nails, proximal femur locking plates (PF-LCP), dynamic condylar screws (DCS), and 95°-angled blade plates [5–15]. Selfdynamisable internal fixator (SIF) with a trochanteric unit (Figure 1) is a new-generation implant used in the treatment of several thousand patients in many clinics including our institution [16–21].

In this paper, operation time and intraoperative fluoroscopy time between the SIF method and IM nail, PF-LCP plate, DCS, and blade plate have been compared.

METHODS

Operation time and intraoperative fluoroscopy time were analyzed in the group of 27 consecutive cases with SIF internal fixation of a subtrochanteric fracture. These surgical interventions were performed at the Clinic for Orthopaedics and Traumatology of the Clinical Center of Niš

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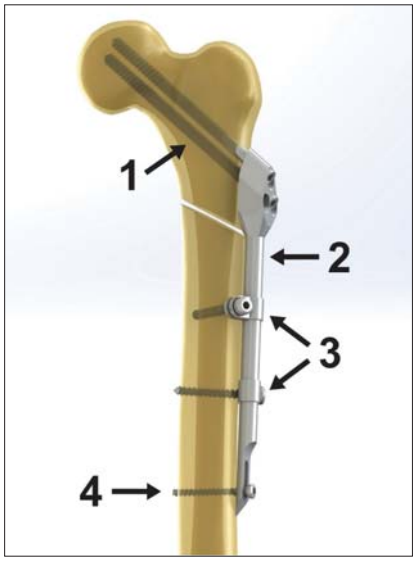

Figure 1. Selfdynamisable internal fixator with a trochanteric unit: (1) lag screws; (2) implant body; (3) clamps with screws for clamps; (4) dynamic antirotational screw; clamps are initially locked, but biomechanical forces can lead to their spontaneous unlocking (without the need for additional surgery) if the union is delayed or absent

between March 1, 2011 and November 1, 2012. We had analyzed the series of patients treated during 2011 and 2012 because the registration of accurate data of intraoperative fluoroscopy time was being performed on the regular bases at that time. SIF internal fixation is the method of choice at our center. In our and other 24 centers, this method has already been applied to 2,500 patients for the internal fixation of trochanteric and subtrochanteric fractures. Aforementioned parameters were calculated for the average values and evaluated for linear correlation.

Operation time and intraoperative fluoroscopy time were also evaluated for values taken from other published papers regarding internal fixation of subtrochanteric fractures with IM nail, PF-LCP, DCS, and 95°-angled blade plate. Average parameters values for each fixation method were analyzed statistically in relation to the values of the SIF group.

Above-mentioned implants are classified into two groups: implants without axial dynamic fixation feature (PF-LCP, DCS, and blade plate) and implants with axial dynamic fixation feature (IM nail and SIF). Axial dynamic fixation of subtrochanteric fractures includes the possibility of controlled fractured fragments sliding along the long axis of the femur, which is a desirable factor to provide compression and further healing of the fracture in some patients. It is still not possible to predict which fracture (patient) will require dynamization in the post-surgery time. Nevertheless, fixation has to be rigid in the initial after-surgery time and the dynamization could be needed later, after several weeks. IM nail method provides the transition from initially rigid to dynamic fixation mode by additional later surgery (interlocking screw removal). In the SIF method, this transition happens spontaneously, without any need for additional surgery, by the clamps spontaneous "unlocking" resulted from the effect of biomechanical forces on initially locked clamps (if the healing process is slow or absent, resulting in longer implant load-bearing time) [16–22].

Statistical analysis was performed by the use of Student's t-test and linear correlation analysis in IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA) with the significance level set at $p < 0.05$.

RESULTS

Average operation time was 62.2 (25–140) minutes, and average intraoperative fluoroscopy time was 43.9 (21–95) seconds in the group of patients with subtrochanteric fracture treated by the SIF method.

Averages of values taken from the literature for subtrochanteric fracture fixation regarding operation time were as follows: 102.1 (43–181) minutes for IM nail, 94.2 (75–129) minutes for PF-LCP, 105.3 (70–166) minutes for DCS, and 221.5 (272–171) minutes for 95°-angled blade plate. Average values from the literature regarding fluoroscopy time were as follows: 109.3 (34–250) seconds for IM nail, 102.3 (47–180) seconds for PF-LCP, and 238 seconds for DCS. No values were found for fluoroscopy time in subtrochanteric fracture fixation using the 95°-angled blade plate (Table 1) [5–15].

Table 1. Average operation time and intraoperative fluoroscopy time for different internal fixation methods in subtrochanteric fractures treatment; the values for the intramedullary nail, proximal femur locking plates, dynamic condylar screws and 95°-angled blade plate were taken from the literature and are placed inside the parentheses

Method	Operation time (minutes)	Fluoroscopy time (seconds)
SIF (trochanteric)	62.2	43.9
IM nail	102.1 (181, 166, 93, 82, 48, 43)	109.6 (250, 45, 34)
PF-LCP	94.2 (129, 91, 82, 75)	102.3 (180, 80, 47)
DCS	105.3 (166, 80, 70)	238 (238)
95° blade plate	221.5 (272, 171)	

IM – intramedullary nails; PF-LCP – proximal femur locking plates; DCS – dynamic condylar screws

The average operative time and average fluoroscopy time from the SIF group were significantly shorter ($p < 0.05$) in relation to the average values for IM nail, PF-LCP, DCS, and 95°-angled blade plate calculated by the use of data taken from the literature.

Pearson correlation coefficient for correlation between operative time and fluoroscopy time in the SIF group was $r = 0.482$.

The results of this study can however be compared as a reference statement, rather than a real indication that the SIF is better.

DISCUSSION

Longer intraoperative time in subtrochanteric fractures treatment using the 95°-angled blade plate and DCS could be explained by the need for achieving reduction before the implant placement procedure. This is required due to

the necessity for proximal part of the implant to be at a certain angle to the previously displaced femoral shaft. This statement is supported by the fact that the average intraoperative time was longer in the blade plate in comparison to the DCS method. Actually, the blade plate is not an adjustable implant and its placement requires more precise 3D orientation of the surgeon than the use of the DCS method (DCS is somewhat adjustable due to the rotation of its cylindrical part introduced in a trochanteric mass). Thus, it could be suggested that higher adjustability of the implant impacts the average operation time.

In addition to the aforementioned reasons, longer operative time in PF-LCP in relation to the SIF method of subtrochanteric fractures treatment could be explained by the higher number of screws in the PF-LCP method. Higher number of screws affects both the operation time and the fluoroscopy time. Longer fluoroscopy time is here primarily caused by the implantation of screws for the proximal femoral fragment, as it is important for the hip screws not to pass behind the medial cortex or into the hip joint.

IM nail fixation requires at least partially closed reduction of the subtrochanteric fracture before introducing a guide-wire into the distal fragment medullary canal. Because of the type of subtrochanteric fracture displacement, closed reduction is often hard to be performed, resulting in repeated fracture reduction and guide-wire introduction maneuvers, and hence in longer operation time and longer fluoroscopy time. However, in some papers, the average operation time of the IM nail method is similar to the SIF group in this paper.

It should be kept in mind that the introduction of the IM nail in the distal medullary canal does not always provide the correct reduction of some forms of the subtrochanteric fracture. There are some papers presenting the subtrochanteric fracture with a varus reduction after the IM nail fixation and with good final results after a switch to an extramedullary fixation (Figure 2) [23].

The SIF implantation does not require previous reduction of a subtrochanteric fracture. It could be enough to introduce one lag screw parallel to the femoral neck axis. Afterwards, fracture reduction is performed indirectly – by leaning of the implant body to the femoral shaft; the implant body position is adjusted by its rotation around the axis of the implanted lag screw (Figure 3). This type of reduction and fixation could be considered as a factor for a shorter average operation time. In this reduction and fixation method, fluoroscopy can be needed during the insertion of lag screws in the femoral neck only, contributing to a shorter average fluoroscopy time.

Pearson's coefficient was > 0.3, supporting the statement that there is a correlation between the operative time and the fluoroscopy time in the SIF group (longer operation time is followed by longer fluoroscopy time). However, the coefficient of < 0.8 rejected this correlation as a strong one, and this is supported by the fact that some of the highest values for the fluoroscopy time were in the cases with almost average values of the operation time. This could be explained by the occasional need for repeated K-wire insertions in the femoral neck before taking a good position for the lag screw, requiring more intraoperative fluoroscopy in a not too long operative time.

Dynamic hip screw (DHS) was not suggested in this paper as one of the most used methods in the treatment of subtrochanteric fractures, due to already confirmed higher frequency of postoperative complications in relation to other methods of internal fixation. Results of earlier studies referred that these complications were almost always associated with medial cortex comminution, which is a very common condition, making subtrochanteric fractures unstable [7, 24, 25].

Excessive sliding of a lag screw in unstable subtrochanteric fractures treated by the DHS can result in medialization of the femoral shaft. Medialization of more than one third of the femoral shaft diameter is followed by a seven times more likely fixation failure, including implant breakage [26, 27].

In an earlier study on 49 consecutive patients with a subtrochanteric fracture treated by the SIF method it was

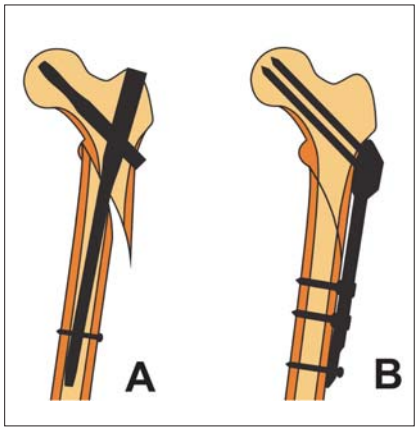

Figure 2. (A) Possible malreduction after intramedullary nailing of a reverse subtrochanteric fracture; (B) extramedullary fixation provides a more accurate and reliable reduction of this fracture type

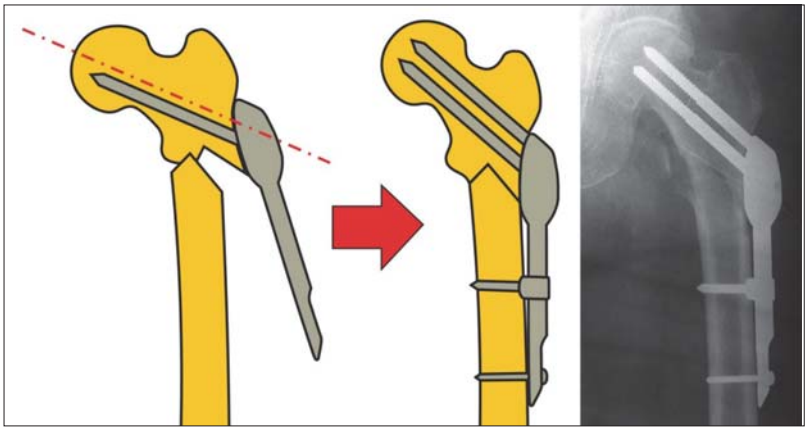

Figure 3. A scheme and an X-ray of subtrochanteric fracture reduction using the selfdynamisable internal fixator method; the first lag screw is positioned parallel to the femoral neck axis, and other screws are implanted after "joystick" reduction of the fracture and adjusting of the implant body position

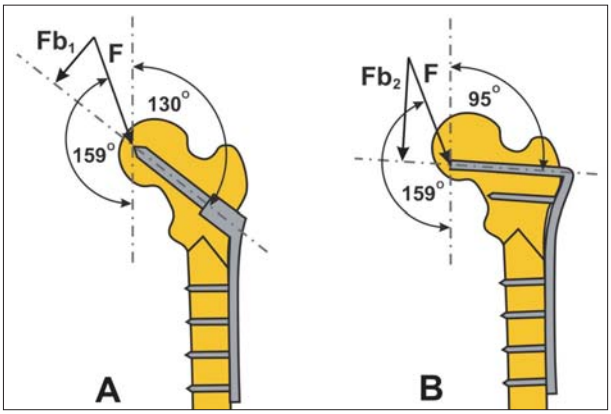

Figure 4. Compression strength in the medial cortex area of a subtrochanteric fracture is higher in a 95°-angled blade plate (B) than in the dynamic hip screw method (A) due to the difference of bending force intensity; F – hip load force at the moment of one leg standing during walking; Fb – bending force that induces a varus cyclic elastic deformation and hence the compression in the medial cortex area

stated that bone healing was achieved in all cases, without the need for surgical revision, and three patients had bone union in varus angulation of less than 10° [19].

The difference in after-surgery complications rate between the DHS and SIF implants can be explained by the fact that the DHS method provides dynamization in just one axis (femoral neck axis) and the SIF implant provides dynamization in two axes (both femoral neck axis and femoral shaft axis). Stabilization of an unstable subtrochanteric fracture after SIF surgery is achieved by the dynamization more in the femoral shaft axis and less in the femoral neck axis. Thus, the excessive medialization of the femoral shaft is rarely obtained in the SIF in comparison to the DHS method in subtrochanteric fractures treatment. Biaxial dynamization could also be the reason for the lower rate of complications in the IM gamma nail method (surgery is performed after the interlocking screw removal) in relation to the DHS method, for subtrochanteric fractures.

The fact that, according to the literature, results of subtrochanteric fractures treatment are more acceptable for the DCS than for the DHS method could today be explained by the need for these fractures to have compression in the area of the medial cortex. Actually, implants without the feature for dynamization in the femoral shaft axis, such as DHS and DCS, can provide this compression only by their own cyclical elastic deformations in the varus direction as a result of everyday biomechanical forces in the hip region. Most of the biomechanical load is transferred to the proximal femur when one leg is standing during walking. It had been determined that the angle of this force vector makes an angle of 159° in relation to the femoral shaft [28, 29].

Due to the difference between the DCS and DHS implants' body angles, force-inducing varus bending elastic deformation (component of the hip load force) has different values between these two fixation types, higher in the DCS method. Thus, the compression force in the medial cortex of the subtrochanteric fracture is higher in the DCS than in the DHS method (Figure 4).

It could be considered that the absence of dynamization in the femoral shaft axis in the DCS and DHS methods is partially "compensated" by the above-mentioned cyclic elastic deformations of the implant. However, cyclic bending forces are relatively high risk for implant fatigue breakage, especially in patients with delayed bone union.

In the treatment of subtrochanteric fractures, some surgeons sometimes use the SIF with the condylar unit. This implant has two thick locking screws with an angle of 95° to the body of the implant. The principle of cyclical elastic deformations, described above for DCS, can be regarded as a risk for fatigue breakage of the condylar SIF implant, but only for a few weeks, during the initial (rigid) phase of the fixation (before spontaneous "unlocking" of the clamps and consequent dynamization of the implant). Higher range of the cyclical varus deformation in the condylar SIF implant may be considered as a factor for earlier "unlocking" of the clamps' initiation, in relation to when trochanteric SIF implant is used. This would be a hypothesis in some further studies.

Entry-point for condylar SIF locking screws in this way is located more proximally than entry-point for trochanteric SIF lag screws. This feature can make condylar SIF more desirable in some types of subtrochanteric fractures than the trochanteric SIF implant.

CONCLUSION

Operative time and fluoroscopy time in internal fixation of subtrochanteric fractures using a trochanteric SIF implant have in average lower values than in the use of DCS, PF-LCP, IM gamma nail, or a 95°-angled blade plate.

It was observed that the operation time in subtrochanteric fractures treatment can be similar between the trochanteric SIF and IM gamma nail fixation. Despite relatively short operation time and minimally invasive surgery in the IM nail method, one should have in mind that extramedullary fixation can provide more accurate reduction and fixation in some shapes of subtrochanteric fractures.

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Време операције и интраоперативне флуороскопије код различитих метода унутрашње фиксације суптрохантерних прелома

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САЖЕТАК

Увод/Циљ Суптрохантерни преломи су нестабилни преломи са тенденцијом ка варусу, антекурвату и деформитету скраћења.

Циљ овог рада је упоређивање дужине операције и времена интраоперативне флуороскопије између различитих метода унутрашње фиксације суптрохантерних прелома.

Методе Анализирана је група од 27 болесника са суптрохантерним преломом, који су лечени унутрашњом фиксацијом СУФ методом (самодинамизирајући унутрашњи фиксатор са трохантерном јединицом). Ове вредности су потом упоређиване са вредностима истих параметара из литературе за ИМ клин (интрамедуларни клин), *PF-LCP*, *DCS* и угаону плочу од 95°.

Резултати У СУФ групи просечна дужина операције је била 62,2 (25–140) минута, а време интраоперативне флуороскопије је било 43 (20–95) секунде. Средње вредности резултата из литературе у вези са временом операције су биле: 102,1 (43–181) минута за ИМ клин, 94,2 (75–129) минута за *PF-LCP*, 105,3 (70–166) минута за *DCS* и 221,5 (171–272) минута за угаону плочу. Просечно трајање интраоперативне флуороскопије, према литератури, било је: 109,6 (34–250) секунди за ИМ клин, 102,3 (47–180) секунде за *PF-LCP* и 238 секунди за *DCS*. Време операције и интраоперативне флуороскопије је било значајно краће код СУФ групе у односу на резултате осталих наведених метода из литературе ($p < 0,05$).

Закључак Наведена разлика у трајању операције и интраоперативне флуороскопије би могла да се објасни потребним степеном прецизности у почетној фази имплантације фиксационог материјала, коришћеним бројем фиксационих завртњева, као и начином репозиције прелома који одређена фиксациона метода омогућава. Време трајања операције код фиксације ИМ клином некада може бити краће него код СУФ методе, што се може објаснити умешношћу хирурга да у краћем року изврши затворену репозицију суптрохантерног прелома адекватну за пласирање игле водиље.

Кључне речи: самодинамизирајући унутрашњи фиксатор; суптрохантерни прелом; динамизација

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Low-intensity extracorporeal shock wave therapy of vasculogenic erectile dysfunction – three-week treatment in a cohort of North Italian patients

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SUMMARY

Introduction/Objective Although phosphodiesterase 5 (PDE 5) inhibitors represent the gold standard for medical treatment of erectile dysfunction (ED), they are not curative. Over the recent years, low-intensity extracorporeal shock wave therapy (LI-ESWT) has been proposed as a valid non-invasive therapy approach for ED.

The aim of our work is to assess the shortened, three-week low-intensity extracorporeal shock wave therapy of vasculogenic ED.

Methods The study involved 32 patients with an International Index of Erectile Function (IIEF) score between 5 and 20, and whose vasculogenic ED had been proven through Doppler ultrasound. All the patients had a washout period of one month after previous therapy and agreed to discontinue the PDE5-I therapy during the follow-up. The LI-ESWT was applied for three weeks, twice weekly, without repeating. The patients were evaluated at baseline, after one, three, and six months with the IIEF, Doppler ultrasound, and the Beck Depression Inventory.

Results All investigated parameters (International Index of Erectile Function, Beck Depression Inventory and penile Doppler ultrasound parameters) showed statistically significant improvement just one month after the treatment, compared to pre-treatment values, in all investigated domains. The international index of erectile function passed from baseline values of 12.75 ± 4.62 to 14.87 ± 5.04 at one month after treatment ($p < 0.01$). This trend remained positive in IIEF and all the parameters tested at the three-month and six-month follow-up.

Conclusion The shortened three-week low-intensity shock wave treatment of vasculogenic erectile dysfunction proved to be clinically effective.

Keywords: erectile dysfunction; low-intensity extracorporeal shock wave therapy; International Index of Erectile Function (IIEF); Doppler ultrasound; Beck Depression Inventory (BDI)

INTRODUCTION

Erectile dysfunction (ED) is a problem of the male population with both high prevalence and incidence worldwide. The Massachusetts Male Aging Study has reported a prevalence of ED between 5% and 35% (Northern Europe) [1]. ED is commonly associated with aging and age-related health problems, such as vascular, hormonal, neural, psychogenic factors, and side effects of therapeutic drugs [2].

Phosphodiesterase-5 (PDE-5) inhibitors, although not curative, have become a standard way of treating ED [3–6]. However, there are still some significant shortcomings of this treatment, such as side effects, drug intolerance, etc.

Low-intensity extracorporeal shock wave therapy (LI-ESWT) was introduced by Vardi et al. [7, 8] as an innovative and promising curative treatment of ED, with the possibility of avoiding side effects and drug intolerance. The majority of therapy protocols studied with non-linear LI-ESWT were based on treatments lasting six weeks, with a three-week pause in between [8–11].

The aim of this pilot study was to investigate the effects of a three-week LI-ESWT in a cohort of patients from north-eastern Italy, all with vasculogenic ED.

METHODS

An open-label, single-arm, prospective pilot study was performed in a private urological care structure (Studio Urologico FG) in accord with the Helsinki Declaration. Thirty-two patients were enrolled in the study after obtaining their written informed consent. The inclusion criteria were as follows: history of ED for at least six months, an International Index of Erectile Function for ED (IIEF-ED) domain score between 5 and 20, responders and non-responders to PDE-5 inhibitor therapy and vasculogenic ED proven by Doppler ultrasound. All the patients had a washout period of one month after previous therapy and

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Table 1. Maximal velocity of arterial systolic flow, resistance index, Beck's Depression Inventory score, International Index of Erectile Function values before and after treatment

Baseline values and follow-up (mean value ± SD)					
Variables	Baseline	1 month	3 months	6 months	p*
Qmax	27.59 ± 12.55	37.39 ± 17.81	39.43 ± 17.22	39.71 ± 17.74	< 0.001
RI	0.67 ± 0.08	0.76 ± 0.08	0.79 ± 0.06	0.79 ± 0.05	< 0.001
BDI	6.59 ± 5.70	4.59 ± 0.57	4.06 ± 4.56	2.96 ± 3.58	< 0.003
IIEF	12.75 ± 4.62	14.87 ± 5.04	17.06 ± 4.04	17.64 ± 4.34	< 0.004

Qmax – maximal velocity of arterial systolic flow; RI – resistance index; BDI – Beck's Depression Inventory score; IIEF – International Index of Erectile Function; *calculated between pre-treatment and post-treatment values after one month; no significant differences were noted between the three-month and six-month follow-ups, except from BDI

agreed to discontinue the PDI-5 inhibitor therapy during the follow-up.

The exclusion criteria were the following: psychogenic ED, neurologic comorbidities, documented hypogonadism (total testosterone serum levels under 10 nmol/L), prior radical prostatectomy, and recovery from any cancer within the past five years.

Treatment protocol

Low-intensity shock wave therapy was delivered using a special probe attached to a compact electrohydraulic unit with a focused shockwave source (Omnispec ED1000, Medispec Ltd, Germantown, MD, USA). Only standard ultrasound gel was applied between contact surfaces. The penis was manually stretched, and the prepuce retracted; the shockwaves were delivered to the distal, mid, and proximal penile shaft, and to the left and right crura.

Each LI-ESWT session lasted for 20 minutes, and comprised 300 shocks per treatment point (a total of 1,500 per session), at an energy density of 0.09 mJ/mm^2 and a frequency of 120/min. The volume of penile tissue that was exposed to shockwaves at each site was cylindrical (diameter: 18 mm; height: 100 mm). The treatment protocol consisted of two treatment sessions per week, for three weeks, without repeating the treatment after three weeks, which is the key difference compared to the previous study protocols with non-linear LI-ESWT [11, 12].

During the treatment period, no psychological intervention or support was provided, and patients were required to maintain their normal sexual habits.

Study protocol

The IIEF was used for the symptomatic evaluation of patients with ED, as this is a widely accepted measurement tool with a high degree of sensitivity and specificity for detecting treatment-related changes in the erectile mechanism [13, 14]. A standard tool was used for the psychological evaluation of patients, the Beck Depression Inventory (BDI) score, and a clinical evaluation was performed on all patients [15]. A grey scale ultrasound followed by a penile Doppler dynamic ultrasound with alprostadil 10 μg intracavernosal injection was performed. Measurements of peak systolic (Qmax) and end-diastolic velocities were obtained in each cavernosal artery at five-minute intervals for a total of 30 minutes. A peak systolic velocity of less than 35 cm/second was used as the threshold for arterial insufficiency. An end-diastolic velocity greater than 5 cm/second was used to predict venous incompetence. Moreover, resistance index (RI) was evaluated and considered to be pathologically reduced when lower than 0.75. A complete study protocol was carried out before the treatment and during the follow-up. A follow-up was carried out one month, three months, and six months after treatment, using IIEF-5 and BDI questionnaires and recording changes in dynamic Doppler ultrasound parameters.

Statistical analysis was performed with a repeated measures analysis of variance (ANOVA). Linear regression analysis was used to prove the correlation between the variables. Statistical difference was considered significant when $p < 0.01$.

RESULTS

The study protocol was applied to 32 middle-aged men (mean: 57.62 ± 7.98; range: 38–68 years) with vasculogenic ED for a mean of 35.2 months. The data regarding pre- and post-therapy IIEF, duplex Doppler ultrasound, RI, and BDI are shown in Table 1.

A statistically significant improvement in all the investigated parameters can be seen one month after treatment, compared to the pre-treatment values, in all investigated domains. The IIEF passed from baseline values of 12.75 ± 4.62 to 14.87 ± 5.04 at one month after treatment ($p < 0.01$). The BDI basic values passed from 6.59 ± 5.70 to 4.59 ± 0.57 after the first months from the treatment ($p < 0.01$). As of penile color Doppler ultrasound parameters, both Qmax and RI values showed a statistically significant improvement at first month after treatment ($p < 0.01$). There was no deterioration of the investigated values during the follow-up.

There is a significant correlation between the improvement in IIEF and Qmax (Figure 1), and a negative correlation between IIEF and BDI (Figure 2). Multiple significant correlations between IIEF, Qmax, and RI are shown in Figure 3.

DISCUSSION

Our results show a significant change in both IIEF and BDI scores, and an improvement in Qmax and RI. Significant improvement remained during the follow-up.

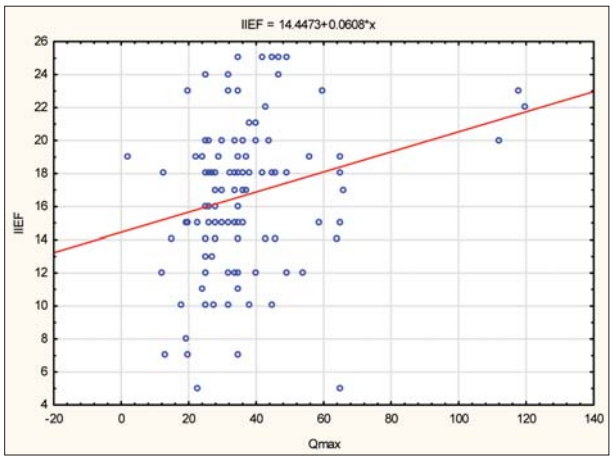

Figure 1. Correlation between the adjusted maximal velocity of arterial systolic flow parameters and the changes in International Index of Erectile Function scores

Qmax – maximal velocity of arterial systolic flow score;
IIEF – International Index of Erectile Function

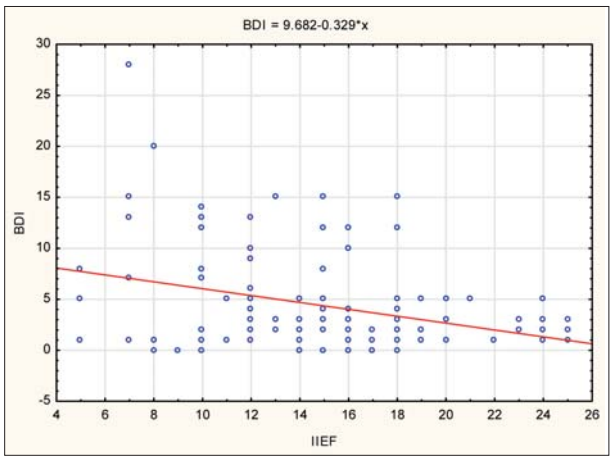

Figure 2. Correlation between the adjusted Beck's Depression Inventory scores and the changes in International Index of Erectile Function scores

BDI – Beck's Depression Inventory score;
IIEF – International Index of Erectile Function

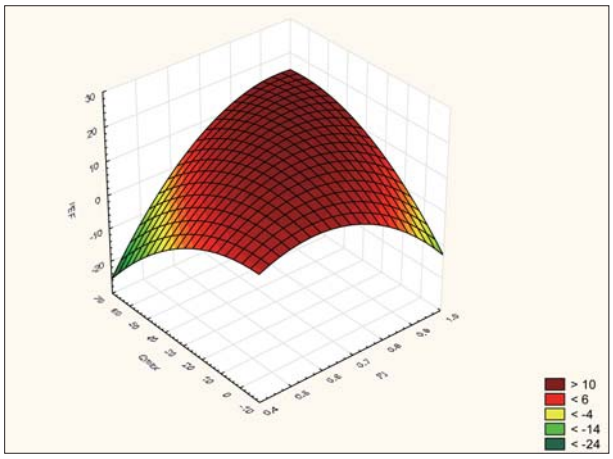

Figure 3. Multiple correlation between the changes in the maximal velocity of arterial systolic flow and resistance index values and the changes in International Index of Erectile Function scores

Qmax – maximal velocity of arterial systolic flow score;
RI – resistance index; IIEF – International Index of Erectile Function

Low intensity shock wave therapy is promising, although the exact mechanism used by LI-ESWT to induce the tissue changes is not known. Thanks to the release of neo-angiogenic factors and the subsequent neovascularization of the treated tissue, LI-ESWT leads to tissue regeneration [16]. Indeed, it has been shown that this low-intensity energy acts on vascularization, inducing a non-enzymatic production of physiologic amounts of nitric oxide [17]. Thus, the latest studies show that IIEF scores increase after treatment with LI-ESW [18]. Even though PDI-5 inhibitors represent the first-line therapy for ED by increasing the IIEF score, they do not represent a curative approach. The increase in IIEF does not last over time; rather, it is strictly limited to the assumption of PDE-5 inhibitors. In addition, some ED patients respond poorly to PDI-5 and need other, more invasive treatments [9, 11, 12].

After the pilot study by Vardi et al. [7], which took into consideration the patients who had previously responded to PDE-5 inhibitor therapy, Gruenwald et al. [10] applied LI-ESWT to patients who had responded poorly to PDE-5 inhibitor therapy. By using the same protocol as in the first study on 29 patients, they concluded that LI-ESWT was again beneficial for this kind of patient, as it had a physiological effect on the erectile mechanism [10].

After those preliminary studies, others were done, but almost all studies on LI-ESWT for ED had the same duration and applied the same treatment doses. The treatment protocol mostly considered the application of LI-ESWT twice a week for three weeks, with re-treatment for another three weeks after a three-week pause. The number of shocks applied was almost always 300 per treatment point with an energy flux density of 0.09 mJ/mm^2 [9].

A very recent study carried out at the Mayo Clinic applied low-energy shock wave therapy to alleviate renal dysfunction in renovascular disease. They treated pigs' kidneys with renal artery stenosis using low-energy shock waves twice a week for only three consecutive weeks, without repeating. Twenty-six pigs were randomized to atherosclerotic renal artery stenosis (ARAS) or normal controls, treated or untreated with LI-ESWT. The results were amazingly positive. A three-week low-intensity shockwave therapy attenuated renovascular hypertension, normalized stenotic kidney microvascular density and oxygenation, stabilized function, and alleviated fibrosis. This was associated with upregulation of the vascular endothelial growth factor expression that was decreased by ARAS, with increased angiopoietin-1, and downregulation of hypoxia-induced factor-1. Moreover, LI-ESWT improved the expression of endothelial nitric oxide synthase that was diminished in ARAS. No detectable injury to the kidney was observed [19].

The encouraging results from this and all the previous studies led us to conduct a prospective pilot study, applying the three-week low-intensity shockwave therapy to patients with ED in order to examine if the shortened therapy could have the same effect as the repeated three-week therapy.

Our primary end points were the change in IIEF-5 and in the penile color Doppler values given through the Qmax and RI values, as well as the BDI score.

The IIEF-5 questionnaire is a widely accepted measurement tool with a high degree of sensitivity and specificity for detecting treatment-related changes in the erectile mechanism [13, 14].

The BDI is one of the most widely used psychometric tests for measuring the severity of depression. The BDI was originally developed to provide a quantitative assessment of the intensity of depression. As it is designed to reflect the depth of depression, it can monitor changes over time and provide an objective measurement for judging improvement and the effectiveness of treatment methods [15]. A systematic review by McCabe [20] showed how ED leads to poor sexual relationships and poor sexual satisfaction, diminished confidence, low self-esteem, and symptoms of depression. After any kind of treatment, there were significant improvements for the baseline regarding most of these parameters, except for overall life satisfaction and overall relationship satisfaction [20]. Although the BDI has its limitations, as do all questionnaires, considering that the person completing it may exaggerate or minimize their score, we considered BDI as an important aspect of treatment success. As far as we know, this is the first study to date that uses BDI in evaluating the results of LI-ESWT to treat ED.

The immediate, statistically significant increase in all variables after the one-month follow up showed that this shortened therapy was efficient in improving erectile function, and that the effects of angiogenesis could be clinically important after the three-week therapy, without repeating.

The fact that the basic BDI values did not show the presence of depression in our patients, excluded the fact that ED was due to depression in our cohort. This also excluded the possible placebo effect that could be expected from our study protocol. The BDI score, although in the normality range at basic values, lowered even more at the six-month follow-up. The mean BDI scores changed from 6.59 ± 5.70 before treatment to 2.96 ± 3.58 at the six-month follow-up, which was statistically significant. Patients sometimes need time to develop self-confidence and improve general well-being after suffering depression-like symptoms for a long time before the therapy. This could be especially true for those patients who did not respond to PDI-5 therapy before the LI-ESWT, and who had lost faith in clinical improvement, considering that, to date, PDI-5 therapy is the gold standard for treating ED. Our results showed an immediate effect on BDI scores after one month, which was maintained after six months without any additional active intervention.

A positive physiological effect on cavernosal tissue is certainly proven by hemodynamic values. As with the Doppler findings, we witnessed an increase in Qmax at the one-month follow-up. This increase was the greatest the first month after treatment, with a slightly greater value at the three-month and six-month follow-up. This represents direct proof that the shortened course of therapy with low-intensity shock waves improves the hemodynamic values of the penis, and that this effect can be observed quite soon after treatment. Vardi et al. [7, 8] stated that most of the treated men reported improvements in erectile function between treatment sessions 6 and 8, which is probably the time needed for LI-ESWT to induce the physiological changes. Nevertheless, those values remained the same with a small but significant increase over three and six months, which is indicative of the durability of the shortened treatment.

We used a scientifically tested machine that had already been proven through 'sham control' to have certain positive effects on penile hemodynamics over a longer follow-up period. Recently, Fojecki et al. [21] showed that exposure to two cycles of linear ESWT to treat ED was not superior to one cycle at the six-month and 12-month follow-up. Although they used a different machine with a linear probe and a five-week treatment session, the number of shockwaves and the energy flux density were the same.

Our patient cohort was mostly homogenous when considering cardiovascular risk factors. Three men had arterial hypertension in medical therapy, one had insulin-dependent diabetes mellitus, and one of the patient's ED was due to previous pelvic trauma. We included patients who had responded, partially responded, or had not responded to previous PDI-5 therapy. This is based on previous studies that showed that LI-ESWT could have beneficial effects on both PDI-5 responders and non-responders [7, 10].

The main limitations of our study were certainly the low number of patients and the lack of a sham-controlled arm. Although the study population comprised only 32 men, this was sufficient to determine whether or not our shortened treatment could have a positive physiological effect on cavernous tissue. Bearing in mind that this was a pilot study, and that Vardi's first study was carried out on a smaller patient cohort, without a sham-controlled arm, these limitations should be considered relative. We would like to emphasize that the most striking clinical observation was that almost every participant gave highly positive feedback on the treatment.

CONCLUSION

The efficacy of a short course of the LI-ESWT therapy to manage ED was confirmed. The LI-ESWT was successful in improving symptomatic, vasculogenic and psychological aspects of vasculogenic ED. Although additional investigations are necessary, the initial results of our study are promising, improving the position of LI-ESWT in the guidelines for curative treatment options for patients with vasculogenic ED.

NOTE

This paper forms part of a doctoral thesis by Dr. Goran Aranđelović with the title "The effects of three-week low intensity shock wave therapy on erectile dysfunction."

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Екстракорпорални ударни таласи ниског интензитета за третман васкулогене еректилне дисфункције – тронедељна терапија на групи болесника из североисточне Италије

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САЖЕТАК

Увод/Циљ Инхибитори фосфодиестеразе типа 5 (*PDE5-Is*) представљају златни стандард у медикаментозној терапији еректилне дисфункције. Упркос томе, медикаментозни третман не представља терапију којом се може трајно излечити еректилна дисфункција. Циљ наше студије је испитати скраћену тронедељну терапију екстракорпоралним ударним таласима ниског интензитета васкулогене еректилне дисфункције.

Методе Студија је укључила 32 болесника са међународним индексом еректилне функције између 5 и 20, са потврђеном васкулогеном еректилном дисфункцијом на доплер ултразвуку. Болесници су имали паузу у трајању од једног месеца од претходне терапије и били су сагласни да прекину терапију *PDE5* инхибиторима у периоду праћења после третмана. Применили смо екстракорпоралне ударне таласе ниског интензитета у трајању од три недеље, два пута недељно, без понављања. Болесници су оцењивани пре терапије, један месец, три и шест месеци после терапије међународним индексом еректилне функције, доплер ултразвуком и Бековим упитником за депресију.

Резултати Сви испитани параметри (Међународни индекс еректилне функције, Беков упитник за депресију, параметри доплер ултразвука пениса) показали су позитивну статистички значајну промену после само једног месеца од терапије. Међународни индекс еректилне функције је забележио пораст првог месеца после терапије и попео се са основних вредности од 12,75 ± 4,62 на 14,87 ± 5,04 ($p < 0,01$). Овај позитиван тренд се задржао како на Међународном индексу еректилне функције тако и на свим тестираним параметрима после три и шест месеци праћења.

Закључак Скраћена тронедељна терапија екстракорпоралним ударним таласима ниског интензитета примењена на васкулогену еректилну дисфункцију показала се клинички ефективном.

Кључне речи: еректилна дисфункција; екстракорпорални ударни таласи ниског интензитета; међународни индекс еректилне функције; доплер ултразвук; Беков упитник за депресију

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The quality of life of patients after lumbar microdiscectomy

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SUMMARY

Introduction/Objective The quality of life (QL) is a modern concept of observing the outcome of the disease and the success of the therapeutic procedure in all fields of medicine.
The aim was to assess the QL of surgically treated patients with lumbar radiculopathy (LR) at the beginning of treatment and three and six months after the initiation of prescribed and applied medical rehabilitation.
Methods The study group included randomized and stratified sample of 50 patients treated with lumbar microdiscectomy (LM). Conservative treatment was carried out using physical therapy procedures, and kinetic and ergonomic therapeutic procedures and educational training program in ergonomics were carried out in all the patients. To assess the condition of the patients, the QL and the efficacy of the rehabilitation treatment, we used two standardized questionnaires, the Short Form Survey Instrument (SF-36) and the Oswestry Disability Index (ODI).
Results The lowest values of the SF-36 – PCS, SF-36 – MCS, and of the ODI were recorded at the beginning of the rehabilitation (PCS: 28.8; MCS: 37.8; ODI: 56.1%). The most significant improvements of the scores were observed three months after the treatment initiation (PCS: 42.8; MCS: 45.2; ODI: 38.9%). At six months of treatment, the scores were slightly higher (PCS: 49.2; MCS: 52.5; ODI: 23.7%) ($p < 0.001$).
Conclusion The QL and the functional status of patients after LM are significantly better after three and six months in comparison with the beginning of rehabilitation, and the state for six months compared to the state for three months.
Keywords: lumbar radiculopathy; microdiscectomy; quality of life; SF-36; ODI; treatment outcome

INTRODUCTION

The main symptom of lumbar radiculopathy (LR) is pain in the lumbo-sacral region with propagation to the lower extremities. The intensity of the neuropathic pain depends on the extent of the local damage and on the individual characteristics of the patient and experiential pain perception [1].

Healthy functioning and the quality of life (QL) of patients with LR depend on the severity of the disease, the intensity of the symptoms and on the degree of incapacity. It has been also largely dependent on the applied therapeutic methods and protocols. In addition, the socioeconomic implication plays a relevant role [2]. The QL provides valuable information about functional ability, level and quality of social interaction, mental state, somatic sensations, and satisfaction with life, reflecting the definition of health by the World Health Organization and reflecting the previous scientific data about the impact of the disease and treatment on disability and daily functioning [3].

Questionnaires, as instruments for measuring the QL, regarding their structure, may be general (generic) questionnaires that are structured to express the extent of injury from the standpoint of patients, and questionnaires for a specific disease. The latter ones are formed with an objective to provide a higher sensitivity and specificity [4]. The choice of instrument should be determined by the clinician, according to the clinical problem and measuring characteristics of the instrument [5].

The aim of this study was to evaluate the QL of patients immediately after lumbar microdiscectomy (LM) at the beginning of the rehabilitation, and then after three months and after six months of the prescribed supervised regular physical rehabilitation treatment. For the evaluation, we utilized both general questionnaire and the questionnaire specific for lumbar pain syndrome (LPS).

METHODS

This randomized prospective clinical study included 50 patients with LR of disc genesis who were treated with LM. In all the patients, rehabilitation treatment was carried out under the regular protocol with the use of physical therapy procedures and ergonomic physical training.

Inclusion criteria for the patients in this study were the following: age between 20 and 65 years, patients of both sexes, orientated in

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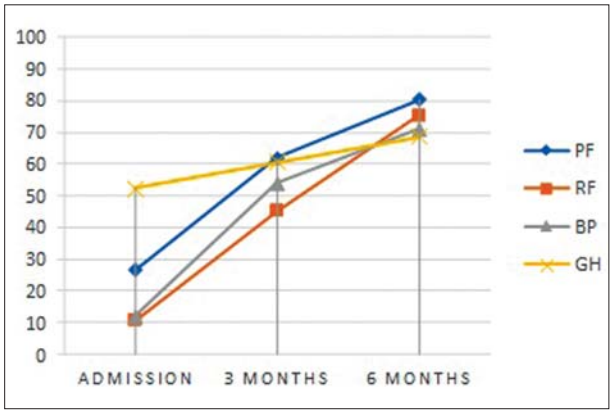

Figure 1. Four basic domains of the Physical Health Composite Scale score change over six months after surgery; PF – physical functioning; RF – role of physical function; BP – bodily pain; GH – subjective feeling of health

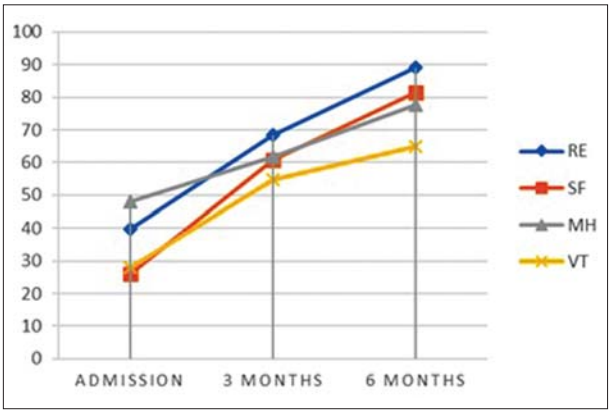

Figure 2. Four basic domains of the Mental Health Composite Scale score change over six months after surgery; RE – role of emotional functioning; SF – social functioning; MH – mental state; VT – vitality

time, space and to other persons, competent to sign an informed consent to participate in the study and with the ability to follow and to adhere to the prescribed treatment regimen and examination, subjects diagnosed with LPS of discogenic etiology (LR, lumbar disc herniation) previously operated.

Criteria for non-inclusion of the patients were as follows: patients who do not meet the criteria for inclusion, patients with diagnosed comorbidity that may affect the current nature of the disease and the QL, participation in other clinical research, inability to comply with the requirements of the clinical trials for any reason.

A sample of the patients included in the clinical trial was determined by simple randomization and by sorting based on the table of random numbers taken from the regular protocol. The total number of patients in the study period from 2014 to 2016 who met the inclusion criteria and entered the selection of research was 84 and the number of patients who met criteria for non-inclusion was eight.

It is important to accentuate that none of the patients who were included in the clinical trial had left the clinical study.

The patients who were involved in the study were interviewed by administering the generic Medical Outcomes Study Short Form 36 (SF-36v2®) and the specific Oswestry Disability Index (ODI) questionnaires in three specific time periods: at the beginning of the medical rehabilitation (immediately after surgery), three months later, and six months after the beginning of the treatment.

SF-36v2® contains 36 questions, issues that include the following eight fields of the QL: physical functioning (PF), the role of physical function (RF), the role of emotional functioning (RE), social functioning (SF), bodily pain (BP), mental state (MH), vitality (VT), a subjective feeling of health (GH). By further grouping into four areas, two summary scores were obtained: physical (PCS) and mental (MCS). The formula for the calculation of the summary scores included the values of all eight single domains and four basic for each of the summary scores (Figures 1 and 2). The minimum score value was zero, and the maximum was 100 – higher score value signifies better QL.

The ODI was generated in ten sections comprising six questions each, and answers were ranked by the Likert scale. The first area assessed the intensity of pain, while the remaining nine covered disabling effect of pain produced by the typical activity: I – intensity of pain (PAIN); II – baseline activities of daily living (CARE); III – lifting (LIFT); IV – walking (WALK); V – sitting (SIT); VI – standing (STAND); VII – sleeping (SLEEP); VIII – working (house chore and office work activities (WORK); IX – social life (SOCIAL); and X – travel (TRAVEL). Each subscale was graded from 0 to 5, where higher values represented greater disability. The sum of 10 results was expressed as a percentage of the maximum score (0–100%).

Calculations were performed by using the IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA) and Health Outcomes Scoring Software 4.5, which is a program designed for the entry and statistical processing of statistical data about the QL of patients. Statistical analysis comprised descriptive and inferential methods (Friedman test, General Linear Model, Student's t-test, Mann–Whitney U-test, linear regression, Spearman's rank order correlation). In all used analyses, an alpha of 0.05 is used as the cut-off value for significance.

RESULTS

General characteristics of the patients included in the study are shown in Table 1. Of the total number of patients, 68% were female and 32% male, the mean age was 47.12 ± 7.63.

Disc herniation was most common at the L4–L5 (50%) and L5–S1 (46%) levels, and just 4% of the patients experienced disc herniation at the L3–L4 level. Most patients (80%) reported the presence of previous episodes of lumbar pain syndrome, while the remaining 20% of patients denied the existence of the previous episodes.

The results of the assessment of the QL obtained by the general SF-36v2® questionnaire and the results of the functional capabilities obtained by the specific ODI questionnaire in surgically treated patients with LR are shown in Table 2.

Table 1. General characteristics of the patients (n = 50)

Characteristics		Number (%) ± SD
Sex	Male	16 (32)
	Female	34 (68)
Age (years)	Mean	47.12 ± 7.63
Education	No primary education	3 (6)
	Primary	15 (30)
	Secondary / high school	22 (44)
	University degree	10 (20)
Marital status	Married / in a relationship	38 (76)
	Divorced/separated	3 (6)
	Widowed	2 (4)
	Single	7 (14)
Level of discus hernia	L_3–L_4	2 (4)
	L_4–L_5	25 (50)
	L_5–S_1	23 (46)
Earlier episodes	No	10 (20)
	Yes, one episodes	11 (22)
	Yes, more episodes	29 (58)

Table 2. Results of the Medical Outcomes Study Short Form 36 and Oswestry Disability Index questionnaire scores

Questionnaire		Admission	3 months	6 months	F-value*	p-value
SF-36	PCS	28.8	42.8	49.2	490.721	< 0.001
	MCS	37.8	45.2	52.5	72.055	< 0.001
MCS		56.1%	38.9%	23.70%	1341.180	< 0.001

SF-36 – Medical Outcomes Study Short Form 36; PCS – Physical Health Composite Scale score; MCS – Mental Health Composite Scale score; *repeated measures ANOVA

Table 3. Comparative overview of the Medical Outcomes Study Short Form 36 scores with the general population

		Results of our research			General population				
		I	II	III	a	b	c	d	e
SF-36	PF	26.5	62	80.3	90.6	85	84.2	85	83.9
	RF	10.5	45	75.2	85.8	81.55	80.9	85	77.5
	RE	39.8	68.5	89.3	79.2	83.5	81.3	80.2	79.7
	SF	26	60.7	81.5	83.7	84.35	83.3	81.4	82.1
	BP	11.9	53.8	71	77.6	79.8	75.2	76.6	71.2
	MH	48	61.8	77.6	69.2	73.8	74.7	70.6	73.6
	VT	28	54.7	64.9	65.1	58.7	60.9	61.7	57.7
	GH	52.4	60.62	68.52	76.1	70.35	71.9	66.3	72.8

SF-36 – Medical Outcomes Study Short Form 36; PF – physical functioning; RF – role of physical function; RE – role of emotional functioning; SF – social functioning; BP – bodily pain; MH – mental state; VT – vitality; GH – subjective feeling of health; I – admission; II – 3 months; III – 6 months; a – Switzerland; b – United Kingdom; c – USA; d – China; e – Australia [6]

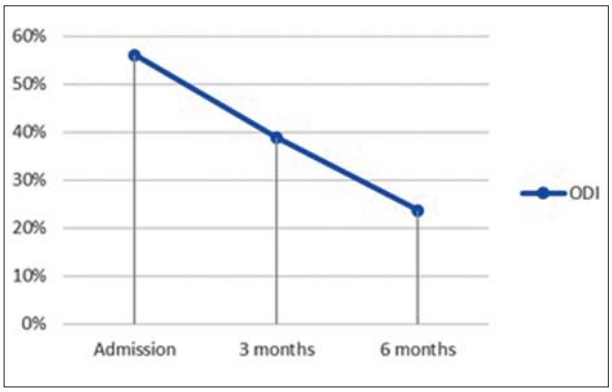

Figure 3. Values of the Oswestry Disability Index score change over six months after surgery

At the start of rehabilitation, we recorded a very low value of the PCS 28.8, while the value of the MCS was slightly higher, but also at a low level (37.8). After three months of rehabilitation, value of all scores on the SF-36V2® questionnaire were significantly increased (PCS = 42.8; MCS = 45.2), and after 6 months, the values approximately reached the levels that characterize the general population (PCS = 49.22; MCS = 52.5). Analysis of variance for repeated measures (RM ANOVA) showed that the values of PCS (Figure 1) and MCS (Figure 2) scores have significantly changed during the study ($F = 490.721$, $p < 0.001$). Both summary scores showed the greatest registered progress in the first three months from the start of rehabilitation treatment.

Furthermore, after examining the results of the six-month research, we found that the domains that participate in the formation of the total PCS and MCS scores and after comparing them with the values given for the general population in different countries, we concluded that the values of the domains moved closer to the general population after six months of rehabilitation. Compared with the general population of Switzerland, Great Britain, United States and China, a statistically significant difference ($p < 0.05$) was registered among the majority of the domain, except for two domains: Switzerland (pSF = 0.26 and pVT = 0.88); United Kingdom (pSF = 0.14 and pGH = 0.27); United States (pSF = 0.35 and pBP = 0.08); China (pSF = 0.96 and pGH = 0.18). When compared with the general population in Australia, a statistically significant difference ($p < 0.05$) was observed in PF, RE, MH, VT, and GH domains, while in the remaining three domains no statistically significant difference was found (pRF = 0.16, pSF = 0.76, pBP = 0.93). The analysis of comparisons of the results of our research with the results in the general population of different countries are shown in Table 3.

Multivariate linear regression analysis showed that the values of PCS and MCS were not significantly related with the monitored characteristics of our patients.

Immediately after surgery, we registered a high ODI score of 56.10%; however, each following test recorded significant improvements in the functionality of the patients, and the ODI score was 38.9% after three months, which decreased to 23.7% after six months of the rehabilitation treatment (Figure 3).

ODI domain values during six months of the follow-up after LM are given in Table 4. The analysis of the presence of individual responses in ODI domain Friedman's test revealed statistically significant differences among three measurements ($p < 0.001$). The biggest improvement was registered in the first three months from the beginning of the rehabilitation treatment.

Multivariate linear regression analysis confirmed that the value of the ODI were significantly associated with marital status. In patients who were married or in a common law marriage, after controlling the effects of all other demographic characteristics, the score was greater by 6.452

Table 4. The mean value of domains the Oswestry Disability Index score over six months after surgery

Domains of ODI	Admission	3 months	6 months	χ^2 value*	p-value
PAIN	2.06	1.28	0.52	85.035	< 0.001
CARE	1.9	1	0.46	31.524	< 0.001
LIFT	4.14	3.4	2.14	66.511	< 0.001
WALK	2.76	1.82	0.78	46.587	< 0.001
SIT	3.38	2.1	1.38	60.336	< 0.001
STAND	3.5	2.46	1.86	51.228	< 0.001
SLEEP	1.42	1.2	1.0	35.086	< 0.001
WORK	3.22	2.32	1.04	28.526	< 0.001
SOCIAL	2.4	2	1.7	29.925	< 0.001
TRAVEL	3.16	1.9	0.9	40.880	< 0.001

ODI – Oswestry Disability Index; PAIN – intensity of pain; CARE – baseline activities of daily living; LIFT – lifting; WALK – walking;SIT – sitting; STAND –standing; SLEEP – sleeping; WORK – working (house chores and office activities); SOCIAL – social life; and TRAVEL – travel;
*Friedman test

than the score found in patients with other marital status (95% CI 1.508–11.397; $p < 0.05$). In patients who were operated on ho had the 'single / never married' marital status, the score was by 7.421 lower than the score in the same group of patients with other characteristics relating to the marital status (95% CI 1.798–13.044; $p < 0.05$).

For the purpose of comparison of the assessment of the QL with a generic questionnaire (SF-36v2®) and with a specific questionnaire for the patients with LR (ODI), we performed the correlation analysis of score values obtained from both questionnaires at all three points of time and for each particular interview. For the SF-36v2®, we used summary scores PCS and MCS, and for the ODI we used PAIN, LIFT, WALK, WORK, and SOCIAL. At the beginning of the treatment, the highest recorded value of the correlation was found between PCS and PAIN ($rs = -0.210$; $p = 0.143$). After three months of rehabilitation, the average value of the correlation coefficient showed better agreement between the selected scores of the selected questionnaire than at the beginning of the treatment process, hence emphasizing the need for the use of the specific questionnaire for assessing the QL during the rehabilitation treatment. At this survey time period, the highest value of the correlation coefficient was observed between the PCS and PAIN ($rs = -0.251$; $p = 0.078$). Six months after the beginning of the rehabilitation, the correlation coefficient values were approximately at the same level as at the second survey time period, wherein the highest value of correlation was between the PCS and PAIN ($rs = -0.312$; $p < 0.05$).

DISCUSSION

The most important goal of any society should certainly be the health of its population and the improvement of the QL. In regards to this, the research related to the evaluation of the QL in patients affected with one of the most common pathology is gaining the raising importance in both clinical and population studies. The patient's own report is considered the gold standard for assessing the QL. Doward et al. [7] have compared the reports of experts from different fields relevant to the QL with patients reports and they noted a high degree of correlation. They concluded that the patient report was not only an indicator of the patient's subjective experience, but also an objective indicator of the QL in relation to health.

A total of 50 patients participated in our study: 34 female and 16 male. In a meta-analysis carried out by Morley et al. [8], the sample comprised 1,672 patients with LPS and women were also more frequently presented (62%). In our study, the average age of patients was 47.12 ± 7.63 years and most of the patients were in the age range of 40–59 years, which is similar to demographic data presented in other researches [9, 10]. These data support the fact that LR affects the working population and that it has been the reason of disability in working population. In regard to educational attainment and marital status, the majority of the patients were secondary and elementary educated and married, which is consistent with other studies [11, 12]. The connection of the occurrence of LR with education and marital status has been reflected primarily in the type of occupation and in the psychological support of the patient influencing the patient's motivation to accelerate the healing. It was noted that educational attainment has no connection with the development of LR, but it was related to the level of difficulty of the physical work that the patients had performed. Shadbolt et al. [13] concluded that family was important for the QL, and that respondents who were married and had children had a better general health and physical functioning than those who were married and did not have children and whose characteristic was having very strong body pain. Shadbolt et al. [13] also said that people who were not married manifested a higher degree of social isolation than people who were married. Patients who were not married had a bigger decrease in physical activity that is the important component dimension of the QL [13].

The most important decision in the process of measuring the QL of patients with LR has been the selection of types of questionnaires that would be used [14]. In the field of rheumatic diseases, the questionnaire SF-36v2® has been proven as the most reliable questionnaire that reflects the QL very realistically and that has a good correlation with the physical and mental capabilities of patients, especially in patients with LPS treated with different treatment modalities. LPS has been the most common rheumatic disease [14]. The most commonly used generic questionnaire SF-36v2® Health Survey was an instrument in our research [15]. Since the SF-36v2® is not sufficiently sensitive to the changes in the QL important for people with LR, there was a need to include a specific instrument that would be focused on domains that were specific to LR and the characteristics of patients with LR. The need to include the specific questionnaire for assessing the QL of patients with LR was pointed out by Suarez-Almazor et al. [16] – in their research, they indicated that SF-36v2® survey does not adequately reflect the changes in the health status of patients with LPS. This statement has been notably reflected in our study in neurological symptoms reported by patients.

For the purposes of this study, as the questionnaire specific to the disease we used the ODI, a specific questionnaire for measuring the QL of patients with LR. It has been a very practical questionnaire for routine clinical use since it was designed as a multi-dimensional test. It measures the pain and functioning, as well as the pain during the activities causing limitations in physical activities; hence, it can be classified as a component of serious research.

Values of PCS and MCS showed statistically significant changes during our study. The biggest improvement was recorded after the first three months of the treatment in both summary scores. After six months from the start of rehabilitation, PCS value did not exceed the standard value of the SFS – 50 for the general US population. Lower values of PCS were justified by the severity of the damage and by recent surgery that both contributed to physical limitations in the early postoperative period as well as by applied precautions for wounds, injury to back and reherniation. The patient's fear of physical activity and body movement had contributed to lower PCS values as well. Johansson et al. [17] reported patients' beliefs in recovery and fears of physical activity as leading factors. Authors recommended that the patients with fears of physical activity should be identified and treated appropriately.

We also concluded that the patients with psychosocial problems more frequently shortened the time spent at work and in other activities, were less efficient, had less attention and motivation regarding work obligations, were more frequently nervous, in a bad mood, tired, with less energy and less active, and more irregular in maintaining social contacts. During the six-month follow-up period of the patients, the MCS values showed continuous increase and at the six-month survey period, these values exceeded the standard value of a healthy population of the United States – 50. When we compared the results of our research to some other research findings, we concluded that there is no agreement that the emotional and psychosocial factors have a major impact on success of the treatment in patients with LR. Johansson et al. [17] and Den Boer et al. [18] noted a more significant psychological impact in surgical patients when compared with nonsurgical. In contrast to these findings, Bošković et al. [19] and Iles et al. [20] after studying the psychosocial factors as predictive factors of the success of treatment in patients with LPS and LR concluded that depression, satisfaction/dissatisfaction with work, psychological stress, and other factors have considerably smaller influence and that has been correlated to our research.

Unlike the SF-36v2® survey, in which the questions referred to the time interval within the previous four weeks, the ODI questions were related to the current status of the patients. The average values of the total ODI score during the examination period changed significantly in both groups of patients, and the differences of these values three and six months after the surgery were highly statistically significant ($p < 0.001$) in comparison to the values at the beginning.

At the start of the hospitalization (and rehabilitation) and at three months from the start of the rehabilitation, half of the patients responded with, "The pain is very mild at the moment." This fact can be justified by the effect of surgery and by early rehabilitation. Six months after the beginning of the rehabilitation, we concluded that in the majority of the patients (56%) a complete relief of pain was achieved.

The decision that the assessment shall be made after the first three months of the treatment was made because it was thought that this was a long enough period for the recovery and for the assessment of the therapeutic treatment outcomes. Assessment in the later period (e.g. after a year or more) could provide similar but also different or inadequate results (if, for example, there was an appearance – emergence – of new herniation of intervertebral discs or other pathological changes of the spine).

The fact that the period of three months after the operation is a long enough period for the assessment of the therapeutic effect and of the degree of recovery was supported by the research carried out by Häkkinen et al. [21]. They compared the score values on the ODI questionnaire administered six weeks after the surgery and then one year following the surgery for LR. They proved that the results obtained six weeks after the operation did not change substantially during the coming year.

Ability to function in terms of daily activities that was covered by the ODI questionnaire at admission and at the beginning of the treatment process was limited to light activities. Three months from the start of rehabilitation, the patients showed improvement but were still limited in their daily activities in regard to performance (adjusting) within proper body position. In the last survey period, the patients were still cautious, so their answers ranged from being rigid to avoid harder activities only, while lighter activities within the proper body position could be performed, to being able to perform heavier activities but with additional pain. Bakker et al. [22] in the review of prospective cohort studies have confirmed that sitting, walking, long standing in one place, as well as playing sports have not been significant risk factors for the development of LPS and LR, unlike most of the mechanical load of the spine during heavier work. Bending, torsion of the torso, and vibrations of the entire body were cited as significant predictors [22]. Roffey et al. [23–27] and Wai et al. [28–30] in eight systematic studies in total performed the analysis of the influence of the mechanical factors on the appearance of LPS and LR in a large number of workers in different professions. In these studies, the mechanical factors that were included were prolonged sitting in an awkward body position [23, 24], prolonged standing and walking [25], lifting and moving of patients [26], pushing or pulling [27], bending or twisting of the body during lifting of a heavy load [28, 29], carrying heavy loads [30].

Low values of correlation coefficients in patients who were operated on and a small correlation value of the SOC (social functioning) ODI domain with other scores and domains tells about the specifics of this domain and about the evident need to assess the QL of patients with LR by using batteries of generic and specific questionnaires. General generic questionnaires are needed to analyze appropriately the QL of patients in comparison to the normal population

and to compare the QL in patients with different diseases, while specific questionnaires are needed in order to assess in detail the health and the QL of these patients.

CONCLUSION

Given that the QL includes all aspects of life in patients who underwent LM, we did not expect an improvement in the first days after the operation. In further monitoring of our patients, we recorded significantly higher values of physical functioning and functioning in emotional and social aspects of the QL at three months and at six months when compared to the beginning of rehabilitation, and at six months when compared to three months of rehabilitation.

A statistically significant negative correlation between PCS and PAIN was recorded on the third repeated measurement. Values of domains and scores and the small values of correlation coefficients indicate that this group of patients feels differently after surgery and rehabilitation, and that this observation requires more detailed analysis and the utilization of the battery of generic and specific questionnaires.

Medical rehabilitation and ergonomic educational training have great importance in the planned structured recovery of patients after LM.

Application of the appropriate questionnaires in patients with LR has been of great importance in the assessment of the impact of the disease on physical, psychological, functional, and work capacity and on the QL, and in patients after LM it plays an essential role in the assessment of the efficacy of the rehabilitation treatment and consequently in the planning of the further management of these patients.

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Квалитет живота болесника после лумбалне микродисцектомије

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САЖЕТАК

Увод/Циљ Квалитет живота (КЖ) представља савремени концепт посматрања исхода обољења и лечења у свим областима медицине.

Циљ је био проценити КЖ оперативно лечених болесника са лумбалном радикулопатијом (ЛРП) на почетку лечења и три и шест месеци после прописане и спроведене медицинске рехабилитације.

Методе Обухваћен је рандомизиран и стратификован узорак од 50 болесника лечених лумбалном микродисцектомијом (ЛМД). Код свих болесника спроведен је конзервативни третман применом физикалних процедура, кинезитерапијских процедура и ергономске едукације. За процену стања болесника, квалитета живота и ефекта рехабилитационог третмана коришћена су два стандардизована упитника – *SF 36* и *The Oswestry Disability Index (ODI)*.

Резултати Најниже вредности *SF*-36 – *PCS*, *SF*-36 – *MCS* и *ODI* забележене су на почетку рехабилитације (*PCS*: 28,8; *MCS*: 37,8; *ODI*: 56,1%), после три месеца забележено је најзначајније побољшање скорова (*PCS*: 42,8; *MCS*: 45,2; *ODI*: 38,9%), а после шест месеци скорови су били мало већи (*PCS*: 49,2; *MCS*: 52,5; *ODI*: 23,7%) ($p < 0,001$).

Закључак КЖ и функционални статус болесника после ЛМД значајно су бољи после три и шест месеци у односу на почетак рехабилитације, као и после шест месеци у односу на стање после три месеца.

Кључне речи: лумбална радикулопатија; микродисцектомија; квалитет живота; *SF*-36; *ODI*; исход лечења

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effectiveness of combined ultrasound and exercise therapy in the treatment of carpal tunnel syndrome – randomized, placebo-controlled investigation

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SUMMARY

Introduction/Objective The aim of the paper was to evaluate the short-term effectiveness of ultrasound treatment procedure on defined clinical parameters and changes of electrodiagnostic parameters at the median nerve in carpal tunnel syndrome patients.

Methods Thirty-five patients (50 hands) were randomly divided into two groups: the experimental group (EG) (20 patients (29 hands)) and the control group (CG) (15 patients (21 hands)). Twenty sessions of ultrasound treatment were performed over a period of seven weeks and control examination was performed during the eighth week from the initial session. Clinical assessment parameters (pain intensity, superficial sensibility, and Tinel sign), and electrodiagnostic parameters (motor distal latency – mDL), median sensory nerve conduction velocity (SNCV), and median sensory nerve action potential (SNAP) were assessed both at baseline (T1) and at control (T2).

Results There is significant improvement of pain intensity (T1 – 10.4/58.6/31; T2 – 65.5/27.6/6.9; $p < 0.001$) and superficial sensibility (T1 – 3.4/69/27.6; T2 – 44.8/34.5/20.7; $p < 0.001$) in the EG after the treatment. In the EG, there is significant reduction in frequency of positive Tinel's sign (T1 – 100/0; T2 – 62.1/37.9; $p < 0.001$), and mDL significantly decreased after the treatment (T1 – 4.7 ± 1.3; T2 – 4.5 ± 1.2; $p = 0.007$), while SNAP (T1 – 20.2 ± 15.4; T2 – 24.4 ± 16.5; $p < 0.001$) and SNCV (T1 – 36.5 ± 9.8; T2 – 42.6 ± 9.7; $p < 0.001$) significantly increased.

Conclusion Ultrasound treatment along with exercises have positive short-term effects and benefits on improvement of clinical and electrodiagnostic findings in individuals with carpal tunnel syndrome.

Keywords: carpal tunnel syndrome; ultrasound treatment; clinical findings; electrodiagnostic parameters; short-term outcome

INTRODUCTION

Carpal tunnel syndrome (CTS) represents the most frequent compressive neuropathy of the median nerve at the wrist level, with the prevalence of around 0.7/10,000 of working population [1]. Such state might be associated with a decrease in productivity, and is the second most common cause of absence from work between 1997 and 2010 [1, 2]. It should be underlined that the frequency of CTS has temporal increase, pointing to the need for further evaluation of prevention methods and treatment modalities [1].

Numerous non-surgical options for the treatment of CTS were studied, among them ultrasound (US), splinting, exercises or mobilization, laser treatment, non-steroidal antiinflammatory drugs, corticosteroids, vitamins, and complementary therapies [3, 4]. So far, there are conflicting data with regard to US treatment efficacy on improvement in patients with CTS. Previous systematic reviews stated that so far there is limited data, of poor quality evidence, suggesting therapeutic effectiveness of US in patients with CTS [5, 6]. As a therapeutic modality, US can be administered with various biological effects as an adjunct modality in treatment of various musculoskeletal pathology. US therapeutic effects can be obtained via thermal (the molecular vibrations generated by acoustic waves while penetrating the tissue) and/or non-thermal (cavitation, standing waves, and media motion) mechanisms [7, 8]. Previous experimental studies stressed that US treatment might have anti-inflammatory and tissue-stimulating effects via numerous mechanisms, including modification of membrane permeability, blood flow, tissue metabolism, connective tissue extensibility, and nerve function [9, 10]. Yildiz et al. [11] suggested that US treatment effects on CTS are more likely due to the process of pressure formation and resolution in carpal tunnel canal, and opposing anti-inflammatory effects. It is also stated that US treatment can influence the ability of nerve fibers to propagate an action potential; however, the potential physiologic mechanisms of such function are not well understood [10]. Positive effects of US therapy on the increase

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of sensory nerve conduction velocity were reported, while there are conflicting effects on motor nerve conductions in terms of increase and decrease of the velocities. These effects on motor nerve conduction velocities are possibly due to the fact that they are intensity-dependent and might be to a certain degree the result of the relationship between thermal and non-thermal effects [10]. Thus, further methodologically rigorous studies are needed in order to obtain more conclusive evidence on the optimal treatment of patients with CTS, including the role of US therapy.

The aim of our study was to evaluate in a placebo-controlled study the short-term effectiveness of US on defined clinical parameters and changes of electrodiagnostic parameters in CTS patients.

METHODS

Patients and study design

The prospective randomized, placebo-controlled double-blind study included 39 patients (55 hands) at baseline with diagnosed CTS. Patients who met the inclusion criteria were included in the study. Prior to inclusion in the study, participants were informed about the study protocol and consent was obtained. The study was conducted at the Institute for Rehabilitation in Belgrade, Serbia, after the study protocol had been approved by the Institutional Review Board (number 02/2-29/2012), and was conducted according to the Declaration of Helsinki.

The patients were randomly divided into two groups: the experimental group (EG) and the control group (CG). In the CG, the US probe was applied without turning the device on. Randomization was allocated by using the "numbered envelopes" method. Printed paper with allocation was put in aluminum foil to prevent possible transparency in strong light. Sealed envelopes were mixed. Every enrolled patient got to pull an envelope from a pile of envelopes. The EG was composed of 20 patients (29 hands) at baseline with no drop-off during the treatment. The CG was composed of 19 patients (26 hands) at baseline with a drop-off of four patients at random during the treatment. Both patient groups followed the same rehabilitation protocol.

Our calculations of the study power revealed that the study has sufficient number of patients to detect a significant difference between the groups regarding the difference between delta motor distal latency (mDL) (1-beta = 0.93), sensory nerve action potential (SNAP) (1-beta = 0.86) and sensory nerve conduction velocity (SNCV) (1-beta = 0.99) for the median nerve.

Electrophysiologic analyses

For all the patients, median and ulnar sensory and motor nerve conduction velocities (NCSs) were determined by Medelec Synergy, Oxford instruments, UK. Motor studies were recorded with supramaximal stimulation at the wrist and registration from the thenar (the *abductor pollicis brevis* muscle) for the median nerve and hypothenar (the *abductor digiti V* muscle) for the ulnar nerve, with a distance of 7 cm between these two sites. SNAPs of median and ulnar nerves were recorded antidromically, with stimulation at the wrist, and registration with ring-electrodes from digit 2 and digit 4 [12–15]. For the confirmation of CTS diagnosis, we followed recommendations for median-to-ulnar comparison studies measured on digit 4, by stimulating both nerves at the wrist, 13 cm proximal to the detection electrode for both sensory median evaluation and sensory ulnar evaluation [13]. In motor and sensory NCSs, the latency was measured from the onset of the stimulus to the initial negative deviation, and the amplitudes were measured from the baseline to the negative peak. All measurements were performed bilaterally, and by the same electromyographer. Hand temperature was registered and maintained at 32–34°C. Electromyography (EMG) testing was performed using a concentric needle electrode on the *abductorpollicis brevis* and the *abductor digiti V* muscles [12]. The patients were assessed electrophysiologically with NCSs at baseline, and at eight weeks after the initial assessment.

The palmar side sensitivity of the first three fingers and half of the fourth finger was determined by the palpatoric differentiation test of the two points. The main outcome measures were pain intensity assessed by numeric rating scale (NRS) (for statistical analyses, we categorized the pain as none – NRS 0, mild – NRS 1–3, moderate – NRS 4–6, or severe – NRS 7–10) and the presence of Tinel's sign [16].

The same board-certified physician evaluated the clinical assessment parameters at both baseline (T1) and eight weeks after (T2) the initial assessment.

Inclusion criteria

The study included patients aged 18 years and above, with symptoms (pain and/or numbness) in at least two digits on one hand (digits 1–4) lasting less than one year, no thenar atrophy, and mild to moderate CTS based on NCSs. Patients were eligible for the study if NCSs demonstrated any of the following: median nerve motor terminal latency above 4.4 ms with distal distance of 7 cm, and/or median nerve sensory distal latency above 3.5 ms with distal distance of 13 cm, and/or median to ulnar sensory distal latency difference from 0.5 ms and above measured on digit 4, with or without pathological EMG findings in the *abductor pollicis brevis* muscle [12, 13].

Exclusion criteria

Patients with severe CTS and with axonal loss of the median nerve confirmed by electrodiagnostic studies (absent or low amplitude of SNAP) and/or absent or low amplitude of compound muscle action potential, and/or presence of denervation potentials and/or presence of neurogenic motor unit potentials on needle EMG examination [13], thenar atrophy, or severe pain intensity (> 7) based on the NRS [16], were excluded from the study. Other criteria

for exclusion from the study were pregnancy, presence of diabetes mellitus, connective tissue disorders or arthritis involving hand or wrist, occlusive blood vessel disease, other neurological diseases (central and peripheral nervous system diseases and traumas), hypothyroidism, B_{12} vitamin deficiency, previous chemotherapy, previous injuries and upper limb surgery, as well as alcoholism in the history. Individuals with the type of employment that could be considered a risk factor for CTS, and previous carpal tunnel release, were excluded.

Treatment protocol

Therapeutic US was administered in EG (In CG Sham US). Probe frequency of the therapeutic dosage of US was 1 MHz, and the intensity was 1.0 W/cm^2, pulsed mode 1:4, with transducer of 5 cm^2 (Eko Medico-Sono Din, Electronic Design Medical, Belgrade, Serbia), and with aquasonic gel as the couplant [17]. The US was applied in contact over the carpal tunnel area of the skin on the volar side of the wrist for 15 minutes. The 1 MHz frequency US mode was used in our study due to the fact that deeper penetration has the potential to reach the median nerve [18]. Before study inclusion of eligible participants, the US devise was calibrated. A total of 20 treatments were administered in each case, with the following schedule: 10 treatments were administered once a day, five days a week (working days only) for two weeks, followed by four treatments every other day for two weeks, and six treatments twice a week for three weeks. Control of eligible study participants was done eight weeks after the initial assessment. No side effects of the treatment were reported.

Individuals from the CG were not given therapeutic US treatment, but placebo (sham) treatment without affecting the normal ultrasonic output when the key was turned to the "on" position (placebo US (0.0 W/cm^2 intensity)).

Patients in both groups were instructed to perform nerve and tendon gliding exercises developed by Totten and Hunter [19], which they continued to perform at home during the investigation period of eight weeks. During tendon gliding exercises, the fingers were placed in five positions. During the median nerve gliding exercise, the median nerve was mobilized by putting the hand and wrist in six different positions. During these exercises, the neck and the shoulder were in a neutral position, and the elbow was in supination and in 90° of flexion. Each position was maintained for 5 seconds. These exercises were applied as five sessions daily. Each exercise was repeated 10 times at each session.

Other treatments, such as acupuncture, physical therapy, and wearing splints, were forbidden. The patients included in the study had neither local, nor oral administration of glucocorticoids for at least one month before or during the investigation period. Paracetamol was allowed for occasional pain relief, but non-steroidal antiinflammatory drugs were not allowed. None of the patients reported using paracetamol during the treatment period.

Clinical assessment and NCSs were evaluated at baseline and at eight weeks after the initial assessment.

Statistical analysis

Data are presented as counts (percentage) or means ± standard deviations (SD) depending on the data type. Group comparisons were performed using Pearson χ^2 test, Cochran–Armitage test (χ^2 test for trend) and Mann–Whitney U-test. Within the group, testing was performed using Wilcoxon signed-rank test. Data analysis was performed in IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA) statistical software. All p-values less than 0.05 were considered significant.

RESULTS

The EG was composed of 20 patients (29 hands) at baseline, with no drop-off during the treatment, two (10%) males and 18 (90%) females, of whom 11 (55%) patients had unilateral and nine (45%) bilateral CTS. The EG patients' age ranged 34–69 years (mean 53.5 ± 8.3 years). The CG was composed of 19 patients (26 hands) at baseline, with drop-off of four patients at random during the treatment. Therefore, we included only those (15 patients, 21 hands) who finished the study. In the CG, there were two (13.3%) males and 13 (86.7%) females, of whom nine (60%) with unilateral and six (40%) with bilateral CTS. The mean age of the CG patients was 52.6 ± 8.7 years (range 35–64 years). None of the patients reported using paracetamol during the treatment period.

In Table 1, personal characteristics and job type of the studied individuals are presented. There were no significant differences between the EG and the CG regarding observed baseline parameters (Table 1).

Table 1. Frequency distributions of demographic characteristics in patients with carpal tunnel syndrome in the ultrasound group (EG) and the control group (CG) (the results are presented as count (%) or mean ± standard deviation)

Personal characteristics	EG n = 20 (29 hands)	CG n = 15 (21 hands)	p-value
Age (years)	53.5 ± 8.3	52.6 ± 8.7	0.758a
Sex			
Female	18 (90%)	13 (86.7%)	1.000b
Male	2 (10%)	2 (13.3%)	
Job type			
Manual labor	9 (45%)	6 (40%)	0.913b
Administrative work	6 (30%)	4 (26.7%)	
Housewife or other	5 (25%)	5 (33.3%)	

[a]t-test;
[b]χ^2 test

There was a significant improvement in the EG regarding pain intensity after the treatment (T2), while such difference was not observed in the CG (Table 2). Significant improvement for superficial sensibility was noticed in the EG as well, after eight weeks (T2) (Table 2).

In the EG, there was a significant reduction in frequency of positive Tinel's sign between the baseline period (T1) and eight weeks from the baseline assessment (T2) (Table 2).

Table 2. Obtained results in patients with carpal tunnel syndrome at baseline (T1) and after eight weeks (T2)

Subjective symptoms	T1 (n) (%)	T2 (n) (%)	p-value[b]
Pain intensity	No pain/Mild/ Moderate	No pain/Mild/ Moderate	
EG	3/17/9 10.4/58.6/31	19/8/2 65.5/27.6/6.9	< 0.001*
CG	1/14/6 4.7/66.7/28.6	2/15/4 9.5/71.4/19	0.083
p-value[a]	1.000	< 0.001*	-
Superficial sensibility	normal/weakened/ extinguished	normal/weakened/ extinguished	p-value[b]
EG	1/20/8 3.4/69/27.6	13/10/6 44.8/34.5/20.7	< 0.001*
CG	1/14/6 4.8/66.7/28.6	1/14/6 4.8/66.7/28.6	1.000
p-value[a]	1.000	0.021*	-
Tinel sign	positive/negative	positive/negative	p-value[b]
EG	29/0 100/0	18/11 62.1/37.9	< 0.001*
CG	0/21 0/100	0/21 0/100	1.000
p-value[a]	< 0.001*	< 0.001	-

CG – control group; EG – experimental group
*statistically significant;
[a]between groups;
[b]within groups

Table 3. Electrodiagnostic findings at baseline (T1) and after eight weeks (T2) (means ± standard deviations)

Subjective symptoms	T1	T2	p-value[b]	Delta
mDL (2nd finger)				
EG (ms)	4.7 ± 1.3	4.5 ± 1.2	0.007*	0.2 ± 0.3
CG (ms)	5.0 ± 2.0	5.0 ± 2.0	1.000	0
p-value[a]	0.794	0.536	-	0.009*
SNAP (2nd finger)				
EG (μV)	20.2 ± 15.4	24.4 ± 16.5	< 0.001*	5.0 ± 3.7
CG (μV)	17.4 ± 12.4	17.9 ± 14.1	0.151	0.6 ± 5.6
p-value[a]	0.758	0.164	-	0.002*
SNCV (2nd finger)				
EG (m/s)	36.5 ± 9.8	42.6 ± 9.7	< 0.001*	6.9 ± 3.2
CG (m/s)	35.3 ± 9.4	36.6 ± 9.8	0.086	1.3 ± 2.9
p-value[a]	0.690	0.047*	-	< 0.001*

CG – control group; EG – experimental group; mDL – motor distal latency; SNAP – sensory nerve action potential; SNCV – sensory nerve conduction velocity;
*statistically significant;
[a]between groups;
[b]within groups

In Table 3, electrodiagnostic findings at baseline (T1) and after eight weeks (T2) are presented. There was a significant reduction in mDL values in individuals of the EG, while a significant increase in SNAP and SNCV were noticed in individuals of the EG. A significant increase in SNCV was noticed in individuals of the EG when compared with CG individuals, eight weeks after initial assessment (T2). For all evaluated electrodiagnostic parameters (distal latency, SNAP, and SNCV) there were significant differences in delta values between the EG and the CG.

DISCUSSION

In our placebo-controlled study, we aimed to evaluate the short-term effectiveness of US on defined clinical parameters and changes of electrodiagnostic parameters in CTS patients. We demonstrated after the treatment (T2) significant improvement in pain intensity and superficial sensibility in the EG group versus the CG group. Furthermore, in the EG, we noticed significant reduction in frequency of positive Tinel's sign between baseline period (T1) and eight weeks from the baseline assessment (T2).

In a recent Cochrane Systematic Review, it was suggested that for those individuals who are experiencing mild to moderate symptoms of CTS, therapeutic US may be offered. However, the effectiveness and duration of the benefit of such an intervention remain unclear [5].

In a systematic review of O'Connor et al. [20], it was pointed out that US treatment in patients with CTS over the course of two weeks is not considered to be beneficial, while in other studies such treatment was shown to be beneficial in improving symptoms after seven weeks [4, 11]. Ebenbichler et al. [17] also stressed positive short-term effects and even suggested satisfying medium term effects for patients with mild to moderate idiopathic CTS.

Our findings are consistent with the studies reporting positive effects of US therapy in CTS patients regarding symptoms' improvement over the period of eight weeks [4, 11]. Our study showed that the proportion of those individuals with CTS with mild to moderate degrees of pain intensity significantly decreased, while those with no pain symptoms increased. This is also true for those with impaired superficial sensibility. Regarding the presence of Tinel's sign, a significant reduction in frequency of those individuals with the positive sign was found in the EG group.

We noticed a reduction in frequency of mild pain intensity symptom by almost one half, while the percentage of patients with moderate pain intensity was reduced almost three-fold. However, greater decrease in the frequency of superficial sensibility was noticed for those with a weakened degree (50%) than for those with extinguished degree (around 25%). These trends imply that in severe cases, US treatment might have more effect on the pain symptom rather than on superficial sensibility.

Because of possible positive effects of US on nerve function and regeneration, as previously mentioned, significant changes in electrodiagnostic evaluation might be absent despite the significantly positive effects on symptom improvements. In the study by Yildiz et al. [11], it was explained that such effects might be due to the fact that electrodiagnostic studies predominantly measure conduction of A fibers, while C fibers, which are responsible for somatic pain, are more sensitive to US treatment. It should also be stressed that prolonged compression in the carpal tunnel canal might lead to the loss of axons along with demyelination, thus disabling significant improvement particularly in the amplitude increase, and in cases with severe axonal losses disabling improvement in conduction velocities as well. Thus, for patients with CTS, early and

adequate diagnosis with a timely and adequate treatment modality is needed for optimal outcome.

Our results regarding electrodiagnostic evaluations in CTS patients treated with US therapy are consistent with previous reports. We obtained a significant reduction in distal latency values in the EG, along with a significant increase in SNAP and SNCV parameters in the EG, thus suggesting positive effects of US treatment on electrodiagnostic findings.

The limitation of the study refers to the number of participants – thus, further studies on larger samples are advised.

The necessity for further research of potential benefits of non-surgical treatment options for individuals with diagnosed CTS is advised due to the fact that despite numerous systematic reviews that have been published, evidence for many treatment modalities, among them US, is inconclusive [6, 7, 21].

CONCLUSION

Our results suggest that US treatment along with exercises has positive short-term effects and benefits on improvement of clinical and electrodiagnostic findings in individuals with CTS.

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Ефекти комбинованог ултразвука и кинезитерапије у терапији синдрома карпалног тунела – рандомизовано, плацебо-контролисано испитивање

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САЖЕТАК

Увод/Циљ Циљ рада је био да се испитају краткорочни ефекти ултразвучне терапије на одређене клиничке параметре и промене електродијагностичких параметара средишњег живца руке (*n. medianus*) код болесника са синдромом карпалног тунела.

Методе Тридесет пет болесника (50 руку) методом случајног узорковања је подељено у две групе: експериментална група (ЕГ) (20 болесника – 29 руку) и контролна група (КГ) (15 болесника – 21 рука). Примењено је 20 сесија ултразвучне терапије током седам недеља и спроведена је контрола током осме недеље од почетка терапије. Праћени су клинички параметри (интензитет бола, површински сензибилитет и Тинелов знак), електродијагностички параметри (моторна дистална латенца – мДЛ), сензорна брзина провођења *n. medianusa* (СБП) и сензорни акциони нервни потенцијал *n. medianusa* (САНП) на почетку третмана (Т1) и на контроли (Т2).

Резултати Дошло је до значајног побољшања у интензитету бола (Т1 – 10,4/58,6/31; Т2 – 65,5/27,6/6,9; $p < 0,001$) и суперфицијалног сензибилитета (Т1 – 3,4/69/27,6; Т2 – 44,8/34,5/20,7; $p < 0,001$) у ЕГ после терапије. У ЕГ је уочено значајно смањење у учесталости позитивног Тинеловог знака (Т1 – 100/0; Т2 – 62,1/37,9; $p < 0,001$), и мДЛ је значајно снижена после терапије (Т1 – 4,7 ± 1,3; Т2 – 4,5 ± 1,2; $p = 0,007$), док су САНП (Т1 – 20,2 ± 15,4; Т2 – 24,4 ± 16,5; $p < 0,001$) и СБП (Т1 – 36,5 ± 9,8; Т2 – 42,6 ± 9,7; $p < 0,001$) значајно већи.

Закључак Ултразвучна терапија са кинезитерапијом има корист и позитивне краткорочне ефекте на побољшање клиничких и електродијагностичких параметара код особа са синдромом карпалног тунела.

Кључне речи: синдром карпалног тунела; ултразвучна терапија; клинички параметри; електродијагностички параметри; краткорочни исход

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Oral rehabilitation of a patient with systemic lupus erythematosus using implant-supported fixed dentures – a case report with review of important considerations

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SUMMARY

Introduction Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease with a variety of oral manifestations (dry mouth, reduced salivary flow, painful mucosal lesions and restricted mouth opening, impaired oral hygiene maintenance), as well as possible far-reaching systemic implications. In the context of SLE, oral rehabilitation with dental implants might be the most appropriate solution. However, a lack of available literature, as well as the absence of treatment protocols, often leads to unsatisfactory management of these patients.

The aim of this paper was to describe oral rehabilitation of a patient with SLE using dental implants and fixed dentures in both jaws.

Case outline A 66-year-old female patient, who had suffered from SLE for over 30 years, was referred for oral rehabilitation as her chief complaints related to the existing mobile partial dentures in the jaws and poor chewing ability. Proposed oral rehabilitation with fixed dentures supported by six dental implants in the maxilla and four dental implants in the mandible, as well as prosthetic restoration of the mandibular teeth, was accepted by the patient. During the follow-up period of three years, no biological complications were observed related to the performed treatment.

Conclusion Dental implants might be the most suitable treatment modality for oral rehabilitation of patients suffering from SLE.

Keywords: dental implants; oral rehabilitation; systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, inflammatory disease with multiple organ involvement and a broad spectrum of clinical manifestations, including mucocutaneous, cardiac, renal, pulmonary, and musculoskeletal complications [1]. The hallmark of this relapsing and remitting disease is the production of autoantibodies and immune complexes, with a consequent inflammatory response that may lead to cell death and organ failure [2].

Orofacial structures and functions may be adversely affected in the presence of SLE. Intraoral manifestations are most frequently presented as painful erythematous erosions, ulcerations and/or leukoplakic areas, localized on buccal, labial, lingual or palatal mucosa [1–3]. The most frequent complaints include xerostomia and burning mouth syndrome, while desquamative gingivitis, marginal gingivitis, and periodontitis are among common findings [1, 3–6]. Musculoskeletal complications may involve painful temporomandibular joint dysfunction, with possible repercussions on intraarticular mechanics. Additionally, immunosuppressive therapy, including corticosteroids and cytotoxic agents, poses a risk of inducing osteoporosis and altered immune response, with an increased susceptibility to oral infections [3]. Regarding reduced salivary flow, painful mucosal lesions may develop and impair oral hygiene regimen; often associated with restricted mouth opening and possible adverse effects of immunosuppressive therapeutic agents. Therefore, providing satisfactory oral rehabilitation of patients with SLE might prove challenging.

The main objective of this paper was to present the case of a patient with SLE, for whom oral rehabilitation with implant-supported fixed dentures was chosen as a treatment modality for partial edentulism. Considerations in regard to SLE complications and their possible impact on oral rehabilitation with dental implants were also discussed.

CASE REPORT

A 66-year-old female patient was referred for oral rehabilitation as her chief complaints related to the existing mobile partial dentures in jaws and poor chewing abilities. Medical records showed that the patient had suffered

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from SLE for over 30 years. Treatment modality for SLE included 400 mg of hydroxychloroquine per day (Plaquenil, 200 mg tablets; Sanofi-Aventis, London, UK). Also, the patient was diagnosed with antiphospholipid syndrome treated with low doses of acetylsalicylic acid (Aspirin, 81 mg tablets; Bayer Pharma AG, Leverkusen, Germany; one tablet daily). Regarding other significant comorbidities, the patient had suffered from diabetes mellitus type 2 (DMT2) for 25 years. Metabolic control regarding DMT2 was satisfactory with glycosylated hemoglobin level < 8%, without microvascular and macrovascular complications registered in the patient's medical record, and DMT2 therapy consisted of diet, oral hypoglycemic agent metformin (Glucophage SR, 750 mg tablets; Merck Pharmaceuticals, UK; two tablets daily) and long-acting insulin analogue (Lantus SoloStar 100 unit/ml solution, Sanofi-Aventis; 36 units daily). A further daily therapy regimen included nifedipine with extended release (Adalat LA, 60 mg tablets; Bayer House, UK; one tablet daily) and atenolol (Atenolol, 50 mg tablets, Actavis, UK; one tablet daily) for essential hypertension treatment, as well as calcium + vitamin D_3 supplements (Calcium 600 mg +D_3, 600 mg – 200-unit tablets; Major Pharmaceuticals, Livonia, MI, USA; one tablet daily) for osteopenia.

Extraoral clinical inspection did not demonstrate facial skin involvement. Intraoral clinical examination presented characteristic bilateral discoid and pigmented lesions involving buccal mucosa, reddened tongue with atrophy of the filiform papilla and sore mouth, with no ulcerations observed (Figure 1). The patient complained of symptoms similar to burning mouth syndrome (BMS), especially when consuming acidic or spicy food, difficulties in swallowing, and dry mouth. However, after salivary flow measurement according to the protocol described by Speight et al. [7], the obtained unstimulated saliva flow rate was 0.2 mL/minute. A problem with limited mouth opening was also reported by the patient, as well as the slight pain in the temporomandibular joints (TMJ) while chewing. Clinical examination of the TMJ did not reveal signs of dislocation, subluxation, or crepitation during mandibular movements. Maximal inter-incisal distance was 24 mm. In the maxilla, only two teeth were present (the second molar and canine on the left side); in the mandible, both central and lateral incisors were present, as well as the canine and second premolar on the left side.

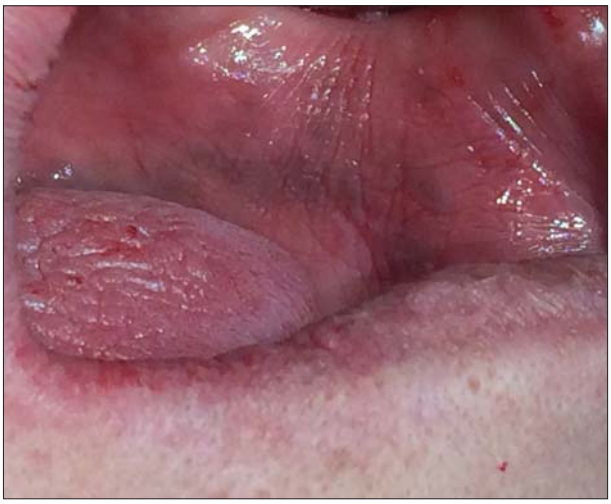

Figure 1. Intraoral manifestations of systemic lupus erythematosus

Periodontal examination in the maxilla revealed severe bone loss, furcation involvement, and pathological mobility of the second molar, while the canine exhibited pathological mobility (an average probing depth of 6.73 mm), and both were determined as irrational for further treatment. In the mandible, gingivitis was present for an average probing depth of 1.62 mm. Moreover, bleeding on probing was observed in both maxillary teeth, as well as in central and lateral incisors on the right side in the mandible.

After taking into account medical history and intraoral status, proposed oral rehabilitation with fixed dentures supported by six dental implants in the maxilla and four dental implants in the mandible, as well as prosthetic restoration of the mandibular teeth, was accepted by the patient.

Preoperative treatment

The patient underwent the hygienic phase of periodontal treatment, including extraction of the teeth that were determined as irrational for treatment (maxillary molar and canine) and scaling and polishing of the remaining teeth; root debridement was also done under local anesthesia (the left canine and the right lateral incisor in the mandible). Additionally, chlorhexidine 0.12% solution was prescribed to the patient to rinse twice daily for four weeks. The patient was advised not to wear partial dentures two weeks prior to surgery. After the hygienic phase and a four-week observation period, teeth preparation in the mandible was performed and temporary polymethyl methacrylate crowns were delivered.

On the morning of the surgical procedure, fasting plasma glucose level was determined and the obtained value was 6.9 mmol/L. The patient also confirmed that she regularly took prescribed therapy for autoimmune, metabolic, and cardiovascular disorders.

Surgical procedure

The surgical procedure was performed under local anesthesia. Previous partial dentures were modified and used as a template in order to more precisely transfer prosthetic planning during implant insertion. Midline crestal incision was performed in the maxilla; the mucoperiosteal flap was elevated and six implants (Straumann® Standard Plus, SLA, Basel, Switzerland) were installed according to manufacturer instructions in positions 16, 14, 12, 22, 24 (4.1 mm in diameter; 10 mm in length), and 26 (4.8 mm in diameter; 6 mm in length). In the mandible, in the same manner, four implants (Straumann® Standard Plus, SLA) were placed in positions 46, 45 (4.8 mm in diameter; 6 mm in length), 43 (4.1 mm in diameter; 10 mm in length) and 36 (4.8 mm in diameter; 8 mm in length and 6.5 mm platform). Appropriate healing abutments were positioned

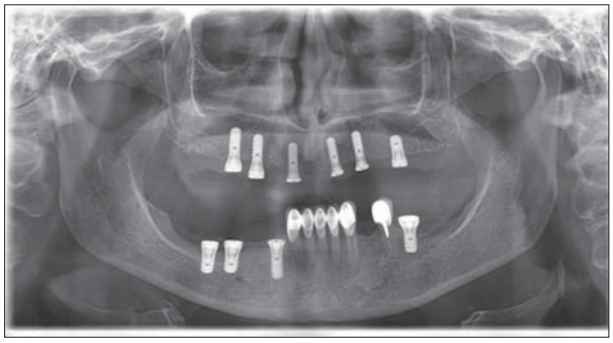

Figure 2. Postoperative panoramic X-ray

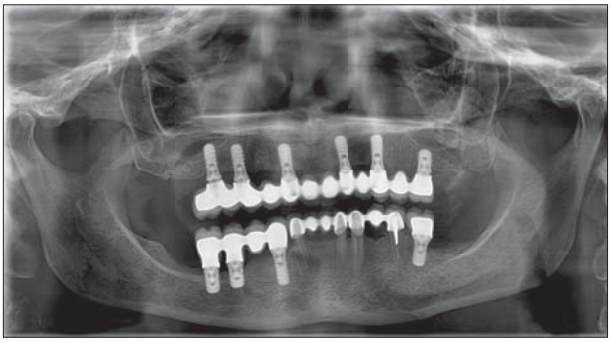

Figure 3. Panoramic X-ray after three years

and the wounds were closed with monofilament sutures. No complications were observed during the surgery. A control panoramic X-ray was obtained immediately after surgery to ensure adequate implant placement (Figure 2).

Postoperative treatment

The postoperative regimen included antimicrobial therapy with 1 g of penicillin (Panclav, Hemofarm A.D., Vršac, Serbia) with probiotic prophylaxis, twice daily for five days and an antiseptic mouthwash (chlorhexidine 0.12% solution) twice daily for ten days. For postoperative pain control, rescue analgesics (Diclofenac Duo®, 75 mg, Pharmaswiss, Nové Město, Czech Republic) were advised. The postoperative course proved uneventful and sutures were removed after eight days. A provisional denture was delivered for the upper jaw.

Prosthetic treatment

In the mandible, both central incisors were extracted due to unsuccessful endodontic treatment. Definitive implant-supported fixed denture in the maxilla, and two implant- and one tooth-supported fixed restorations in the mandible were delivered nine months after surgery, following a delayed implant loading protocol. Inter-arch distance was determined precisely, having in mind the TMJ problems that were previously detected. Bilaterally balanced occlusion was obtained during eccentric movements in order to minimize lateral forces.

During the 36-month follow-up period, no major complications occurred (Figure 3). After nine months, ceramic chipping was observed on one tooth, which was repaired during the same visit. Periodontal examination revealed no gingivitis, periodontitis, or periimplantitis. Additionally, the patient reported no subjective symptoms such as a burning sensation or difficulty in eating, and overall improvement and satisfaction with fixed restorations were noticeable.

DISCUSSION

Implant treatment for patients suffering from SLE is not documented to a satisfactory extent in current literature. Moreover, no clear clinical guidelines are available regarding this topic, which can lead to possible mistreatment of patients. In this paper, the case of uneventful installation of dental implants and successful prosthetic rehabilitation of a patient with SLE was presented, and specific considerations with which a dentist should be familiar when treating such patients were pointed out.

Pathogenesis of SLE includes deposition of autoimmune antibody complexes in the connective tissue of various organs with subsequent immune response, and almost 90% of those affected are women ranging from young to middle age [8]. The presence of SLE may impair orofacial structures and functions in various ways. Major complaints include xerostomia, burning and tingling of oral mucosa, and painful mucosal lesions [1]. A patient's discomfort is aggravated by mobile dentures that constantly irritate oral mucosa, thus leading to a poorer quality of life. In the presented case, typical bilateral, painful mucosal lesions localized on buccal mucosa were confirmed, with symptoms of xerostomia and sore mouth, as well as the presence of unsatisfactory mobile dentures. Xerostomia, as the most common oral symptom in patients with SLE, is attributed secondarily to Sjogren's syndrome, but this diagnosis was not confirmed from the patient's medical chart [9]. Although the patient reported a subjective feeling of dry mouth, hyposalivation was not confirmed by measuring the resting saliva flow, since the obtained saliva volume was higher than 0.1 ml/minute. In this case, the presence of SLE was accompanied by long-term DMT2, which could also contribute to the aggravation of orofacial symptoms. It is reported that DMT2 by itself, due to underlying neuropathic and microvascular changes in oral tissues, may cause xerostomia, salivary gland dysfunction, periodontal disease, tooth loss, TMJ dysfunction, and burning and tingling of oral mucosa [10–14].

SLE may affect TMJ in up to 60% of patients, with painful and limited mouth opening [15]. The patient reported only slight pain bilaterally during mandibular movement with decreased interincisal distance. The observed condition was most probably due to tooth loss and inadequate interocclusal dimension achieved with previous removable dentures, rather than SLE itself, since mouth opening improved and interincisal distance increased after oral rehabilitation to 26 mm during the follow-up period. Also, the patient reported improvement in chewing, while pain during TMJ movement gradually disappeared.

Frequent systemic complications of SLE include Libman-Sacks endocarditis, which may be present in up to

50% of patients. Deposition of autoimmune complexes in the endothelium of cardiac valves leads to nonbacterial thrombotic endocardial lesions, which may be colonized during transient bacteremia [16]. Therefore, oral surgical treatment of such a patient would require antibiotic prophylaxis. Since there was no endocardial involvement recorded in the patient's medical chart, antibiotic prophylaxis was not performed. However, the usual postoperative antimicrobial regimen was prescribed.

Antiphospholipid syndrome, also known as a lupus anticoagulant syndrome, is an autoimmune prothrombotic disorder with deep venous thrombosis as the most frequent clinical manifestation. SLE is the most common cause of secondary antiphospholipid syndrome, since it affects 30–60% of patients suffering from SLE [17]. Thrombotic tendency in venous, arterial, or microcirculatory vascular beds is a consequence of antibodies binding with the phospholipids in the platelets' membrane, leading to increased activation and aggregation of platelets. The patient was treated daily with 81 mg of Aspirin, since these low doses (up to 100 mg per day) are effective in the prevention of thromboembolic episodes [17, 18]. Adverse bleeding events were not observed intraoperatively or postoperatively, and hemostasis was obtained with usual local hemostatic measures. During outpatient dental surgery, it is not recommended to interrupt low-dose Aspirin therapy in patients at risk of thromboembolic events, since local hemostatic measures are usually effective if intraoperative or postoperative bleeding occurs [19].

Osteopenia and osteoporosis are considered a significant comorbidity of SLE and decreased bone mineral density may be present in up to 67% of women with SLE [20]. Corticosteroid therapy is regarded as one of the major risk factors, but other factors such as early menopause, renal impairment, low levels of vitamin D, lupus duration and older age may also contribute to the risk [21]. In the presented case, where the patient also suffered from osteopenia, SLE was treated with an antimalarial agent, and corticosteroids were not included in regular therapy. Antimalarial therapy is proven to be safe with respect to spine and hip-bone mineral density in female patients with SLE, although there is no data available concerning the impact of antimalarials on jaw bone metabolism [22]. While it is well documented that the presence of DMT2 may lead to altered bone metabolism, it seems that DMT2 does not impair mandibular bone mineral density [23]. In this case, it was not observed that the presence of SLE and the prescribed antimalarial therapy affected the osseointegration of dental implants and soft tissue healing over a 36- month follow-up period. Likewise, no signs of periimplantitis were noticed during functional loading during the same observation period.

Recently, Ergun et al. [24] also reported implant-supported prosthetic rehabilitation of a middle-aged female patient with SLE. The patient's complaints were similar to those experienced by the patient in this case, including xerostomia, sore mouth, and difficult opening of the mouth. However, characteristic mucosal lesions were more pronounced, involving hard palate and lips' mucosa. After the uneventful installation and healing of six implants in the posterior parts of both jaws, fixed implant-supported restorations were delivered. At the end of a 24-month follow-up period, the authors concluded that rehabilitation was successful, with improvements regarding subjective symptoms and limited mouth opening, and proposed that dental implants may be successful and preferred treatment option in patients with SLE. Correspondingly, in the presented case, clinical and radiographic findings revealed that peri-implant bone levels, as well as soft tissue volume remained stable after a 36-month follow-up period.

In conclusion, on the basis of currently limited data, clinicians might consider dental implants as probably the most satisfactory treatment modality when planning prosthetic rehabilitation for patients suffering from SLE. The present report showed an uneventful follow-up period of three years, with only minor dental complications observed (ceramic chipping). Regarding oral manifestations of SLE and imposed challenges in oral rehabilitation, fixed dentures supported by implants or teeth should be the therapeutic goal. SLE is characterized by multiple systemic complications and often accompanied by concomitant chronic diseases, which may affect physical condition to varying degrees, and meticulous assessment of each individual patient is necessary before any procedures are performed. Further clinical trials are warranted, to result in clear guidelines for clinicians regarding implant treatment of patients with SLE.

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Орална рехабилитација болесника са системским еритематозним лупусом фиксним зубним надокнадама на зубним имплантатима – приказ случаја и преглед значајних сазнања

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САЖЕТАК

Увод Системски еритематозни лупус (СЛЕ) јесте хронично аутоимуно обољење са различитим системским и оралним манифестацијама (ксеростомија, болне слузокожне лезије и болно отварање уста, отежано спровођење адекватне оралне хигијене), као и могућим системским компликацијама.

Орална рехабилитација болесника са СЛЕ фиксним зубним надокнадама ношеним зубним имплантатима може представљати најприкладнији вид терапије. Међутим, услед ограничених информација из доступне литературе, као и недостатка терапијских протокола, и данас се у пракси ови болесници неадекватно протетски збрињавају мобилним надокнадама.

Циљ овог рада је био да прикаже болесницу оболелу од СЛЕ која је збринута фиксним зубним надокнадама ношеним зубним имплантатима у обе вилице.

Приказ болесника Жена, 66 година стара, са еволуцијом СЛЕ од 30 година, упућена је на оралну рехабилитацију због проблема са мобилним парцијалним протезама обе вилице и немогућности жвакања. Прихватила је препоручену оралну рехабилитацију са шест денталних имплантата у горњој и четири у доњој вилици. Током периода праћења од три године нису уочене биолошке компликације.

Закључак Терапија зубним имплантатима се може сматрати најбољим терапијским модалитетом у оралној рехабилитацији болесника оболелих од СЛЕ.

Кључне речи: зубни имплантати; орална рехабилитација; системски еритематозни лупус

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Diagnostic dilemmas of Rasmussen's encephalitis in adults

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SUMMARY

Introduction Rasmussen's encephalitis (RE) represents a rare, progressive, and inflammatory disease of the brain. Its detection in adults is a great challenge in clinical medicine.
The aim of this paper is to highlight the diagnostic dilemma of RE in adults.

Case outline A 46-year-old woman was hospitalized due to persistent intense diffuse headaches, followed by nausea and the urge for vomiting that made her wake up during the night. On several occasions, she had transitory speech and memory disorders, and right hand numbness. Magnetic resonance (MR) imaging findings were as follows: occipitoparietal left in the deep white matter, as well as subcortical T2/flair white matter hyperintensities, T1-hypointense change involving the corpus callosum. MR spectroscopy showed an increased level of choline/creatinine (Cr) (2.12), a reduction of N-acetylaspartate/Cr (1.27), an increased level of myo-inositol/Cr (1.20), and the presence of lactate. The patient refused lumbar puncture. Due to the described changes close to the speech center, cerebral biopsy was not taken. Even after five years, MR and spectroscopic findings are unchanged, while the clinical condition remains stable and unchanged.

Conclusion This case highlights the diagnostic dilemmas that arise in adult-onset RE and suggests that this diagnosis should be considered in patients of any age with the appropriate clinical picture.

Keywords: Rasmussen's encephalitis; adult; diagnostic; dilemma

INTRODUCTION

Rasmussen's encephalitis (RE) represents a rare, progressive, and inflammatory disease of the brain. Its detection is a great challenge in clinical medicine. It is usually associated with intractable motor seizures, mainly focal seizures, epilepsia partialis continua (EPC), and progressive cognitive impairment with hemiparesis, as well as with language and cognitive disorders [1].

The disease was originally described by Rasmussen et al. [2] in 1958. According to the author's opinion, the first RE attack most frequently occurs during childhood period between the first and the 11th year of life in previously healthy children. Forty years later, cases of chronic encephalitic epilepsy in adults and adolescents, independent of gender, were presented as RE variants [3]. The oldest patient presented in the literature was a 54-year-old female from Australia [4].

The greatest enigma connected with RE is the etiological basis of the disease. The most recent attempts in the identification of pathogenic viral agents are incomplete and contradictory. A great number of researches involves the identification of antibodies responsible for the development of RE. Rogers et al. [5] published a hypothesis that the antibody has a major etiological role against glutamate/AMPA subunit 3 receptor (GluR3). This theory is based on the fact that rabbits vaccinated with GluR3 antibodies show similar clinical features as patients with RE. However, neither GluR3 nor other antibodies have been detected in all RE patients and are not strictly specific to RE but could also be found in other types of severe epilepsies. Today, autoimmune hypothesis of RE is presented more often due to transitory efficiency of plasmapheresis or other immunomodulatory drugs in the RE treatment [6]. Attempts to prove a genetic cause of this disease were also unsuccessful. In contrast from its unclear etiology, there are four various pathogenic forms defined by brain biopsy findings [7].

Diagnosis is based on electroencephalogram (EEG) and magnetic resonance imaging (MRI) findings, as well as on clinical and/or histological characteristics. Bien et al. [8] (European Consensus Group) suggested diagnostic criteria for RE (Table 1).

Evaluation of the disease requires neuroimaging such as positron-emission tomography (PET), single-photon emission tomography (SPECT), or spectroscopic magnetic resonance imaging (sMRI). The listed methods are invaluable in the diagnostics and the follow-up of RE.

The aim of this paper is to highlight the diagnostic dilemma associated with RE in adults.

CASE REPORT

We present a case of a 46-year-old female, right-handed, hospitalized at the Institute for Neuro-

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Table 1. Diagnosis criteria according to the European Consensus Statement [8]; Rasmussen's encephalitis can be diagnosed if either all three criteria of Part A or two out of three criteria of Part B are present

Part A	1. Clinical 2. EEG 3. MRI	1. Focal seizures (with or without EPC) and unilateral cortical deficit(s) 2. Unihemispheric slowing with or without epileptiform activity and unilateral seizure onset 3. Unihemispheric focal cortical atrophy and at least one of the following: Grey or white matter T2/FLAIR hyperintense signal Hyperintense signal or atrophy of the ipsilateral caudate head
Part B	1. Clinical 2. MRI 3. Histopathology	1. EPC or progressive unilateral cortical deficit(s) 2. Progressive unihemispheric focal cortical atrophy 3. T cell-dominated encephalitis with activated microglial cells (typically, but not necessarily, forming nodules) and reactive astrogliosis Numerous parenchymal macrophages, B cells or plasma cells or viral inclusion bodies exclude the diagnosis of RE.

EEG – electroencephalography; MRI – magnetic resonance imaging; EPC – epilepsia partialis continua; RE – Rasmussen's encephalitis

surgery due to headaches followed by nausea and the urge for vomiting which kept her awake at night. The disease onset occurred with the patient in full health, after a three-day subfebrile temperature (37.1°C). During the previous two months, she experienced everyday diffuse headaches rated 9–10/10. The pain occurred at the dorsal aspect of the head, left, with propagation toward the apex, resistant to analgesic therapy. In addition to the headache, she experienced vertigo and unsteady gait, followed by movement to the left. She had frequent short-lasting numbness of the right hand and transitory dysphasic problems: inability to either correctly pronounce a started sentence or to recall it later. She dismissed head injury on birth or during lifetime. She had a family history of stroke and was a smoker for twenty years (20 cigarettes per day).

Physical findings of the patient were as follows: conscious, afebrile, actively movable, psychically unremarkable, of normal vital parameters (blood pressure, heart frequency), internistic, neurological and ophthalmological findings within the normal limits). The patient underwent transcranial Doppler of cerebral blood vessels, electroencephalography, echocardiography, electrocardiography, heart and lungs radiography, blood analyses (glycemia, electrolytes, total blood count with thrombocytes, prothrombine (INR) and partial thromboplastin time, lipid status, renal and liver functions, tests for thrombophilia, hormone level in the blood). All the findings were within normal limits. Head computed tomography (CT) scan revealed supraventricularly parietally left, axially, a smaller zone of ischemically changed brain parenchyma /SEQ 17 et 18/. The EEG activity was normal.

PET/CT (positron emission tomography/computed tomography) finding (Figure 1) was as follows: in the projection of the periventricular brain, white matter parieto-occipitally left intensive accumulation of fluorodeoxyglucose as compared to the level of accumulation in brain structures contralaterally at the analogue level. Hypermetabolic zone of this white matter region can correspond differentially-diagnostically to a benign lesion feature; however, the possibility of the presence of a low-grade tumor lesion (glial TU) cannot be excluded with absolute certainty.

MRI was performed with endocranial spectroscopy, as well as angiography of the intracranial blood vessels. Sagittal TIW, T2W transversally, FLAIR transversally, and T2W coronary of the head were also performed, as well

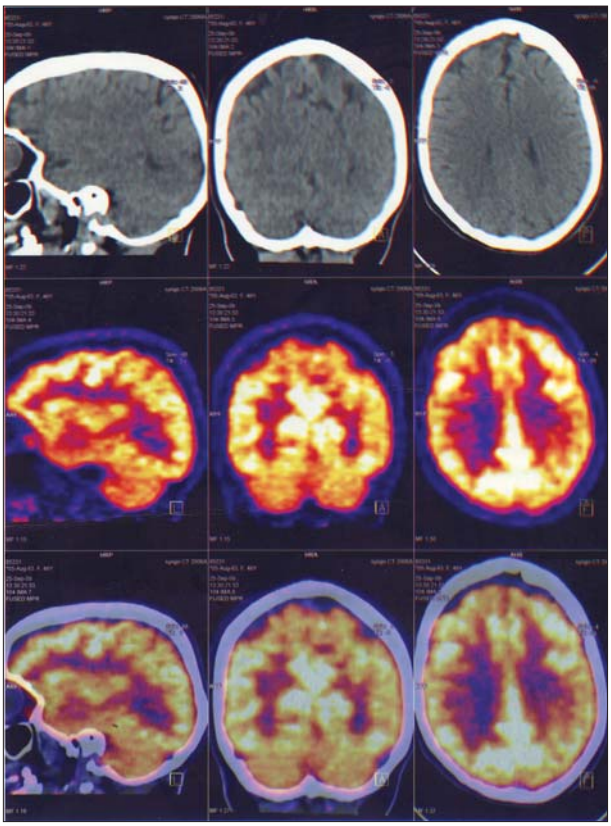

Figure 1. Positron emission tomography/computed tomography finding

as multi-voxel sMRI of the pathologic process of the left cerebral hemisphere and the corresponding location of the right hemisphere. Parieto-occipitally left deep in the white matter of the brain, as well as subcortically, T2/flair hyperintense, T1 hypointense change involving the corpus callosum splenium of the left side could be visualized (Figure 2). There was a mild atrophy of the left lateral horn but without strong effect on the surrounding cerebral parenchyma, diffusion restriction, or increased post-contrast. In the surrounding region, there are signs of occipitoparietal atrophy. There are stained non-specific lesions in the parietal subcortex right, and stained microvascular ischemic lesions in the medial aspect of the right thalamus. Sulci at the convexity were mildly expanded in the interparietal segment bilaterally and perilesionally. The cerebral cortex and two hemispheres were without any pathological

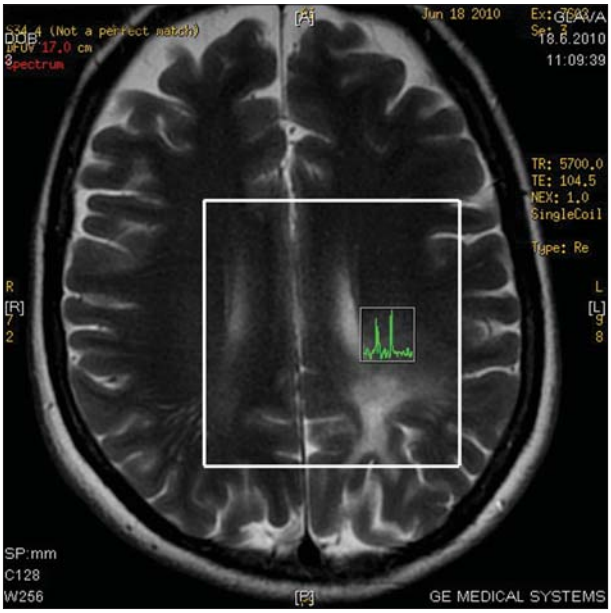

Figure 2. Magnetic resonance finding

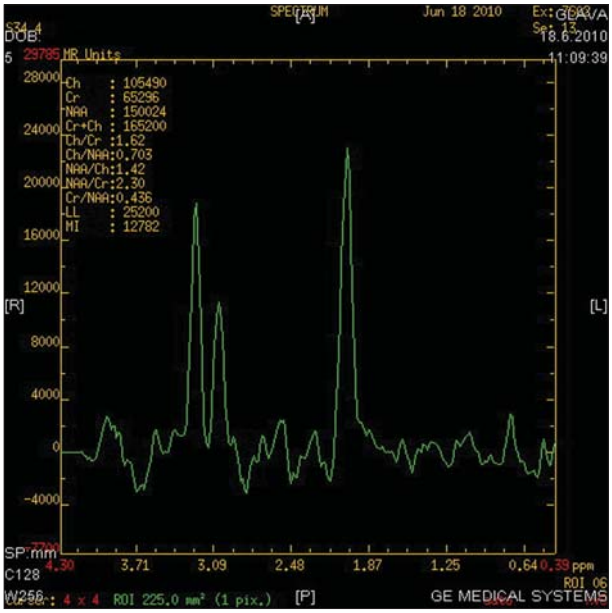

Figure 3. Spectroscopy finding

changes. The orbits were without pathological changes. Nerve complexes VII to VIII were bilaterally of normal pathological form. The foramen magnum was free.

Spectroscopically, inside the pathological process, there was an increased level in the relation choline (Cho)/creatinine (Cr) reduction (1.27), N-acetylaspartate (NAA)/Cr increased the level of myo-inositol/Cr (1.20) and the presence of lactate (Figure 3) [2].

As concluded, the pathological process of the supratentorial white matter of the parietal segment according to MR characteristics corresponds to inflammatory/post-inflammatory sequels. Given the focal perilesional atrophy and suspicion of Rasmussen's encephalitis, an immunological examination of the cerebrospinal fluid was indicated in order to determine the presence of oligoclonal bands. However, the patient refused lumbar puncture. Due to the described change close to the speech center, cerebral biopsy was not undertaken. The decision of the Neurosurgical Consilium was that at the time there were no indications for surgical intervention. The patient was released with antiepileptic and antidepressant therapy. Follow-up MRI was performed at six months, one year, and five years after the dismissal. Even after five years, MRI and spectroscopic findings are unchanged, while the clinical condition of the patient remains stable and unchanged. There is, however, the following dilemma: Is this adult-onset Rasmussen's encephalitis?

DISCUSSION

In about 10% of cases, RE onset occurs after the age 37 years, as in the presented case [3]. This chronic, progressive inflammatory disease most often involves only one cerebral hemisphere, left in our patient. Several clinical and electrophysiological studies suggest bilateral cerebral involvement with, for example, mild contralateral atrophy [8, 9].

Regardless of innovations in the domain of medicine, even after 50 years since RE discovery, etiology of this disease has remained unclear. Three hypotheses have been forwarded: (a) a direct viral insult, (b) an autoimmune process triggered through a viral agent, and (c) a primary autoimmune process. The first two hypotheses have been confirmed by case reports of patients with minor infections before the disease onset (our patient was subfebrile) [9]. Recently, three phases of the disease have been described: the prodromal phase, lasting 0–8.1 years, the acute phase, with manifested symptoms of the disease (seizures, neurological disorders: hemiparesis, hemianopia, disorders of cognitive functions, and speech disorders) of the average duration of 8 months, as in our patient, and the third, residual phase, with the stabilization of the condition, with variable duration [10].

Based on the suggested diagnostic criteria for RE [8], presented in Table 1, our patient has fulfilled two of the three criteria in part A: 1) clinical: symptoms of a simple partial attack (speech disorder, i.e. nominal dysphasia and memory disorder, hand numbness, without loss of consciousness) and one-sided cortical deficit (occipitoparietal left); 2) MRI: occipitoparietal left in the deep cerebral matter and subcortically T/2 FLAIR hyperintense change, ipsilateral atrophy is visualized. Oguni et al. [10] quantified clinical types of attacks (clinical seizure types) during the disease. According to the authors, simple partial attacks involving one side of the body are most frequent (in about 77% of cases). There is scientific evidence that electrocardiography can contribute to reaching the diagnosis of RE in the early phase of the disease [9].

Serial MRI findings of several patients have been published in recent years. The opinion of Chiapparini et al. [11] is that MRI demonstrates the progression of RE and can suggest diagnosing the disease in the early phase, often before the onset of neurological deficite. PET and SPECT are usually used in the late phase and do not provide con-

crete results. Early RE diagnosis is crucial in the selection of patients who require aggressive medicamentous therapy or surgical intervention such as hemispheroctomy.

According to Rasmussen [12] and Rasmussen and Andermann [13], standard cerebrospinal fluid tests are not reliable for the confirmation or rejection of the RE diagnosis. Serological cerebrospinal fluid tests are usually applied in order to exclude infections by well-known neurotropic viruses. Our patient refused lumbar puncture. In most cases, the PET method detects large hypometabolic zones of the involved hemisphere, while new zones with focal hypermetabolism are found in a somewhat lower number [11, 14]. Lee et al. [15] have proposed that PET may guide brain biopsy in cases with inconclusive or normal MRI findings, especially in the early stages. sMRI investigation indicates that lowering the level of N-acetylaspartate (NAA) and increasing (or normal) levels of Cho results in the increased relation NAA/Cho that indicates the loss of dysfunction [9]. Increased level of present lactates as in our case is associated with the presence of EPC. Therefore, PET, SPECT, and sMRI techniques are not adequate for defining inflammatory nature of RE. They can be helpful in the confirmation of the unihemispheric nature in the early phase of suspected RE. Cerebral biopsy is not necessary in all REs because other criteria could be sufficient in making the diagnosis (Table 1).

Corresponding tests should be applied to confirm RE and exclude other diseases. Most frequently used cerebral scans are MRI, SPECT, and, if necessary, fluorodeoxyglucose-PET scans. Next, blood tests for the exclusion of infection, lumbar puncture for confirming inflammation and infection, and finally cerebral biopsy to confirm the diagnosis are necessary. In our patient, differential-diagnostic considerations were aimed at the following: 1) other unilateral neurologic syndromes (stroke, tumor); 2) other reasons for EPC (drugs, cerebral gliomatosis), or 3) other inflammatory or infectious diseases that mimic RE (vasculitis, multiple sclerosis, viral or toxoplasmosis encephalitis) [9]. Although lumbar puncture can show whether there is inflammation and cerebral infection, our patient was not willing to undergo the procedure. Although cerebral biopsy is necessary in the absolute diagnostics of RE, due to the described change and the speech center, it was not performed in our patient.

After reaching the diagnosis, medicamentous or surgical treatment can be applied. To treat RE, antiepileptics alone or in combination with other drugs (as in the presented case) have only limited effect in the control of focal attacks and EPC; the general rule is that the number and dosage of antiepileptics should be as low as possible, as was in the presented case. Recently, long-term treatments have been attempted with corticosteroids, intravenous immunoglobulins, plasma-exchange, or tacrolimus [16]. Only a few patients have been treated with rituximab as the alternative therapy for RE [17].

Surgical treatment (hemispherectomy) remains the most efficient therapy in the prevention of attack progression caused by RE. In our patient, surgery was not indicated, but only MRI follow-up.

This case highlights the diagnostic dilemmas that arise in adult-onset RE and suggests that this diagnosis should be considered in patients of any age with an appropriate clinical picture. Rasmussen's encephalitis in adults can be a challenging diagnosis.

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Дијагностичке дилеме код Расмусеновог енцефалитиса одраслих

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САЖЕТАК

Увод Расмусенов енцефалитис (РЕ) ретко је, прогресивно, инфламаторно обољење мозга које је тешко доказати код одраслих особа.

Циљ овог рада је да истакне дијагностичке дилеме код РЕ одраслих.

Приказ болесника Жена стара 46 година хоспитализована је због упорних дифузних, интензивних главобоља, праћених мучнином и нагоном на повраћање, због којих се будила ноћу. Више пута је имала транзиторни поремећај говора и памћења и утрнулост десне руке. МР налаз је показао следеће: окципитопаријетално лево у дубокој белој можданој маси, као и субкортикално уочава се *T2/flair* хиперинтезна промена, Т1 хипоинтензна промена захвата *corpus callosum*. Спектроскопски се евидентира повишена вредност односа холин / креатинин (Кр) (2,12), редукован ниво азот-ацетил-аспартата / Кр (1,27), повећана вредност миоинозитола / Кр (1,20) и присуство лактата. Болесница је одбила лумбалну пункцију. Због близине описане промене и центра за говор није урађена биопсија мозга. После пет година МР и спектроскопски налази су непромењени, а стање болеснице стабилно.

Закључак Овај случај наглашава дијагностичке дилеме код РЕ одраслих и указује на то да ову дијагнозу треба узети у обзир код болесника било којег узраста са одговарајућом клиничком сликом.

Кључне речи: Расмусенов енцефалитис; одрасли; диференцијална дијагноза; енцефалитис, дијагноза

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

TNFRSF1A gene variant identified in a boy with recurrent episodes of fever

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SUMMARY

Introduction Fever of unknown origin is an important diagnostic challenge. Although rare, periodic fever syndromes may often present with a chronic or recurrent febrile condition with a variable temporal pattern of occurrence. Although clinical characteristics often indicate the syndrome in question, there are many atypical forms, and the genotype–phenotype relationship is highly complex, warranting in many cases the designation of a "syndrome spectrum" rather than a syndrome *per se*.
The aim of this paper was to present a boy with recurrent fever of unknown origin.

Case outline We hereby present a boy with recurrent fever of unknown origin who was by clinically guided partial exome sequencing found to have a heterozygous variant 434A>G in the *TNFRSF1A* gene, otherwise connected with tumor necrosis factor receptor-associated periodic fever syndrome. The patient responded well to short courses of glucocorticoids and is no longer subjected to unnecessary antibiotic treatment he had frequently received in the past.

Conclusion Periodic fever syndromes should be kept in mind as a differential diagnostic possibility in children with fever of unknown origin.

Keywords: fever; autoinflammatory disorders; TRAPS; genotype–phenotype correlation

INTRODUCTION

Prolonged or recurrent fever of unknown origin constitutes an important diagnostic problem that may be connected to a multitude of potential etiological factors and nosological entities [1, 2]. Although exceedingly rare, autoinflammatory disorders often present with a febrile condition of unknown origin. Depending on the syndrome in question, febrile spells may occur in relatively regular intervals, or there may be no discernible time pattern in their occurrence [3, 4]. Of all periodic fever syndromes, periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome exhibits by far the greatest incidence. However, this syndrome is not readily explained by a defined genetic aberration(s) and is thought to be an etiologically (and to some extent also pathogenetically) heterogenous category, diagnosed *per exclusionem* by the presence of fever and inflammation in a person without signs of infection and with a prompt resolution of symptoms upon glucocorticoid treatment [5]. Most common periodic fever syndromes of autoinflammatory nature with fully characterized genetic causes include familial mediterranean fever (FMF), cryopyrin-associated periodic syndromes (CAPS), mevalonate kinase deficiency (MKD)/hyperimmunoglobulinemia D and periodic fever syndrome, and tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS) [6]. Symptoms and signs other than fever, such as joint pains, skin rash, serositis, or abdominal aches may be very helpful in the establishment of diagnosis [7].

Treatment partly depends on the syndrome in question and in many cases may be successfully guided by clinical tools such as the Auto-Inflammatory Diseases Activity Index (AIDAI; Table 1) [8]. Early and appropriate treatment can greatly reduce the risk of complications, including the most serious – amyloidosis [9]. It is therefore of utmost importance to systematically evaluate children with fever of unknown origin for possible autoinflammatory disorders. If performed thoroughly, this very often results in a precise diagnosis [10].

We hereby present the case of a boy with recurrent episodes of fever that were eventually plausibly explained by the result of genetic testing.

CASE REPORT

Repeated instances of febrile illness in an otherwise healthy boy began at the age of six years. They were separated by an interval of several months. Bodily temperature usually reached 40°C, while C-reactive protein was in the 40–100 mg/L range, and the erythrocyte sedimentation rate was typically about 30 mm/h. A mild splenomegaly was also noted. Febrile

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episodes lasted from a few days (usually about seven) to several weeks. Antimicrobial treatment had no effect on the time to resolution.

Before the onset of the disease, the patient's personal history was unremarkable. He received all the obligatory vaccines according to the official vaccination schedule in the Republic of Serbia. He did not suffer from any allergies. His mother and brother were allergic to pollen, and both parents, as well as the paternal grandparents, suffered from cardiovascular disorders at a relatively young age (most of them in the fifth decade of life). No other diseases or problems were reported.

On three occasions (at the ages of eight, 11, and 12 years) the boy was hospitalized in another pediatric tertiary center for a detailed diagnostic investigation. Repeated ultrasound (US) and magnetic resonance imaging (MRI) examinations confirmed a persistent, although mild hepatosplenomegaly and slightly enlarged retroperitoneal and mesenteric lymph nodes. However, peripheral lymphadenopathy was absent at all times. During some of the febrile episodes, the boy also complained of joint pains, particularly in the left temporomandibular joint. These were never accompanied by any other signs of arthritis. On one occasion he also felt acute pain in the heel, indicating a possible bout of enthesitis. He never had a skin rash, but occasionally suffered from eye irritation and redness. When febrile, the patient was usually prescribed prolonged courses of broad-spectrum antibiotics, lasting up to 21 days. Between the febrile episodes, he was quite well, and participated in sporting activities at school.

Laboratory examination yielded a hemoglobin concentration in the 12–13 g/L range; during febrile intervals, he often also had a borderline thrombocytopenia (typically $90–100 \times 10^9$/L), but never any leukocytosis. Total protein, albumin, glucose, urea, creatinin, electrolytes, transaminases, bilirubin, alkaline phosphatase, γ-glutamyl transferase, creatine kinase, and α-amylase were at all times within the reference range. The results of urine analysis were also normal. Plasma immunoglobulin levels were within the age-specific reference range, including IgD. Extensive autoantibody testing (ANA, ANCA, ASCA, anti-LKM, ASMA, dsDNA, anti-tTG, anti-endomysial, anti-Tg, anti-TPO) showed completely negative results. C3 and C4 levels were normal. Bone marrow biopsy (also at the age of eight years) gave a normal result, as did karyotype analysis (46, XY). During the detailed endocrinological examinations, a mild elevation of total cholesterol (7.4 mmol/L) and LDL (2.98 mmol/L) was detected in the plasma, as well as that of cortisol. Thyroid hormones were at all times within the normal range, and so was TSH. Plasma ceruloplasmin, ACE, and fecal calprotectin were also at normal values, as were CEA, NSE, and AFP. The electrocardiography and the cardiac US examination revealed no abnormalities. The same was true for the ear, nose, and throat specialist examination. Virus serology testing detected anti-EBV IgG antibodies, while anti-HCV antibodies and anti-CMV antibodies (both IgG and IgM) were absent. HBsAg was also found to be absent. Purified protein derivative (PPD) testing for tuberculosis yielded a negative result. Given the absence of pharyngitis, cervical lymphadenitis, aphthous stomatitis, and the appropriate temporal pattern of fever, the patient never satisfied the diagnostic criteria for PFAPA syndrome, although the possibility of an atypical form has repeatedly been considered in differential diagnosis.

At the age of 14, he came to our attention and two new febrile episodes separated by three months were successfully and promptly terminated by a short (ca. four days) course of glucocorticoids. This time, a bilateral acute uveitis also appeared, and was subsequently shown to be of granulomatous nature by slit-lamp examination. It responded well to topical glucocorticoid treatment. On US examination, the spleen reached a maximal craniocaudal diameter of 145 mm. At this time, a monogenic autoinflammatory disorder was first suspected. Considering the presence of uveitis, investigations were initially directed toward a highly atypical form of systemic juvenile arthritis. However, HLA typing excluded the presence of the B27 allele, while MRI showed no lesions of sacroiliac joints that would be indicative of spondyloarthropathies. Serum amyloid A concentration was measured within physiological limits. Given the great number of potential genetic alterations that are known to fit the clinical presentation and disease course, clinically guided partial exome sequencing was undertaken, with an emphasis on genes with a known function connected with autoinflammatory disorders. Partial exome analysis, performed at University Clinical Center Ljubljana, Slovenia, revealed the existence of heterozygous variant in the *TNFRSF1A* gene (*TNFRSF1A*: c. 434A>G).

At the time of writing, the patient is feeling well and has no symptoms. In the meantime, he experienced only one episode in the period of 14 months. His spleen completely receded to physiological bounds and is now 127 mm in the AP diameter. His most recent monthly AIDAI (Table 1) was 20, as compared to 108 at the time of peak disease activity. The patient is also instructed to undergo yearly US examinations and routine blood analyses of inflammatory parameters.

Table 1. Autoinflammatory Disorder Activity Index (AIDAI) [8]

a. Fever ≥ 38°C
b. Overall symptoms
c. Abdominal pain
d. Nausea/vomiting
e. Diarrhea
f. Headaches
g. Chest pain
h. Painful nodes
i. Arthralgia or myalgia
j. Swelling of the joints
k. Eye manifestations
l. Skin rash
m. Pain relief taken
FMF: a + c + g + i + j + l
MKD: a + c + d + e + h + i
TRAPS: a + b + c + i + k + l
CAPS: a + f + i + k + l

FMF – familial mediterranean fever; MKD – mevalonate kinase deficiency; TRAPS – tumor necrosis factor receptor-associated periodic fever syndrome; CAPS – cryopyrin-associated periodic syndromes;
All variables are scored 0–3, except fever (0 or 1); monthly AIDAI is a sum of 31 daily values

DISCUSSION

Clinically, our patient exhibited clear signs of a long-standing inflammatory condition with elements of some autoinflammatory disorders (episodes of fever, joint pains, splenomegaly, possible enthesitis of the Achilles' tendon, uveitis, prompt response to glucocorticoids). However, diagnostic criteria for any specific disorder were not satisfied, suggesting either an extremely rare nosological entity or some rather untypical clinical variant of a more common one. Bearing in mind that it is usually, if not universally, reasonable to assume that the latter is vastly more likely that the former, we decided it is worthwhile to perform clinically guided partial exome sequencing in order to identify potential gene variants that could explain the observed symptoms and signs.

Mutations in *TNFRSF1A* cause tumor necrosis factor (TNF) receptor-associated autoinflammatory syndrome (TRAPS) [11]. TRAPS was formerly called "familial Hibernian fever" because it had initially been described in a family of Scottish ancestry (Hibernia being the Roman name for Scotland) [12]. *TNFRSF1A* encodes a member of the TNF receptor superfamily and is therefore extensively involved in inflammatory processes associated with both innate and adaptive immune mechanisms and processes. It is mainly expressed on mononuclear phagocytes, but may also be found on a number of other cell types, such as lymphocytes, natural killer cells, granulocytes, astrocytes, and keratinocytes [13]. Numerous different variants in *TNFRSF1A* have been described, with a highly complex genotype–phenotype relationship [14]. Prognosis is variable and primarily dependent on the existence of complications of chronic inflammation, such as amyloidosis. Variant 434A>G is recorded in the ClinVar database (No. 97703) and the Infevers registry, and designated as a genetic variant of unknown significance [15, 16]. However, the same variant has been reported in a patient listed in the EUROFEVER registry with clinically apparent TRAPS [17].

Although there is no possibility of final proof that the detected gene variant indeed plays a causal role in our patient's ailment, it is certainly plausible that it has at least some effect, based on obvious pathophysiological mechanisms (i.e. uncontrolled inflammation) and known functions of the *TNFRSF1A* gene (including inflammatory signaling). Considering the relatively innocuous disease course so far and the absence of any signs of permanent organ damage or amyloidosis, the outlook for our young patient appears to be favorable. The example we describe here could be used as a good illustration of the concept of "genomic landscape" of congenital autoinflammatory (as well as other) syndromes; the complexity of this landscape very often does not allow a clear demarcation line to be drawn between a pathological and a physiological gene variant, particularly when seen in the light of the less-than-predictable relationship between the nature of genetic alteration and its clinical consequences, if any. Low-penetrance *TNFRSF1A* variants are well known and appear to cause a mild or moderate autoinflammatory condition in some, though not all, affected persons [18]. Furthermore, the low-penetrance variants appear to produce their effects through a different pathophysiological mechanism compared with clearly pathogenic gene alterations, and are, at least in part, connected to the functional status of regulatory T cells [19]. An analysis of a series of patients who carry a well characterized low-penetrance variant has shown that severity of symptoms and risk of complications are highly variable and at least partially correlated with the age of onset [20]. In the light of all this, it appears quite justified to speak of a "TRAPS spectrum" as a diagnostic category (as opposed to the diagnosis of TRAPS *per se*). The rationale for using the latter designation appears rather strengthened by the fact that our patient constantly exhibited some, but never all, features of PFAPA syndrome, begging the question how many patients classified within this highly heterogenous diagnostic category are (or were) actually affected by *TNFRSF1A* variants, among other defects in genes connected to inflammation. This and a myriad of analogous possibilities in other autoinflammatory disorders, such as, for instance, FMF, CAPS, and MKD (to name the most frequent ones in our population, aside from TRAPS) warrants particular attention when the physician is faced with a patient clinically exhibiting some, but not all features of a known autoinflammatory syndrome. In such instances, clinically guided partial exome sequencing, if available, generally tends to become the diagnostic method of choice. On the other hand, it is an exceedingly costly and somewhat time-consuming procedure, and this adds to the importance that all physicians, and especially pediatricians, be satisfactorily acquainted with the full range of clinical situations where it is rational to order such an analysis. This appears to be of the essence, since the usefulness of extensive genetic testing without proper clinical guidance is very doubtful, as highlighted, for instance, by the recently published experience in autoinflammatory disorders from a center in Trieste [21]. A deeper knowledge of possible genetic alterations and their complex consequences should ensure the necessary amount of critical thinking in determining whether testing is indicated or warranted, and this is, indeed, more than appropriate for the practice of medicine in the genomic age.

The distinction between TRAPS and the proposed designation of "TRAPS spectrum" can also be viewed as highly meaningful from the treatment standpoint. While TRAPS patients are usually best treated with IL-1 antagonists such as anakinra [22, 23] or canakinumab [24], most patients with low-penetrance *TNFRSF1A* alterations either require no treatment or sufficient disease control can be achieved by occasional short courses of glucocorticoids, administered as needed [18].

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Варијанта гена *TNFRSF1A* код дечака са рекурентном фебрилношћу

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САЖЕТАК

Увод Нејасно фебрилно стање је значајан дијагностички изазов. Мада су ретки, синдроми повремене грознице се често могу испољити у виду фебрилног стања које се понавља у различитим интервалима и траје краће или дуже време, или је пак хронично. Премда клиничка слика неретко указује на синдром о коме се ради, однос генотипа и фенотипа је веома сложен, што често оправдава сврставање у „спектар синдрома" уместо у посебан синдром.

Циљ овог рада је био да прикажемо дечака са понављаним налетима грознице непознатог узрока.

Приказ болесника Код дечака са понављаним налетима грознице непознатог узрока клинички усмерено делимично секвенцирање егзома показало је хетерозиготну варијанту *434A>G* у гену *TNFRSF1A*. Овај ген је иначе повезан са синдромом *TRAPS*. Болесник је показао добар терапијски одговор на краткотрајно давање глукокортикоида и више се не лечи дуготрајним давањем антибиотика, што му је често ординирано у прошлости.

Закључак У диференцијалној дијагнози код деце са грозницом непознатог узрока ваља имати на уму и синдроме повратне грознице.

Кључне речи: грозница; аутоинфламаторне болести; *TRAPS*; однос генотип–фенотип

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Hyponatremic dehydration and metabolic alkalosis as dominant manifestation in cystic fibrosis infants with mild phenotype – a case series

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SUMMARY

Introduction Due to increased losses of chloride and sodium in the sweat, children with cystic fibrosis (CF) are predisposed to develop episodes of hyponatremic/hypochloremic dehydration with hypokalemia and metabolic alkalosis when they sweat excessively. Even the patients with mild phenotype may have such episodes of dehydration and salt depletion.

Outline of cases Six cases of pancreatic sufficient (PS) CF patients complicated with episodes of severe hyponatremic dehydration with metabolic alkalosis in infancy are presented. The mean age was 6.3 ± 2.16 months at admission. All the cases had no symptoms suggestive of CF before admission. The most common clinical symptoms at the time of hospitalization were vomiting, anorexia, weight loss, dehydration, irritation, or lethargy. Mean values of blood pH, serum bicarbonate, sodium, chloride, and potassium (mmol/l) were as follows: 7.59 ± 0.06, 41.73 ± 5.78, 117.52 ± 2.88, 66.0 ± 11.58 and 2.62 ± 0.37, respectively. Sweat chloride test was pathological and ranged 69–120 mmol/L. The determination of fecal elastase-1 proved that they were PS (values > 200 μg/g stool). CF transmembrane conductance regulator gene analyses in six cases confirmed the diagnosis of CF; namely, patients were compound heterozygotes for F508del and other rare mutation or compound heterozygotes for two rare mutations.

Conclusion Distinctive about these cases is that they were PS and had very mild presentation of CF. Without these episodes of dehydration, these patients would have remained undiagnosed until later age. CF should be considered in infants and children presenting with hypoelectrolytemia and metabolic alkalosis even in the absence of respiratory or gastrointestinal symptoms.

Keywords : cystic fibrosis; CFTR genotype; hyponatremic dehydration; metabolic alkalosis

INTRODUCTION

Cystic fibrosis (CF) is a multisystem disease caused by mutations in a gene on chromosome 7, which encodes the CF transmembrane conductance regulator (CFTR) protein. CFTR functions primarily as a chloride channel and controls the movement of salt and water into and out of epithelial cells in the affected organs. Almost 2,000 different CFTR mutations have been identified, resulting in different consequences on protein function, ranging from complete protein absence to defective protein activity at the plasma membrane [1, 2]. Hence, phenotypic expression of the disease varies widely among individuals with CF [3].

In countries without neonatal screening for CF, the disease is usually diagnosed during childhood by respiratory and/or gastro-intestinal symptoms. Hyponatremic hypochloremic dehydration with hypokalemia and metabolic alkalosis is a rare but typical presentation of CF in infants [4, 5, 6]. Dysfunctional CFTR in the sweat ducts are responsible for the excessive chloride and sodium losses, especially during warm months. The extracellular fluid volume contraction and salt depletion will lead to activation of renin–angiotensin system and secondary hyperaldosteronism. The resulting effect is increased renal potassium and hydrogen losses for the exchange with sodium in the distal tubule. The consequenced hypokalemic alkalosis is a metabolic mimicry of Bartter's syndrome; therefore, the condition is known as pseudo-Bartter's syndrome in CF.

In our previous study of pseudo-Bartter's syndrome in CF, all patients with metabolic alkalosis and hypoelectrolytemia were pancreatic insufficient (PI). Respectively, they had severe mutations with regard to pancreatic exocrine function [7]. Over the last few years, we have noticed the emergence of severe hyponatremic hypochloremic dehydration with metabolic alkalosis in pancreatic sufficient (PS) CF infants, which had very mild disease expression further on in the clinical course.

REPORT OF CASES

Clinical records of six patients, three boys and three girls, presenting in infancy with metabolic alkalosis and electrolyte abnormalities such as hyponatremia, hypochloremia, and hypokalemia, which were later found to have CF, were analyzed.

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Table 1. Biochemical features of the pancreatic sufficient cystic fibrosis patients with pseudo-Bartter's syndrome

Parametars	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	M ± SD*
pH	7.6	7.67	7.6	7.61	7.57	7.49	7.59 ± 0.06
Bicarbonate (mmol/L)	42.9	49.1	42.8	44.6	39	32	41.73 ± 5.78
Sodium (mmol/L)	113	121	117	116	118	120	117.52 ± 2.88
Chloride (mmol/L)	61	65	54	56	78	82	66 ± 11.58
Potassium (mmol/L)	2.1	2.7	2.4	2.6	3.2	2.7	2.62 ± 0.37

*Mean values ± standard deviation

Table 2. Genotypes of the pancreatic sufficient cystic fibrosis patients with pseudo-Bartter's syndrome

Case No.	Mutation I cDNA name / legacy name	Mutation II cDNA name / legacy name
1	c.377G>A / G126D	c.1366G>T / V456F
2	c.377G>A / G126D	c.1753G>T / E585X
3	c.1521_1523delCTT / delF508	c.579+3A>G / 711+ 3A- >G
4	c.1521_1523delCTT / delF508	c.579+3A>G / 711+ 3A- >G
5	c.1521_1523delCTT / delF508	c.349C>T / R117C
6	c.1521_1523delCTT / delF508	c.1070C>T / A357V

The mean age of children was 6.3 ± 2.16 months (range being 3–9 months). Biochemical features of the patients at the admission phase are summarized in Table 1. Mean values of blood pH, serum bicarbonate, sodium, chloride, and potassium (mmol/L) at admission were as follows: 7.59 ± 0.06, 41.73 ± 5.78, 117.52 ± 2.88, 66 ± 11.58, and 2.62 ± 0.37, respectively. Urine chloride concentrations in all the patients were below 20 mmol/l. For case 1 it was the second episode, for case 4 the third episode, and for cases 2, 3, 5, and 6 the first episode of dehydration. All episodes of dehydration occurred during the summer and early autumn months. The most common clinical symptoms in these patients were vomiting, anorexia, weight loss, dehydration, irritation, or lethargy. We did not obtain a history of recurrent chest infection or loose stools in any child. Therefore, all cases had no symptoms suggestive of CF before admission.

After rehydration and correction of metabolic abnormalities in the blood, a subsequent sweat chloride test and genotyping confirmed the diagnosis of CF in these infants. Sweat chloride tests were pathological and ranged 69–120 mmol/L. Assessment of the pancreatic functional status by determining the values of fecal elastase-1 showed that all six infants were PS (fecal elastase values were over 200 μg/g stool). CFTR gene analyses determined that the patients were compound heterozygotes for F508del (the most common CFTR mutation, class II) and other rare mutation or compound heterozygotes for two rare mutation (Table 2). A new mutation c.1070C>T (A357V) was detected in case 6.

Monitoring the clinical course of the disease in these children within the next two to five years showed that they have mild expression of CF mainly manifested as recurrent sinusitis and nasal polyps in case 3. Only case 4 had another hospitalization for treating acute exacerbation of lung disease with *Pseudomonas aeruginosa* infection. Very mild pulmonary involvement was found on the chest X-ray in all six cases.

DISCUSSION

Metabolic alkalosis in association with low serum electrolyte concentration is not a common metabolic disorder in infancy. Conditions associated with repeated vomiting, especially pyloric stenosis, continuous gastric drainage without appropriate electrolyte replacement, chloride-losing diarrhea, potassium-losing nephropathy, Bartter's syndrome, the use of thiazide diuretics, and salt depletion by sweating in CF can lead to such a disturbance [8, 9].

Metabolic abnormalities in the so-called pseudo-Bartter's syndrome in CF can have mimicking biochemical features of Bartter's syndrome. Although the biochemical hallmark of both Bartter's and pseudo-Bartter's syndrome is abnormally low plasma electrolyte concentrations, there are important differences between the two diseases. In Bartter's syndrome, the sweat electrolyte profile is normal and the renal handling of electrolytes is defective. In CF, sweat electrolyte losses are increased, and intensive electrolyte reabsorption occurs in the renal tubules. In all our CF infants presenting with electrolyte depletion and metabolic alkalosis, the initial diagnosis of Bartter's syndrome was excluded by hypochloruria (< 20 mmol/L). Determination of urinary chloride before therapy is especially useful to distinguish these two conditions.

In our previous study, all CF infants with pseudo-Bartter's syndrome were PI [7]. We considered that biochemical abnormalities due to insufficient CFTR chloride canal function are more pronounced in CF patients with "severe" disease-caused mutations (class I, II, and III). Compared to the "severe" CFTR mutations, certain "mild" mutations tend to be associated with significantly lower sweat chloride concentrations [10]. However, the emergence of severe hyponatremic hypochloremic dehydration with metabolic alkalosis in PS CF infants, which had mild disease expression in the further clinical course, indicated that neither the CFTR genotype nor sweat chloride levels are correlated with the occurrence of dehydration episodes. Our present analysis showed that two rare mutations (G126D and 711+ 3A- >G) were found

in two cases, each. G126D is a missense mutation in exon 4 of the CFTR gene, resulting in amino acid change (glycine to asparagine at 126) in CFTR chloride channel and 711+ 3A- >G is a splicing mutation in intron 5, resulting in an mRNA splicing defect. This may arouse doubt that certain genotypes are more predisposed to the development of this metabolic disorder. Higher rate of sweating and electrolyte losses with sweat may be the reason why some CF individuals are biochemically more vulnerable, but the risk factors for the development of dehydration with electrolyte depletion in CF are still not defined.

In conclusion, any CF patient, even a patient with a mild form of the disease, may experience an episode of dehydration with metabolic alkalosis and hypoelectrolytemia, particularly during the hot weather conditions. CF should be considered in the differential diagnosis of infants and children presenting with these biochemical abnormalities, even in the absence of respiratory or gastrointestinal symptoms. Missing the diagnosis of mild forms of CF may lead to life-threatening complications, such as severe hyponatremic dehydration with hypovolemia or diffuse bronchiectasis at a later age [11].

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Хипонатремична дехидратација и метаболичка алкалоза као доминантна манифестација код одојчади са цистичном фиброзом и благим фенотипом – серија случајева

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САЖЕТАК

Увод Због повећаних губитака хлора и натријума у зној, деца са цистичном фиброзом (ЦФ) предиспонирана су да развију епизоде хипонатремичне/хипохлоремичне дехидрације са хипокалемијом и метаболичком алкалозом када се претерано зноје. Чак и болесници са благим фенотипом могу имати такве епизоде дехидрације и исцрпљивање соли.

Приказ болесника Приказано је шест случајева панкреасно суфицијентних (ПС) болесника са ЦФ који су као одојчад имали као компликацију епизоде тешке хипонатремичне дехидрације са метаболичком алкалозом. Просечна старост је била 6,3 ± 2,16 месеци на пријему. Нису сви случајеви пре пријема имали симптоме који указују на ЦФ. Најчешћи клинички симптоми у време хоспитализације били су: повраћање, анорексија, губитак тежине, дехидрација, иритација или летаргија. Средње вредности *pH* крви, серумских бикарбоната, натријума, хлора и калијума (*mmol/l*) биле су, редом: 7,59 ± 0,06; 41,73 ± 5,78; 117,52 ± 2,88; 66 ± 11,58 и 2,62 ± 0,37. Знојни хлоридни тест био је патолошки и варирао је од 69 до 120 *mmol/l*. Одређивање фекалне еластазе-1 показало је да су ПС (вредности > 200 *μg/g* столице). ЦФТР генска анализа код свих шест случајева потврдила је дијагнозу ЦФ; наиме, болесници су били сложени хетерозиготи за *F508del* и другу ретку мутацију или сложени хетерозиготи за две ретке мутације.

Закључак Карактеристично за ове случајеве је то што су панкреасно суфицијентни и имају веома благу презентацију ЦФ. Без ових епизода дехидрације, ови болесници би остали недијагностиковани до каснијег узраста. ЦФ треба узети у обзир код одојчади и деце код којих се манифестују хипоелектролитемија и метаболичка алкалоза, чак и у одсуству респираторних или гастроинтестиналних симптома.

Кључне речи: цистична фиброза; ЦФТР генотип; хипонатремна дехидрација; метаболичка алкалоза

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

HeartMate 3 fully magnetically levitated left ventricular assist device for advanced heart failure – initial Serbian experience

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SUMMARY

Introduction As the waiting time for heart transplantation continues to increase due to shortage in organ donation, supporting patients with advanced heart failure with left ventricular assist device (LVAD) increases as well. The latest generation of LVAD, left ventricular assist system (LVAS) started to expand worldwide due to more promising outcomes.

The aim of this article was to present the case of treating advanced heart failure in a patient who underwent implantation of HeartMate 3 LVAS as the bridge to transplantation.

Case otline The patient was a 59-year-old man with advanced heart failure requiring inotropic drug support, with ischemic cardiomyopathy as the underlying cause of heart failure. Therefore, in the absence of an adequate donor, it was decided to incorporate the LVAS as a bridge to transplantation. Functional capacity, cardiac, renal, and liver functions improved in the patient.

Conclusion The use of the HeartMate 3 in an advanced heart failure patient results in improvements in functional capacity, cardiac, renal and liver function. Further studies should be performed in order to identify whether improved outcomes are sustained with a longer follow-up period.

Keywords: LVAD; heart failure; heart transplantation

INTRODUCTION

Patients with advanced heart failure (HF) have quite limited possibilities for therapy, so the morbidity and mortality in connection to the disease are unacceptably high. In light of the insufficient availability of donor hearts and a growing number of heart transplantation (HT) ineligible patients, left ventricular assist devices (LVAD) are often used to support patients with advanced HF awaiting HT or as destination therapy (DT) [1]. In order to improve clinical outcomes of LVAD therapy, technological advances have been made through different types of LVAD pumps over the past 30 years, from pulsatile to continuous flow (CF) and now back to artificial pulsatility. Compared to the pulsatile flow HeartMate (HM) XVE, the newer generation of LVAD and CF-LVAD is considerably smaller, with significantly lower incidence of adverse events and has become the standard of care as a bridge to transplantation (BTT) [1]. HM II (Abbott Corporation, Chicago, IL, USA) is an axial pump that provides CF, which requires a tissue pocket and a larger body surface of the patient, while other intrapericardial CF pumps, like HeartWare (HeartWare Inc., Framingham, MA, USA), utilize a magnetically levitating rotor system to decrease mechanical wear in order to reduce hemolysis and the incidence of pump thrombosis. Also, due to smaller size, it is suitable for patients with smaller body surface area [2]. Despite the fact that with the newer generation of LVAD survival rate is much better, the overall adverse events are still significantly high [3]. Therefore, technology enhancements of LVAD have become increasingly important in order to improve post-LVAD outcomes and to reduce the rate of adverse events. The latest generation pump, HM 3 (Abbott Corporation) is intrapericardial fully magnetically levitated CF-LVAD with artificial pulsatility with large, consistent pump gaps designed to reduce blood trauma and minimize stasis of blood.

The aim of this article was to present a case of treating the end-stage of HF in a patient in whom the latest generation of LVAD, left ventricular assist system (LVAS), HM 3, was implanted.

CASE REPORT

The patient was a 59-year-old man with advanced HF, with ischemic cardiomyopathy as the underlying cause. Ten months prior to hospitalization at our institution, the patient suffered from acute heart infarction of the anterior wall as the first manifestation of coronary disease. Since the patient was admitted to a local hospital after 24 hours had passed, neither percutaneous coronary intervention nor fibrinolysis was applied. At the local hospital, the

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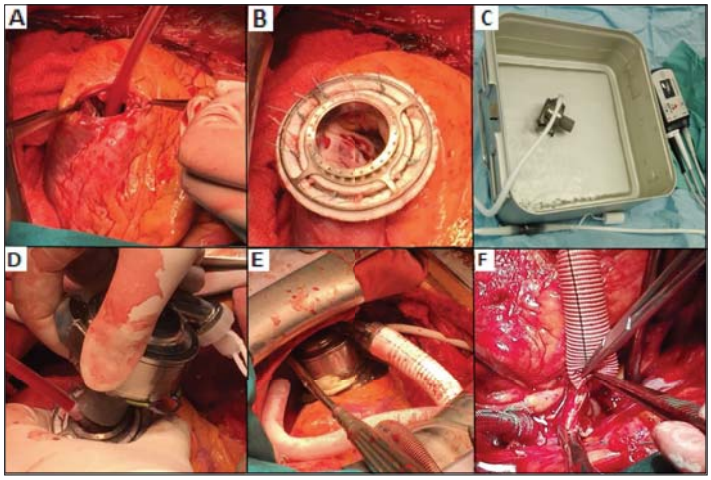

Figure 1. Left ventricular assist system, HeartMate 3 implantation: a) left ventricle open at the top; b) sewn ring at the left ventricle; c) preparation of the pump; d) connecting the pump to the ring; e) connected pump in the pericardial cavity; f) outflow graft sewn to the aorta

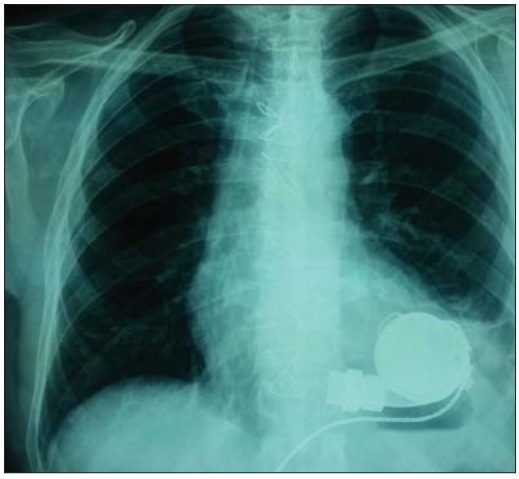

Figure 2. Radiographic finding after implanted HeartMate 3 left ventricular assist system

patient underwent coronary angiography that showed an occlusion of the left anterior descending coronary artery and stenosis of the proximal circumflex coronary artery and he was treated with medicaments. After the acute ischemic phase, the hospital treatment was hindered by the development of left ventricular (LV) aneurysm and the appearing symptoms of HF. He complained of fatigue while at rest, of choking, chest pain, and swelling in the legs. Ten months after the myocardial infarction, he came to our institution due to symptoms of advanced HF and required inotrope support drugs. Both two-dimensional transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were performed in the standard manner using Vivid E 9 (GE Medical Systems, Milwaukee, WI, USA) and showed a volume overload of LV (EDV 257 ml), increased LV end-diastolic (LVEDD) and end-systolic diameters (LVESD), 7.4 cm and 6.3 cm, respectively, and significantly decreased ejection fraction of LV (LVEF) to 18% calculated by the Biplane method. There were akinesis in the LV septum, apex, apical part of anterolateral and inferior walls, apical and medial part of the anterior wall with LV apex aneurysm without visible thrombotic masses. Severe mitral regurgitation (MR 3+) was present. The right ventricle had regular dimensions (2.6 cm) with good systolic and longitudinal functions (global fractional area change of 27%, tricuspid annular plane systolic excursion of 21 mm, and right ventricular systolic excursion velocity of 18 cm/s). There was severe functional tricuspid regurgitation (TR 3+) with high right ventricle systolic pressure (RVSP 77 mmHg). Single-photon emission computed tomography showed the absence of viable myocardium of the septum, anterior and lateral wall of the LV. Preoperative hemodynamic data showed pulmonary capillary wedge pressure (PCWP) of 27 mmHg, central venous pressure (CVP) of 11 mmHg, cardiac index (CI) of 1.9 L/min./m^2. In order to assess the possibility of LVAS implantation, the nature of the LV apex aneurysm was estimated by performing magnetic resonance imaging of the heart. At the part of LV apex aneurysm, the myocardial wall thickness was 3–5 mm with aneurysmal extension, which was a borderline finding for pump implantation. Based on all the performed tests, it was concluded that the patient was in the end-stage of HF (New York Heart Association (NYHA) IV, Interagency Registry for Mechanically Assisted Circulatory Support 3), with significantly impaired LV function requiring continuous inotropic support; therefore, it was decided in the absence of an adequate donor to incorporate the LVAS as a BTT.

The patient underwent surgery under general anesthesia. The surgery included the implantation of LVAS, HM 3. After median sternotomy, in conditions of extracorporeal circulation without aortic clamping and stopping of the heart, the LV was opened at the top, the ring was sewn, and after preparation, the pump was connected to the ring. The driveline was placed through the skin in the form of double tunneling and connected to the pump controller and the energy source. Finally, a graft was sewn to the aorta (Figure 1). Unlike the LVAD HM 2 device, where it is necessary to form a tissue pocket to place the device, LVAS HM 3 was applied fully intrapericardially. The intervention was without complications.

The postoperative recovery was uneventful. After the LVAS implantation, a standardized anticoagulation regimen was used with initiation of infusion of heparin, followed by the transition to warfarin and aspirin. Anticoagulation therapy was included in order to maintain the international normalized ratio between 2.0 and 3.0. There was normal flow through both the pump's inflow and outflow cannula. The pump speed was set at 4,900 rpm, with pump flow being 3.4 L/min. and pump power 3.2 w. There were stable LVAS parameters and data on the pump controller. The radiographic finding was regular (Figure 2). Postoperative hemodynamic data showed PCWP of 10 mmHg, CVP of 7 mmHg, CI of 3.2 L/min./m^2. Functional cardiac (TTE and brain-type natriuretic peptide – BNP), renal and liver function assessments were done before the LVAD implantation, at discharge from the hospital and at 12 months. The TTE examination at discharge showed improvement in the LVEDD and the LVESD from baseline values of 7.4 and 6.3 to 5.5 and 4.5, respectively. This

improvement was sustained over the time of the follow-up. For LVEF and BNP (pg/ml), the baseline values of 18% and 670 improved to 39% and 173, respectively, and continued to improve during the period of 12 months to 50% and 120, respectively. The dimension of the right ventricle was sustained in the normal range (2.6 cm) with a good systolic function. At discharge, NYHA functional classification improved from IV at baseline to II and continued to improve to I during the period of 12 months. There were improvements in renal function from baseline-estimated glomerular filtration rate (ml/min./1.73 m^2) and serum creatinine (nmol/L) of 40 and 155 to 57 and 114, respectively, and there was no change over the entire follow-up period. With regard to hepatic function, total bilirubin (μmol/L) showed a reduction at the discharge point (25.8 *vs.* 12.4), with no further change afterwards. There were no significant changes of aspartate transaminase (IU/L), and alanine transaminase (IU/L) values during the entire follow-up period.

DISCUSSION

HT remains the treatment of choice in cardiac replacement therapy for patients with end-stage HF. As the waiting time for HT continues to increase, supporting patients with LVAD increases as well. LVAD support enables an improved quality of life and survival compared to medical therapy [4]. However, despite all of these benefits of new technology of LVAD, there is still significant incidence of device-related complications that may have lessened enthusiasm for investigating LVAD therapy in less sick patients [5]. LVAD technology is advancing continuously and rapidly. Smaller devices, total implantability, artificial pulsatility, and remote monitoring are being investigated, which will broaden the LVAD technology application. The outcomes in patients supported by the LVAD have improved along with experience and technology advances. The HM 3 LVAS is a new centrifugal-flow device which uses full magnetic levitation allowing wide and consistent flow paths and an artificial pulse designed for enhanced hemocompatibility. It uses a fully magnetically levitated rotor with frictionless movement that excludes heat generation and wear of the moving component. During operation, blood from the LV enters the inflow cannula and pump along a central axis and is propelled through the wide-gap impeller blades of the rotor and finally out through the outflow graft. The power cable from the pump housing is externalized and connected to a modular cable that is attached to the external system controller and a power supply. The pump receives power from a power module or mobile power unit for wall power, or from a pair of 14-V lithium-ion batteries. The pump operates at a rotor speed in the range of 3,000–9,000 rpm and the maximum flow rate is 10 L/min. The LVAS operates continuously in an artificial pulse mode, where the rotor speed changes rapidly every 2 seconds to generate pulsatile flow from the pump [6].

The use of a HM 3 in advanced HF patients results in improvements in functional capacity, cardiac, renal, and liver function. LVAD technology is quickly evolving and its accessibility is increasing if compared to HT. Further studies should be performed in order to identify whether improved outcomes are sustained with a longer follow-up period.

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HeartMate 3 систем за асистирану потпору левој комори са потпуно магнетним левитирајућим мотором за узнапредовалу срчану слабост – прва искуства у Србији

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САЖЕТАК

Увод Услед недостака донорских органа, време чекања на трансплантацију срца све је дуже и све је већи број болесника у узнапредовалој срчаној слабости који су лечени уређајима за асистирану циркулацију левог срца. Због добрих резултата, широм света је започела примена најновије генерације уређаја за асистирану циркулацију левог срца, система за асистирану потпору леве коморе.

Циљ овог рада је био да прикаже лечење болесника у узнапредовалој фази срчане слабости имплантацијом система за асистирану потпору леве коморе – *HeartMate 3*, као премошћавање периода до трансплантације срца.

Приказ болесника Приказујемо мушкарца старог 59 година на инотропној потпори лековима, у узнапредовалој фази срчане слабости и исхемијском кардиомиопатијом као њеним основним узроком. У одсуству донора, болеснику је уграђен систем за асистирану потпору леве коморе за премошћавање периода до трансплантације срца. Код болесника је дошло до побољшања функционалног капацитета, срчане, реналне и хепатичке функције.

Закључак Употреба *HeartMate 3* код болесника у узнапредовалој срчаној слабости доводи до побољшања функционалног капацитета, срчане, реналне и хепатичке функције. Даља истраживања треба спровести у циљу откривања да ли се са временом праћења побољшани исходи одржавају.

Кључне речи: уређаји за асистирану циркулацију; срчана слабост; трансплантација срца

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Unruptured tubal pregnancy in early second trimester

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SUMMARY

Introduction Most ectopic pregnancies are tubal pregnancies. They are potentially life-threatening conditions with a high mortality rate if unrecognized. The diagnosis is established when the first warning symptoms occur, or during the first prenatal visits to a gynecologist. The diagnosis in the second trimester is extremely rare, since clinical presentation resulting either from the expulsion of the fetus into the peritoneal cavity or from the tubal rupture is manifested by that time. If there is no rupture or the expulsion of the fetus, the pregnancy is allowed to continue and ectopic pregnancy diagnosis may be established in the second trimester.

Case outline We present a case of a 31-year-old second gravida with a vital intrauterine pregnancy confirmed at the first examination. In the early second trimester, the patient visited her doctor due to vaginal bleeding. After a gynecological examination and ultrasonography, ectopic pregnancy was suspected, so the patient underwent laparotomy. Ectopic pregnancy was confirmed and adnexectomy was performed.

Conclusion Early ultrasound examinations have to confirm whether eutopic pregnancy is present. A misdiagnosis and monitoring of ectopic pregnancy as eutopic one is potentially life-threatening for a pregnant woman.

Keywords: unruptured pregnancy; tubal pregnancy; early second trimester

INTRODUCTION

Ectopic pregnancy is a condition where an embryo implants itself in a location other than the uterus. The most common site for an ectopic implantation is the fallopian tube, but it can occur at other locations as well. Potential locations of ectopic gravidities include the ovary, the abdomen, the cervix, intraligamentous locations, and the intramyometrial segment [1, 2, 3].

The incidence of ectopic pregnancies is about 1.3–2.4% in relation to the total number of registered pregnancies [4]. The incidence of ectopic pregnancies has been increasing since the 1970s (0.5%) to date (2%) [5]. In the USA, the incidence of ectopic pregnancy is about 2.3%. The rate among the African-American women is almost double and the mortality risk is five-fold higher than in white women in all the states in the USA [6, 7].

Risk factors responsible for the development of ectopic pregnancy include previous pelvic inflammatory diseases, abdominal surgeries, previous ectopic pregnancy, hematoperitoneum of any etiology, the use of intrauterine devices, and previous Cesarean section [8, 9]. The probability of ectopic pregnancy is 2.5–5-fold higher following assisted reproduction methods. The incidence of ectopic pregnancy after in-vitro fertilization is 1.4–5.4%. Patients with reduced ovarian reserve and confirmed tubal pathology are also at high risk [10, 11]. Previous pelvic surgery, manipulation, and surgical procedures including the fallopian tubes increase the probability of ectopic pregnancy development [3, 12].

Failure in diagnosing ectopic pregnancy, especially at uncommon sites of an embryo implantation, is one of the leading causes of maternal deaths in early pregnancy [6, 7, 13, 14]. Careful clinical monitoring and timely diagnosis reduce the probability of potentially fatal maternal risks [15]. Ectopic pregnancy is usually diagnosed in the first trimester of pregnancy and it is the most common life-threatening condition in early pregnancy [3, 6, 7, 12, 13]. However, the diagnosis can be established in the second or third trimester in patients without tubal rupture. Late diagnosis is rare, since the ultrasound examination in the first trimester confirms the diagnosis of ectopic-eutopic pregnancy during the first examination [14].

CASE REPORT

Our patient was a 31-year-old primipara, second gravida. She was referred to our institution by a doctor from the local health center at the 17th week of amenorrhea, with fetal death and suspected abdominal pregnancy.

The patient had no pain and visited her gynecologist due to vaginal bleeding. It was her second examination regarding the pregnancy. After clinical and ultrasound examinations, a practicing gynecologist suspected ectopic pregnancy and referred the patient to the regional

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health center. Due to suspicion of abdominal pregnancy, the patient was transported to the tertiary healthcare center.

She has been a healthy person, non-smoker, without significant diseases, allergies, or surgeries. Menarche occurred at the age of 16. Menstrual cycle was with bleeding at 35–38 days. The bleeding lasted 7–10 days. The patient had one pregnancy with vaginal delivery on due date, without obstetric surgery or postpartum complications. The delivery had been two years before she presented to our Clinic. She reported no use of intrauterine contraception, but used a condom as a physical barrier contraception.

The patient contacted a gynecologist for pregnancy confirmation and underwent clinical and ultrasound examinations. During that first examination, she reported that amenorrhea lasted nine weeks. On that occasion, the presence of a gestational sac and a vital embryo with a biometry consistent with about eight weeks were confirmed. Extrauterine pregnancy was not suspected and it was monitored as intrauterine pregnancy.

Then, fetal biometry was performed (crown-rump length was 16 mm – corresponding to a gestational age of eight weeks and two days, gestational sac having the diameter of 40.1 mm, corresponded to a gestational age of nine weeks), and fetal viability was confirmed by fetal cardiac activity. Such an examination should have detected the position and shape of the gestational sac, as well as a double decidual sac halo. The position of the sac and the absence of this sign on initial ultrasound examination could have raised doubts about ectopic pregnancy. Chorionic gonadotropin values were not determined in the pregnant woman's blood. The patient had no health problems until scarce vaginal bleeding occurred with amenorrhea lasting 16 weeks and five days. The patient visited the same gynecologist, who performed the first examination. On that occasion, fetal death and ectopic pregnancy were confirmed and the patient was referred to the General Hospital. After an ultrasound examination there, ectopic pregnancy was confirmed, as well as fetal death. Due to suspected ectopic, probably abdominal pregnancy, the patient was referred to the specialized clinic.

On admission to our clinic, the patient was conscious, afebrile, normotensive, and painless, with scarce vaginal bleeding, and was cardiocirculatory stable. The abdomen was insensitive to superficial and deep palpation. Speculum examination revealed cylindrical cervix, transversal orifice, moderate bleeding from external orifice, and dark blood. Proust pain sign was negative. On bimanual examination, the uterus was enlarged and softened, slightly shifted to the left in retroversioflexion (RVF). The left adnexal region was palpable without tumefactions. In the right adnexal region and below the uterus, a soft, tense, and insensitive formation about 10 cm in diameter was palpated. Transabdominal ultrasonography examination (Toshiba Nemio, XG, 6 MHz; Toshiba, Tokyo, Japan) with the bladder not full enough revealed the presence of the gestational sac with developing anterior wall placenta and the fetus without heart action and with positive Spalding's sign (overlapping of skull bones), Figure 1. Transvaginal ultrasonography revealed the uterus shifted to the left in

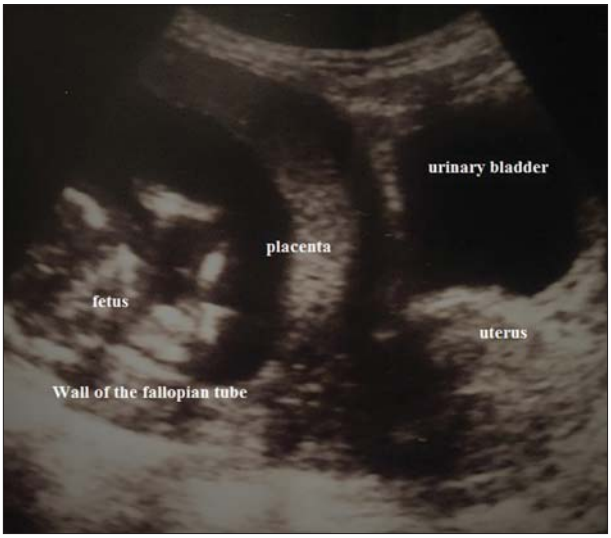

Figure 1. The embryo, a dilated tube, the uterus – transverse imaging

RVF (dimensions: 80 mm × 54 mm × 56 mm, endometrium 14 mm). In the right adnexal region, a cystic formation was observed and suspected to be a dilated right fallopian tube. The borders and the walls of the cystic formation were clear, with the dimensions 92 mm × 84 mm × 65 mm). No fluid was collected around the tumefact in the pouch of Douglas. On the upper pole of the formation, a hyperechogenic formation was observed and considered to be the placenta. Fetal biometry was as follows: biparietal diameter (BPD) 28.5, head circumference (HC) 101.8 mm, abdominal circumference (AC) 85.9 mm, femur length (FL) 14.5 mm. Fetal biometry was consistent with fetal gestational age of 14 weeks and five days. Below the cystic formation (gestational sac and the embryo) the right ovary was registered, 44 mm × 38 mm × 28 mm in size. The left ovary was normal, 28 mm × 22 mm × 17 mm in size. Both ovaries had normal sonographic features. Upon the completion of the ultrasound examination, an intact right tubal pregnancy was suspected.

The patient was admitted to hospital and upon anamnestic, clinical, and ultrasound procedures, laboratory investigations were performed. Laboratory analyses on admission were as follows: blood group A Rh (D) negative; biochemical analyses and coagulation factors within referential values. Coagulation status was as follows: the prothrombin time – 93%; activated partial thromboplastin time – 25 seconds; factor I – 2.3g/L; prothrombin time –1.0. After anamnestic, clinical and ultrasound procedures and after obtaining laboratory results, we decided to perform a laparotomy. The patient was prepared for surgery that was performed under general endotracheal anesthesia.

Surgical procedure and findings

Lower transversal laparotomy was performed, as well as the tamponade of the bowels; there was no free fluid in the abdominal cavity. A cystic, tense tumefact, with leaden-coloured walls and about 10 cm in diameter dominated in the pelvis minor. The uterus was enlarged and shifted to the

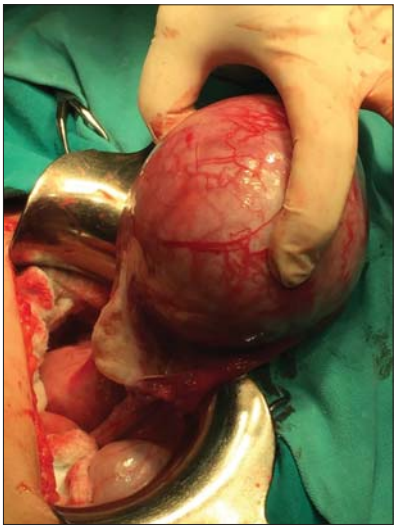

Figure 2. The uterus, a dilated tube with the product of conception, an ovary

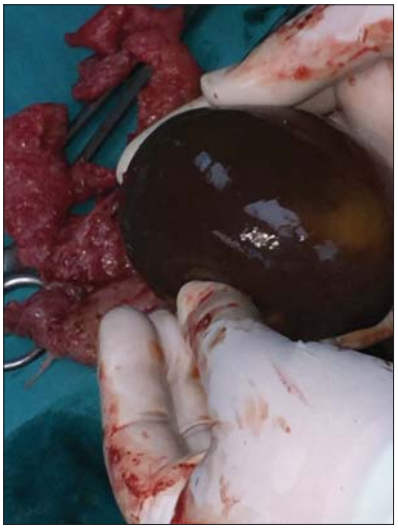

Figure 3. Cut tubal wall and peeled gestational sac

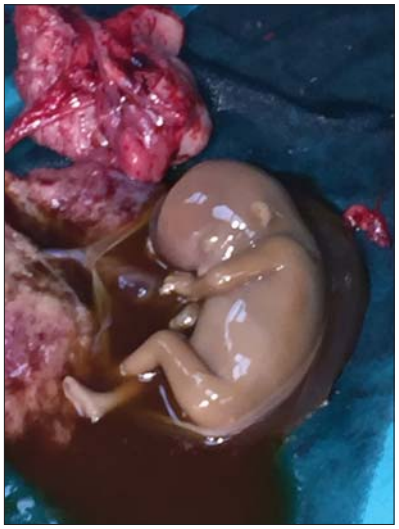

Figure 4. The embryo, placenta, cut tubal wall

left. There were no morphological changes in the left adnexal region. The tumefact was shifted from the pelvis and after the positions of the right ovary, ligament of the uterus, and tumefact were defined, it was confirmed that the ampullary portion of the tube was highly distended. The wall of the tube was very tense, with stretched and highly dilated infundibulopelvic ligament (Figure 2). The tumefact was semi-torquated around the isthmic portion of the tube. The ovary was in close contact with ampullary and isthmic sections of the tube. There was no bleeding on the fimbria of the affected tube. Due to heavily distended and stretched ligaments and the vicinity of the ovary, it was almost impossible to preserve the ovary with an adequate homeostasis, so it was decided to perform adnexectomy. A straight clamp was applied next to the uterus and the tube next to the uterus was fastened, as well as a dilated and stretched ovary clamp with the uterus. Curved Pean forceps were used to fasten the distended infundibulopelvic ligament to the right. Sample: entire adnexa was removed without serious bleeding. Cut sections were sutured. Homeostasis was checked and after peritonization and rinsing, a control drain was placed in the pouch of Douglas pararectally. The abdomen was then closed in layers. The sample was carefully cut, so all the structures and the embryo described by the ultrasound were observed (Figures 3, 4). After closing the abdomen, the patient was placed in lithotomic position and instrumental revision of the uterine cavity was performed because of heavy vaginal bleeding during the surgical procedure. An abundant specimen was obtained. Both the removed adnexa and the specimen were subjected to a histopathological examination. The surgical procedure lasted 50 minutes. The postoperative course was uneventful. The control drain in the pouch of Douglas was removed on the third postoperative day. The patient was discharged on the fifth postoperative day with fully restored passage and normally healing wound. Postoperative ultrasound finding was normal. On the second postoperative day, the patient was given Immunorho No. I immunoprophylaxis.

Histopathological examination confirmed the embryo age of 15 gestational weeks. No fetal anomalies were detected. In the samples obtained by the check-up curettage, decidual endometrial alterations without the presence of fetal elements were confirmed. The presence of the yellow body was detected in the removed ovary.

DISCUSSION

It is necessary to determine whether eutopic pregnancy is present on receiving the first ultrasound examination. If the pregnancy in the uterine cavity is not confirmed in the presence of amenorrhea, pregnancy signs, and positive pregnancy tests, a pregnant woman requires careful monitoring until ectopic/eutopic pregnancy is diagnosed. The diagnosis is established by repeated application of transvaginal ultrasound and adnexal mass identification, or by the diagnosis of intrauterine pregnancy. The use of maternal serum serial chorionic gonadotropin levels is also significant [15]. The possibility of heterotopic pregnancy, especially in patients after *in vitro* fertilization, should not be ignored.

Errors are possible due to poorly trained staff, uncooperative patients, atypical symptoms, and unusual localizations [16]. A complete clinical manifestation of ectopic pregnancy is most commonly symptomatic in the period of 6–8 gestational weeks, unless diagnosed earlier. The tube is not a well-suited site of embryonic implantation and the decidual reaction is minimal. Trophoblasts spread and erode maternal blood vessels. The tube is thinned and muscle fibers undergo hypertrophy, but limited hyperplasia. Timing of the tubal rupture depends on the nidation site and the degree of the tubal wall invasion and the level of hemorrhage in the tubal wall as well [17]. Unrecognized ectopic pregnancy develops in the ampullary region and its progression depends on the degree of tubal invasion and the way of trophoblastic growth. The trophoblast growth can be intraluminal, extraluminal, and combined. In predominately intraluminal trophoblastic invasion, the

degree and velocity of hemorrhage development depend on the degree of maternal blood vessels involvement. The tubal rupture does not necessarily occur immediately after a bleeding attack. Tubal distension occurs as a consequence of conceptual mass growth and bleeding. The possibility of intact endosalpinx epithelium and the absence or minimal hemorrhagia can be seen in intraluminal trophoblastic spread, but trophoblastic invasion of the maternal blood vessels is more intensive and tubal rupture occurs earlier in extraluminal extension [18]. The appearance and regularity of the gestational sac and the presence of crescent-shaped visible placental tissue (other authors also used similar diagnostics criteria before surgery) were the guidelines in making differential diagnosis between abdominal and tubal pregnancy [19]. We decided to perform lower transverse laparotomy due to low probability of abdominal pregnancy. In the case of our patient fetal death occurred. There was no blood in the abdomen, nor tubal rupture. Other authors also reported their experience in patients with unruptured tubal pregnancy. There are no literature data on preserving the affected tube following an ectopic pregnancy in the second trimester. After abdominal opening and confirmation of the right tubal ectopic pregnancy diagnosis, we made an assessment and decided to perform adnexectomy as a safe alternative in our patient to maintain more effective homeostasis. The vicinity of the right ovary and the tube with the conceptus, as well as heavily distended thinned ligaments made us doubt on performing salpingectomy as the most sparing surgery, so we performed adnexectomy. Clinical manifestation of ectopic pregnancy in the second trimester may be severe, with prominent hemorrhage and life-threatening to the mother [20, 21]. Surgical treatment of the second trimester ectopic pregnancies is an inevitable procedure, most commonly including salpingectomy, but adnexectomy may be performed as well, depending on the findings obtained [22]. Hysterectomies in patients with advanced tubal pregnancies have also been described [23]. Timely diagnosis (38th–68th gestational day) provides successful surgical treatment by using minimally invasive procedures, while preserving the affected tube [24]. Embryo implantation outside the uterus is always associated with endometrial changes. Proliferation, cystic hyperplasia, secretory transformation, hyper-secretory changes, asynchronous secretory changes between the glands and the stroma, and decidua reaction were histopathologically verified [25, 26]. Instrumental curettage of the uterine cavity is not a standard post-surgical line of therapy in ectopic pregnancy management, except in heavy or prolonged uterine bleeding, or in cases of suspected heterotopic pregnancy.

Early ultrasound examination is performed to confirm whether the pregnancy is eutopic. A misdiagnosis and monitoring of ectopic pregnancy as eutopic one is potentially life-threatening for a pregnant woman. Surgical treatment should be as sparing as possible, regarding preservation of reproductive organs, especially in patients wishing to have more children. Early diagnosis of tubal ectopic pregnancy may also enable the preservation of the tubes. The advancement of ectopic pregnancy towards the second trimester decreases the likelihood that the patient will have a sparing surgery.

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Неруптурирана тубарна трудноћа у раном другом триместру

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САЖЕТАК

Увод Најчешћа ектопична трудноћа је јајоводна. Ради се о могућем животно угрожавајућем стању са високом смртношћу код непрепознатих случајева. Дијагноза се поставља при појави првих симптома или приликом првих посета гинекологу. Дијагноза у другом триместру је значајно ређа јер до тада обично долази до манифестовања потпуне клиничке слике која је последица или експулзије заметка у перитонеалну шупљину или руптуре јајовода. Уколико до руптуре јајовода или експулзије заметка не дође, могућ је наставак трудноће и дијагноза ектопичног гравидитета у другом триместру.

Приказ болесника Тридесетједногодишња секундигравида, са првом виталном интраутеринoм трудноћом, у раном другом триместру јавила се лекару због појаве вагиналног крварења. После гинеколошког и ултрасонографског прегледа постављена је дијагноза ектопичне трудноће и урађена лапаратомија. Потврђена је тубарна трудноћа и урађена аднексектомија.

Закључак Прве ултразвучне контроле морају да потврде еутопичност трудноће. Погрешна дијагноза и праћење ектопичне као еутопичне трудноће може да буде угрожавајуће за трудницу.

Кључне речи: неруптурирана трудноћа; тубарна трудноћа; рани други триместер

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REWIEV ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Cardiac arrest and cardiopulmonary resuscitation in the operating room

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SUMMARY

The occurrence of cardiac arrest during anesthesia and surgery is nowadays associated with many challenges imposed by 21st century medicine. On the one hand, good education of healthcare practitioners, sophisticated anesthetic techniques and equipment, along with safer anesthetics and improved surgical techniques have significantly reduced the risk of cardiac arrest during the perioperative period. Still, the introduction of new, invasive diagnostic and therapeutic procedures in the aging patients and those with comorbidities carries along new risk and challenges.

Epidemiological data indicate that intraoperative cardiac arrest is an extremely rare event.

Due to variety of moral and ethical prejudices, intraoperative cardiac arrest is frequently presented as if it has happened in the immediate postoperative period, following surgery and anesthesia. The preventive measures, the etiology and diagnosis of cardiac arrest, as well as the specificities regarding organization and performance of cardiopulmonary resuscitation in the operating room, result in a better prognosis compared to other hospital departments.

The article also describes the specifics of cardiopulmonary resuscitation in the catheterization laboratory, while a separate section is dedicated to cardiopulmonary resuscitation following systemic toxicity of local anesthetics.

Since intraoperative cardiac arrest and death represent very rare complications, European Resuscitation Council has only recently published Guidelines for Resuscitation for performing cardiopulmonary resuscitation in the operating room – in 2015.

Keywords: heart arrest, etiology, therapy; cardiopulmonary resuscitation; operating room; anesthesia, adverse effects; anesthesiology, methods, standards; medical errors, prevention, control

INTRODUCTION

The perioperative cardiac arrest (CA) is much less likely to happen nowadays due to contemporary education in anesthesiology, good preoperative preparation of patients, the use of modern anesthesiologic techniques, equipment and safe anesthetics, and improved surgical techniques. On the other hand, the introduction of new, invasive diagnostic and therapeutic procedures in the aging patients and those with comorbidities carries along new risks and challenges. CA is the most dramatic and most urgent situation for a physician in the operating room (OR). A trained team of OR personnel and specific work organization, mandatory monitoring, the availability of equipment and medications for cardiopulmonary resuscitation (CPR), secured airway and placed intravenous cannulas facilitate perioperative CPR and increase survival rates [1].

Since intraoperative cardiac arrest and death represent very rare complications, European Resuscitation Council (ERC) has only recently published Guidelines for Resuscitation for performing cardiopulmonary resuscitation in the operating room – in 2015 [2, 3, 4].

Due to a variety of moral and ethical prejudices, intraoperative cardiac arrest is frequently presented as if it has happened in the immediate postoperative period, following surgery and anesthesia. When CA happens in the OR, many doctors feel unjustified guilt that some intervention during anesthesia or surgery may have contributed to CA occurrence, so they feel responsible and obligated to perform CPR, even in situations when it is completely clear that it should not be performed (i.e. terminal illnesses, signed "Do not resuscitate" protocol). That is why the operating team starts CPR in order to achieve return of spontaneous circulation (ROSC), finish the surgery, and transport the patient from the OR, although they are fully aware that in the immediate postoperative period ROSC will briefly result in a death outcome. Therefore, the majority of epidemiological data regarding the frequency of CA in the OR should be carefully considered.

The low incidence of CA caused by anesthesia and surgery prevents conduction of controlled studies in this area [5, 6].

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PROGNOSIS AND OUTCOMES OF CARDIAC ARREST DURING ANESTHESIA AND SURGERY

In developed countries, the incidence of CA during anesthesia is 0.2–1.1 cases per 10,000 procedures in adults, and 1.4–2.9 cases per 10,000 procedures in children (with a considerably higher incidence in newborns), which is much more rare than 30 or more years ago (20 in 10,000) [1, 7, 8, 9]. Certainly, there are higher-risk groups of patients among whom perioperative CA is seen much more often (Table 1) [2, 10, 11]. Data from the Mayo Clinic indicate that the incidence of CA perioperatively during general anesthesia is three times higher than during regional anesthesia [2, 9].

Table 1. Risk factors for operating room cardiac arrest

	Risk factors
1.	Urgent surgery 163/10,000 patients
2.	Elderly patient 54/10,000 patients
3.	Children < 2 years
4.	Male sex
5.	COPD
6.	Hypotension (shock) AP < 90 mmHg
7.	AKI, CKD
8.	Malignant disease
9.	Major surgery

COPD – chronic obstructive pulmonary disease; AP – arterial pressure; AKI – acute kidney injury; CKD – chronic kidney disease

The differences related to the organization and execution of CPR in the OR compared to other hospital departments reflect different survival rates for CA patients. Documented reports show that patients' survival following intraoperative CA is 34.5–43.9% [8]. In situations when CA was associated exclusively with anesthesia, survival rates were as high as 70–80%, which is much higher than survival rates in other hospital wards: only 15–20% [1, 12].

ETIOLOGY OF CARDIAC ARREST IN THE OPERATING ROOM

Numerous factors are associated with perioperative CA: the preoperative factors (comorbidities), poor risk assessment, inadequate monitoring, mistakes during anesthesia and surgical procedures [9, 13].

The universal mnemonic "4H and 4T", which causes of CA defined by the ERC, Moitra et al. [14] have described as many as 16 (8H and 8T) potentially reversible causes of CA in the OR (Table 2) [2].

According to the literature data, the most frequent causes of intraoperative CA are as follows:

- hemorrhage (with the highest fatal outcome rate of 10.3%);
- heart complications, myocardial infarction;
- medications (anesthetics, muscle relaxants), complications of central venous catheterization;
- hypoxia caused by compromised airway or complications associated with mechanical ventilation [8, 9, 15].

Table 2. Potentially reversible causes of cardiac arrest in the operating room

8H	8T
Hypoxia	Toxins (anaphylaxis/anesthesia)
Hypovolemia	Tension pneumothorax
Hyper-/hypokalemia	Thrombosis/embolus, pulmonary
Hydrogen ion (acidemia)	Thrombosis, coronary
Hypothermia	Tamponade
Hypoglycemia	Trauma/hemorrhagic shock, CV injury
Malignant hyperthermia	QT prolongation
Hypervagal reaction	Pulmonary hypertension

CV – cardiovascular

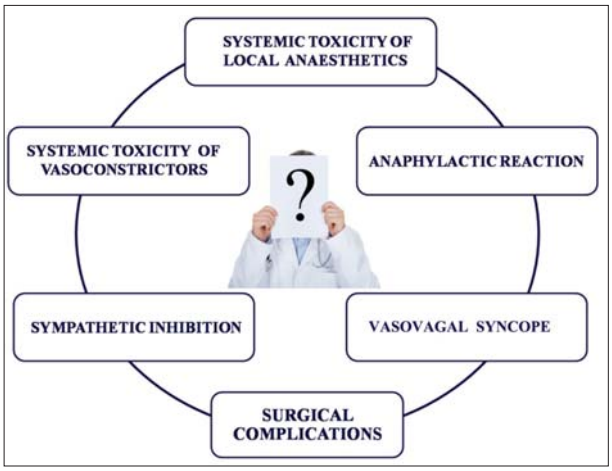

Figure 1. The most frequent causes of a patient's deterioration during regional anesthesia

The most frequent causes of CA in the OR in children are the airway obstruction caused by laryngospasm and bronchospasm, hypovolemia (blood loss) and hyperkalemia (from transfusion of stored blood) [2, 16].

Unlike seen in out-of-hospital CA and in other hospital departments, the most frequent CA rhythm seen in the OR during general anesthesia is asystole (Figure 1). Fortunately, the prognosis of CPR following asystole in the OR is much better than in other hospital departments [2, 7, 9].

PREVENTION OF INTRAOPERATIVE CARDIAC ARREST

The prevention of intraoperative CA begins with good pre-operative preparation of patients, assessment of comorbidities and current physical status (according to the American Society of Anesthesiologists – ASA score), and stabilizing any concomitant chronic conditions. The prevention of operating room CA is affected by the choice of anesthesia technique (general or regional), which depends on the type of surgery, the condition of the patient and comorbidities, but also on the patient's personal desires and the anesthesiologist's experience. Furthermore, the choice of the optimal operative technique depends on the surgeon's experience. Teamwork in the OR has contributed to more rapid recognition and timely reversal of any deterioration of the patient, whereby the occurrence of CA is prevented [2, 17].

The physician's failure to notice the deterioration of the patient's condition in time is the most frequent cause of CA in the OR [2, 17]. The patient's state can sometimes worsen within minutes, but also over hours during the intraoperative period, so appropriate monitoring and timely correction of pathophysiological changes are crucial.

THE DIAGNOSIS OF CARDIAC ARREST IN THE OPERATING ROOM AND MANDATORY MONITORING – CONTROL OF CPR QUALITY

If the minimum mandatory monitoring standard is ensured in the OR, there should be no delay in making a diagnosis of CA. Insertion of an arterial line for invasive blood pressure monitoring in high-risk patients is invaluable for prompt diagnosis of CA. It is recommended that these patients should be equipped with self-adhesive defibrillation pads prior to anesthesia induction [2, 8].

Asystole and ventricular fibrillation (VF) must be identified immediately in the OR. However, in the case of pulseless electrical activity, the diagnosis of CA should be verified by capnography ($EtCO_2$) and pulse oximetry, and definitely confirmed by the pulse or the arterial line curve (Table 3).

Table 3. Incidence and pattern of cardiac arrest rhythms in the operating room (Mayo Clinic data) [2]

Pattern of cardiac arrest rhythms	Incidence (%)
Asystole	41.7
Ventricular fibrillation	35.4
Pulseless electrical activity	14.4
Unknown	8.5

Performing proper and uninterrupted chest compressions is essential for the success of CPR. There are multiple ways to assess the quality of chest compressions and check the success of CPR in the OR. Palpation of the carotid or femoral artery pulse during CPR is not a proper indicator of chest compressions' quality. Some newer generation defibrillators can provide feedback regarding the quality of compressions. Non-invasive blood pressure monitoring has no relevance in the CA diagnosis, in the quality of CPR, nor in the prediction of CPR success, and can only be used following ROSC. When hypotension and hypoxia are present, pulse oximetry is not an appropriate monitoring touchstone for a prompt CA diagnosis or for assessing chest compressions' quality. Capnography, a part of minimum mandatory monitoring, is very important in assessing CPR quality. When $EtCO_2 > 20$ mmHg, ROSC is much more likely to occur than in cases when $EtCO_2 < 10$ mmHg is achieved with chest compressions. If there is an arterial line in place, diastolic pressure (DP) over 40 mmHg is also associated with higher ROSC incidence. Monitoring central venous pressure (CVP) and diastolic pressure in the OR during CPR permits the calculation of coronary perfusion pressure (CPP) based on the following formula: CPP = DP - CVP. CPP values of over 15 mmHg during CPR are associated with higher survival rates [8, 18, 19, 20].

However, activation of various alarms due to monitoring failure while the state of the patient is satisfactory is a very frequent occurrence in the OR. This may happen due to detachment of an ECG electrode from the patient's chest, the pulse oximeter slipping off the patient's finger, or technical problems in CO_2 sampling. Such occurrences may sometimes lead the anesthesiologist to ignore the monitoring alarms and to miss a serious deterioration of the patient's condition. Regardless of the mandatory monitoring, "the physician is the most important monitor in the operating room" [8].

RESPONSIBILITIES OF THE OPERATING TEAM MEMBERS IN PERFORMING CPR – THE TEAMWORK

Good communication among members of the resuscitation team in the OR is the key to the success of resuscitation. Confusion or miscommunication must not be permitted during CPR, and no time must be wasted while resuscitation procedures are being performed. This is why teamwork, good organization, following the team leader's instructions and the availability of equipment in good working order are crucial in the performance of CPR measures. In order to advance the teams' professionalization, simulation sessions are held periodically to practice handling of this type of crisis situation. The responsibilities of the surgical team members in performing CPR measures are shown in Figure 2 [21, 22, 23].

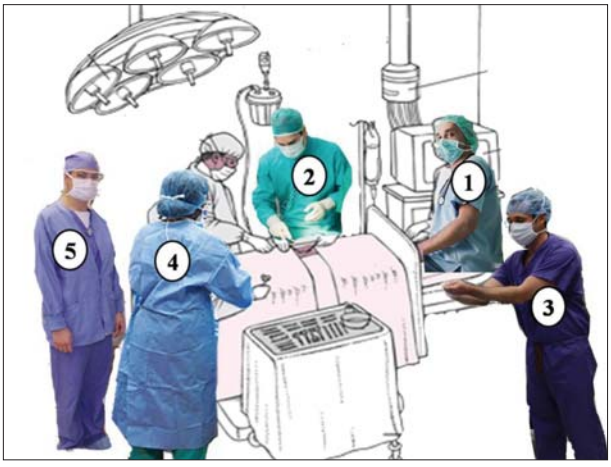

Figure 2. Operating room (OR) team members' tasks during cardiopulmonary resuscitation (CPR): 1) the anesthesiologist makes the diagnosis of cardiac arrest, acts as the CPR team leader, executes advanced life support and removes any reversible causes; 2) the surgeon halts the surgical procedure, controls bleeding, protects vital organs, executes the anesthesiologist's orders and performs chest compressions; 3) the anesthetist executes the anesthesiologist's orders, prepares the defibrillator and takes part in the defibrillation, prepares and applies treatment ordered by the anesthesiologist; 4) the scrub nurse monitors and secures the sterility of the wound and the operating field, and of the surgical equipment; 5) the circulating nurse calls for additional assistance, adjusts the height of the table, oversees OR comings and goings, retrieves and delivers disposable materials and equipment [23]

PERFORMING CPR IN THE OPERATING ROOM

It is interesting to note some authors' comparison of general anesthesia and CPR. While it is completely inaccurate to declare that general anesthesia is an "ongoing resuscitation," there are certain similarities between the two medical procedures. Under general anesthesia, as in CPR, the patient is unconscious. Both procedures require maintaining and monitoring of the airway and mechanical ventilation. Administering vasopressors and antiarrhythmic drugs, which are mandatory during CPR, is not unusual during general anesthesia. As in advanced life support (ALS) measures of CPR, continuous monitoring is present during general anesthesia too. Based on this, one may raise the question regarding differentiation of the routine procedures done during general anesthesia in the OR and the urgent skills required in CPR. According to some authors, the only difference that draws the medical line between these two procedures is the need for defibrillation and the execution of chest compressions [5].

The advantages and disadvantages of CPR in the OR are shown in Table 4.

Table 4. Advantages and disadvantages of cardiopulmonary resuscitation in the operating room

Advantages	Disadvantages
1. CA is always observed by witnesses; 2. CA cause is usually known and reversible; 3. Airway is secured and mechanical ventilation is ongoing; 4. Multiple vein lines, CVC in place; 5. Continuous monitoring, arterial line is often in place; 6. Entire CPR team is present; 7. CPR equipment and medications are available	1. False alarms, interruption of ECG, pulse oximetry connection; 2. Hypotension and bradycardia that may be discounted or overlooked; 3. Impossibility of adequate monitoring (obesity, the patient's position on the operating table); 4. Contamination through non-sterile contact; 5. Medically and ethically unjustified reasons

CA – cardiac arrest; CPR – cardiopulmonary resuscitation; CVC – central venous catheter; ECG – electrocardiography

In the OR, the time of CA occurrence is always observed by witnesses and the direct cause of the CA is usually known. That is why, along with the progress of CPR, reversible causes should be removed (bleeding, hypoxia, etc.) [3].

When non-shockable rhythms are found and accompanied by the inability to palpate the pulse for more than 10 seconds along with a drop in the capnographic and arterial curve, chest compressions should be started immediately, following ALS protocols for non-shockable rhythms [2, 24]. In view of the surgeon's position relative to the patient, he or she should begin chest compressions, or direct heart compression, depending on whether the thorax is surgically open [8]. The height of the operating table should be adjusted in order to permit the performance of high-quality chest compressions [2]. CPR is optimally performed on a patient in a supine position, but in certain situations it is possible to perform CPR on patients in prone position if it is not feasible to place the patient in a supine position quickly [3, 4]. Chest compressions in prone patients may be performed manually or using a mechanical chest compression device in continued compression (10 compressions/minute) if an endotracheal tube is in place [2, 3]. If a supraglottic airway device has been inserted and there is an air leak, the CPR should be performed at a ratio of 30:2 [18, 25]. Depending on the ECG rhythm (shockable or non-shockable), CPR should be performed immediately based on new ERC guidelines for CPR [2, 24].

- The decision when to terminate CPR is complex and often, in addition to the medical aspect, includes a series of moral, ethical, and legal elements. Adhering to medical positions, CPR should be terminated when the following criteria are met:fatal injuries or signs of certain death are present;
- an objective suggestion has been made by a senior – the team leader;
- an assessment has been made that all further CPR would be futile and useless;
- asystole has been present for over 20 minutes despite ALS measures and there are no reversible causes [18, 19, 20].

CARDIAC ARREST AND CPR IN THE CATHETERIZATION LABORATORY

CA may occur during percutaneous coronary intervention in patients with myocardial infarction, but it can also arise as a complication of angiography. Most complications will lead to VF, which requires urgent defibrillation. This is why a patient in the catheterization laboratory must be continuously monitored, with a defibrillator standing by. In high-risk patients, self-adhesive radiolucent defibrillation pads should be placed prior to starting the procedure. If the defibrillation is not successful or VF re-occurs, defibrillation should be repeated urgently two times [2]. If VF persists after the third defibrillation, begin chest compressions and ventilation without delay, and continue the angiography in order to find the cause of the CA. It is extremely important not to interrupt chest compressions during the angiography. On an angiography table, where the image intensifier is located above the patient, it is almost impossible to perform high-quality chest compressions, and there is the risk of exposing the practitioner to dangerous radiation. This is why it is strictly advised to use a mechanical chest compression device. In patients with non-shockable rhythm, immediate transthoracic echocardiography should be performed in order to diagnose the cause (pericardial tamponade or another issue) [26, 27].

CARDIAC ARREST CAUSED BY SYSTEMIC TOXICITY OF LOCAL ANESTHETICS

CA as a consequence of systemic toxicity of a local anesthetic (LA) occurs in 1.8 cases per 10,000 regional anesthesia procedures [28]. Significant clinical experience is needed to find the cause of a patient's deterioration during regional

anesthesia (Figure 1), since this determines the type of the treatment. If systemic toxicity of LA is not recognized and not treated promptly, it may lead to CA.

The typical development of the clinical features is the result of a progressive biphasic effect on the central nervous system (CNS) and subsequently on the cardiovascular system (CVS), which are highly sensitive to changes of tissue electrophysiology. Since the CNS alterations are the first ones to occur, this compartment is considered the "mirror" of LA concentration in the blood. Initially, patients become agitated and logorrheic, feel a metallic taste in their mouths, and may experience nystagmus, tinnitus, dysphagia, and confusion. Further progression of the intoxication produces muscle tremors and the development of convulsions. Nausea and vomiting may also be present, along with breathing disturbances, respiratory vasomotor depression, and loss of consciousness [28].

The CVS is considered more resistant to LA effects than the CNS, and cardiotoxicity occurs as a consequence of the direct negative inotropic effects of the anesthetic on the heart and the direct relaxant action on the smooth muscle tissue of the blood vessels. Cardiotoxicity associated with systemic LA toxicity is characterized by hypotension, AV block, idioventricular rhythm, bradycardia, and cardiovascular collapse. The cardiotoxic effect of the LA is exacerbated by hypoxia, hypoventilation, acidosis, and hyperkalemia [28].

In the case of CA, perform ALS according to the ERC guidelines for CPR [2, 3, 24].

Patients with cardiovascular collapse and CA caused by systemic LA toxicity can benefit from a 20% lipid emulsion applied intravenously during ALS [2, 28]. The widely accepted hypothesis of the mechanism of action of the 20% intravenous lipid emulsion in the treatment of cardiotoxicity is based on the absorption and removal of the circulating lipophilic toxin – the LA – from the blood, which reduces the amount of free LA able to bind to the myocardium. This non-specific removal of LA from the plasma or heart tissue is called "lipid sink" in Anglo-Saxon literature [29]. Another possible mechanism is that the intravenous lipid emulsion acts directly on the heart muscle by neutralizing the inhibitory effect of LA on fatty acid oxidation in mitochondria, whose ultimate purpose is creating energy – adenosine triphosphate, thus preventing the depressive effect of LA on the functioning of the heart muscle [29, 30]. Some authors suggest that successful resuscitation could be due to spontaneous clearance of the instigating LA within of routine ALS without administering intravenous lipid emulsion. [31, 32].

Clinical recommendations for the dosage of 20% intravenous lipid emulsion during CPR were published in ERC guidelines for CPR in special circumstances in 2015 [2, 3, 4]. However, many questions remain open: should the lipid dose be titrated by patient weight, local anesthetic dose, or the symptoms, severity of toxicity; what is the best rate and total dose and what are the possible complications or adverse effects of lipid infusion? Furthermore, pediatric doses of IV lipid emulsion to treat systemic LA toxicity have not been defined. [30, 31, 32].

CONCLUSION

Cardiac arrest in the OR is associated with pre-existing medical or surgical diseases, the quality of preoperative evaluation and preparation for anesthesia and surgery, but also with the anesthetic and surgical technique.

Good organization and well-trained operating room team members, along with appropriate monitoring and readily available equipment and medication, result in a better prognosis when CPR is performed in the OR compared to other hospital departments.

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Акутни застој срца и кардиопулмонална реанимација у операционој сали

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САЖЕТАК

Акутни застој срца током анестезије и операције је у данашње време повезан са многим изазовима које доноси медицина XXI века. С једне стране, добра едукација здравствених радника, савремене технике анестезије и опрема, безбедни анестетици и усавршене оперативне технике значајно су смањили ризик за настанак акутног застоја срца у периоперативном периоду. Међутим, увођење нових, инвазивних дијагностичких и терапијских процедура код све старијих болесника са коморбидитетом доноси нове ризике и изазове.

Епидемиолошки подаци указују да се ради о изузетно ретком догађају. У медицинској пракси, због моралних и етичких предрасуда, интраоперативни акутни застој срца се често приказује у непосредном постоперативном току, после операције и анестезије. Мере превенције, етиологија и дијагноза акутног застоја срца, као и специфичности у организацији и извођењу кардиопулмоналне реанимације у операционој сали дају бољу прогнозу у поређењу са другим одељењима болнице.

У овом раду описане су и специфичности кардиопулмоналне реанимације у сали за катетеризацију срца и посебно после системске токсичности локалних анестетика.

С обзиром на то да акутни застој срца и смртни исход током интраоперативног периода представљају веома ретке компликације, Европски савет за реанимацију је први пут објавио препоруке за извођење кардиопулмоналне реанимације у операционој сали тек 2015. године.

Кључне речи: акутни застој срца, етиологија, лечење; кардиопулмонална реанимација; операциона сала; анестезија, нежељени ефекти; анестезиологија, методе, стандарди; медицинске грешке, превенција, контрола

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ИСТОРИЈА МЕДИЦИНЕ / HISTORY OF MEDICINE

Срби на Корзици у Великом рату – 2. део

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САЖЕТАК
Историографија српског народа из Великог рата одала је дужно поштовање великим биткама и славним победама, није изоставила голготу повлачења српске војске и народа, Солунски фронт и друге фронтове. Мање је позната судбина 35.000 српских регрута, расељених младих људи, сага српске избегле колоније широм европских простора и даље. Циљ овог рада је да истакне судбине српских избеглица на Корзици и ода признање њиховим исцељитељима, који су долазили са различитих страна света као представници дипломатских, хуманитарних и медицинских мисија Србије, Француске и Велике Британије. Живот избегле српске колоније на Корзици у Француској био је организован залагањем представника краљевске Српске владе у Француској, Француског комитета за помоћ рањеницима, болесницима и избеглицама, Српског потпорног фонда, Болница шкотских жена, локалних власти и бројних појединаца на Корзици. Посебно је истакнута Болница шкотских жена на Корзици, која је за српске војнике и српске избеглице организовала Јединицу Корзика, са седиштем у Ајачу, изоловану болницу у Лазарету, док су амбуланте и диспанзери били распоређени по селима. У време када се обележава стогодишњица од Првог светског рата узвраћамо захвалност за посвећеност и пожртвовање свим странама, посебно Болници шкотских жена и др Елси Инглис, оснивачу и руководиоцу ове медицинске мисије.
Кључне речи: Први светски рат; француска медицинска помоћ; Српски Црвени крст; Српски потпорни фонд; Болнице шкотских жена; Корзика; Србија; Елси Инглис

Др Елси Инглис, оснивач и руководилац Болнице шкотских жена (The Scottish Women's Hospital for foreign service)

Др Елси Мод Инглис (*Dr. Elsie Maud Inglis*, 1864–1917), оснивач и руководилац Болница шкотских жена широм Европе, дошла је у Србију априла 1915. и заменила др Елеонор Солто, која је руководила Првом јединицом Болнице шкотских жена у Крагујевцу. Истовремено је основала болнице у Ваљеву, Младеновцу и Лазаревцу. Окупацијом Србије одбила је да се повуче и остала да негује преко хиљаду рањеника и болесника у крушевачкој болници. По повратку у домовину, организовала је прославу Видовдана, на челу Организационог комитета промовисала српску борбу за ослобођење, основала нову болницу и отишла на Руски фронт и Добруџу, у пратњи Прве српске добровољачке дивизије [1, 2].

Др Елси Инглис, оснивач и „покретачки дух" чланица Болница шкотских жена широм Европе, била је прва жена носилац високог српског одликовања – Ордена белог орла. Меморијална чесма на Црквенцу, у Младеновцу, најлепши је споменик посвећен др Елси Инглис и чланицама Болница шкотских жена који је српски народ подигао у време рата, као дар захвалности за њихову племенитост и пожртвовање. У знак сећања и поштовања на др Инглис, Болница шкотских жена је формирала Јединицу „Др Елси Инглис" као појачање болницама на

Слика 1. Др Елси Мод Инглис (1864–1917)
Figure 1. Dr. Elsie Maud Inglis (1864–1917)

Солунском фронту. Меморијална болница „Др Елси Инглис" у Единбургу је још један од споменика који подсећа на дела др Елси Инглис. Биста др Елси Инглис, поклон српског народа а дело Ивана Мештровића, изложена је у Националној галерији Шкотске, у Единбургу. После Првог светског рата комитети Болница шкотских жена у Лондону и Единбургу помогли су изградњу Меморијалне болнице за мајку и дете „Др Елси Инглис" на Дедињу, у Београду (Слика 1).

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Слика 2. Болница шкотских жена за Србе у Ајачу, на Корзици
Figure 2. The Scottish Women's Hospital in Ajaccio, on Corsica

Мање је познато да је у оквиру Болнице шкотских жена др Инглис основала Јединицу Корзика, која је прихватила српске избеглице на Корзици (Слика 2). Др Елси Инглис је лично посетила болницу на Корзици, била задовољна руководством др Мери Блер и организацијом болнице у Ајачу, као и бројним диспанзерима. На самом почетку рада болнице др Мери Блер је са шеснаест сестара и болничарки имала тежак задатак да „излечи и поврати у нормалан живот део изнемогле српске нације... Било је то поновно стварање нације сломљене и расуте по свету – опоравити и вратити у живот људе, жене и децу, која умиру" [3].

Извештај др Мери Блер о првој групи српских избеглица на путу за Корзику

Извршни комитет Болница шкотских жена донео је одлуку о оснивању једне болнице на Корзици, са локацијом у Ајачу, која је имала циљ да се брине о српској избеглој колонији. Једно од сведочанстава о тим данима показује извештај др Мери Блер, којој је поверено руководство Јединице Корзика.

На путу за Корзику, децембра 1915. године, др Блер извештава са брода „Амазон" [4]:

„Деветог децембра др Андерсон (*Dr. Catherine Emslie Anderson*, 1881–1934) и ја смо отишли са сер Едвардом Бојлом и др Ђоком Ђурићем на четвородневно путовање у правцу Монастира (данашњег Битоља). Сер Бојл је пошао на пут у име Српског потпорног фонда да организује поделу помоћи избеглицама у Водени и Флорини. Ми смо пошли да бисмо видели стање и број избеглица и проценили њихове потребе за медицинском помоћи. Након што смо посетили избеглице у разним градовима, добила сам идеју о њиховим болничким потребама и обиму посла. У Водени је било око 150 избеглих породица, њих педесеторо је требало хитну помоћ, док је другима требала помоћ за неколико недеља."

„У Флорини смо видели најтужније призоре српских војника, који су се довукли преко прелаза од Охридског језера... Видели смо знатан број оних који су седели или лежали дуж пута, исцрпљени, гладни, рањених стопала. Неки су били тешко болесни... Сер Едвард Бојл је средио да ови људи и шест или седам стотина избеглих породица остану тамо док све не буде спремно да могу да их приме у Флорини. Један лекар и две медицинске сестре из друге јединице послати су да се брину о њима привремено, све док се избеглице не сместе."

„Док је био у Флорини, сер Едвард ми је рекао да је по доласку у Солун наш најхитнији посао био да брзо склонимо избеглице на сигурно место. За тај задатак он се ослонио на нашу јединицу. Док смо били на путу, госпођица Хантер (*Miss Hunter*) организовала је рад са избеглицама у станици. Пре поласка питала сам сер Едварда Бојла, ако жели да то ми радимо, да ли ћемо имати материјалну помоћ Српског потпорног фонда за ту сврху. Док смо чекали наша сопствена задужења и распоред, понудили смо да обезбедимо особље. На нашем повратку из Флорине затекли смо све у најбољем реду – чај и хлеб да се окрепе избеглице по повратку, разапет шатор да се сместе преко ноћи и уговорен свакодневни превоз избеглица и њиховог пртљага у привремени логор на земљишту у околини руске болнице. Сер Едвард је био задовољан како је брзо организован и завршен посао, посебно што је то обављено упркос свим потешкоћама које су постојале у Солуну."

„Убрзо након овог он (сер Едвард Бојл) позвао ме је и изложио своје планове. Стигла је понуда француске владе о бесплатном превозу избеглица до Ајача и за смештај тамо. Прва група требало је убрзо да крене. Замолио ме је да поведем своју групу тамо – известан број особља би ишао са сваким транспортом како би бринуо о избеглицама при путовању. Он је желео да ја преузмем управу здравствене службе избегле колоније, јер неће постојати друго болничко особље осим нас. Направио је један изузетак, који се тицао др Лилијас Хамилтон. Она се прикључује колонији и вероватно

ће преузети посао у кућама, као што је санитарна инспекција."

Др Лилијас Хамилтон (*Dr. Lillias Hamilton*, 1858–1925) рођена је у Аустралији, обучила се за медицинску сестру у Ливерпулу, завршила Медицински факултет за жене у Шкотској, стекла титулу доктора медицине 1890. Живела је и радила у Индији у Калкути (1890–94) и у Авганистану, где је радила као лични лекар емира (1894–1897). Аутор је неколико књига, које су биле инспирисане њеним боравком у Авганистану. Године 1915. била је члан медицинске мисије Српског потпорног фонда – Јединице Комитет за бригу о рањеним савезницима (*Wounded Allies Relief Committee*), која је радила у Србији и Црној Гори (Подгорица). Учествовала је у повлачењу преко Албаније, а на Солунском фронту прикључила се Болници шкотских жена, која је основала болницу у Ајачу, на Корзици.

„Ја (др Блер) преузимам здравствену бригу за избеглице на броду. Плашим се да ће се једна жена породити на броду пре него што стигнемо на Корзику. Надам се да се то неће догодити пре него што стигнемо, али, у сваком случају, мислим да можемо да се побринемо за њу. Сматрам да ће бити пуно корисног посла за нас међу Србима на Корзици. Очекује се да ће их тамо бити пет или шест хиљада" [4].

Др Мери Алис Блер, прва управница Болнице шкотских жена на Корзици

Др Мери Алис Блер (*Mary Alice Blair*) није само учествовала у оснивању Јединице Корзика Болнице шкотских жена на Корзици, већ је била и њена прва управница. Болница шкотских жена у Ајачу на Корзици почела је да ради 8. октобра 1915. и радила је до априла 1919. Болница је на почетку имала капацитет од 60 постеља, од којих је 40 било намењено мушкарцима и 20 женама. Гинеколошки случаји и породиље су такође били укључени, што ће се показати од непроцењиве вредности. Свакодневно је велики број болесника тражио медицинску помоћ у истуреним диспанзерима. Кућне посете и обиласци болесника у забаченим селима су такође били у домену деловања болнице на Корзици. Мада потреба за хируршким интервенцијама није била јако заступљена, Болница шкотских жена је установила малу операциону салу, што се показало корисним. У току деловања болнице обављене су 72 веће операције и 40 мањих. Поред честих појава маларије, треба истаћи да је туберкулоза била у порасту међу члановима српске избегле колоније, па отуда одлука да се оснује болница-санаторијум у Саланшеу.

Болница шкотских жена у Ајачу у току свог рада примила је око 1.700 болесника, од најстаријих до најмлађих чланова српске избегле колоније. У истуреним амбулантама и диспанзерима лечено је 15.515 болесника, док је у породилишту рођено 79 беба.

Руководиоци Болнице шкотских жена у Ајачу биле су др Мери Блер (*Dr. Mary Blair*), др Мери Филипс (*Dr. Mary Phillips*), др Елизабет Кортолд (*Dr. Elizabeth Courtauld*), др Матилда Макфејл (*Dr. Matilda MacPhail*), др Една Гест (*Dr. Edna Guest*) и др Онорија Кир (*Dr. Honoria Keer*). Поред лекара руководиоца, у болници су радиле лекарке: др Кетрина Емсли Андерсон (*Dr. Catherine Emslie Anderson*), др Едит Холвеј (*Dr. Edith Blake Hollway*), др Софија Б. Џексон (*Dr. Sophia Bangham Jackson*) и др Мери Мичолина Грант Фергусон (*Dr. Mary Micholina Grant Ferguson*).

Августа 1915. др Мери Блер је са својим особљем пошла из Енглеске као испомоћ Болници шкотских жена у Ваљеву, којом је руководила др Алис Хачинсон (*Dr. Alice Hutchinson*). Окупацијом Србије, у великом повлачењу са српском војском су се повлачиле и савезничке медицинске мисије. Тако је др Блер на путу за Србију остала на Солунском фронту.

У повлачење са српском војском кренули су велика колона народа, хиљаде регрута, велики број породица са децом и старима. Чланови Српског Црвеног крста заједно са члановима савезничких хуманитарних друштава, Српским потпорним фондом и Болницом шкотских жена обишли су логоре избеглог народа, а медицинско особље је предложило хитност решавања њиховог збрињавања. У Солуну се др Мери Блер са осталим члановима Француског комитета, Српског Црвеног крста и Српског потпорног фонда организовала да прими, прехрани и пронађе привремен смештај за велики број српских избеглих породица, пре њиховог транспорта у Француску.

Симболично, на дан Божића, 25. децембра 1915. кренула је прва група са триста избеглица, којом је руководила др Мери Блер. Брод „Амазон" са избеглицама пловио је преко Медитерана ка коначној дестинацији – острву Корзика. Убрзо је стигао још један брод са 500 српских избеглица. Док је Болница шкотских жена преузела организацију здравствене службе за српску колонију, чланице Српског потпорног фонда су имале задатак да раде на социјалним питањима.

Руководити Јединицом Корзика у Ајачу није био нимало лак задатак. Бродови су непрестано пристизали са избеглицама, а сваки нов почетак је доносио проблем уклапања и адаптирања на климу, нове обичаје и законе. „Дочекани су као хероји. Али какав један призор, били су то скрхани људи, многи нису могли да стоје, толико истрошени и изнурени, неки без ногу, други рањени, сви једно запуштени, али одлучни, отресити до последњег" [3].

„Почели смо са организацијом болнице... То је заиста прелепо место на дивном положају, са погледом преко мора на супротну страну планинске обале. Узимајући у обзир све околности, болница је дивна", писала је госпођица Калбард (*Miss C. M. Culbard*), административна радница болнице.

У Болници шкотских жена у Ајачу са организовањем здравствене службе, која је била намењена искључиво српској избеглој колонији, основани су мушко, женско и дечје одељење. У извештају др Блер од 8. фебруара 1916. године стоји да су најчешће болести пегави тифус, маларија, пнеумонија и туберкулоза и да је болница примила 42 пацијента, од којих је било 24 војника. Почетком априла 1916. у болници се лечило

Слика 3. Др Мери Елис Блер (1880–1962)
Figure 3. Dr. Mary Alice Blair (1880–1962)

Слика 4. Др Мери Елизабет „Епинт" Филипс (1875–1956), године 1919.
Figure 4. Dr. Mary Elizabeth "Eppynt" Phillips (1875–1956), in 1919

62 пацијента, али се осећала велика потреба за већим бројем болничког особља. Болница са комплетним женским особљем имала је поред лекарки, медицинских сестара, болничарки, рендген техничара, санитарног техничара, жене шофере, масере, администратора, куварице и праље.

Др Елси Инглис је посетила Болницу шкотских жена на Корзици априла 1916. и била је врло задовољна радом др Блер и целокупног болничког особља. Др Мери Блер је имала помоћ др Кетрин Андерсон (*Dr. Catherine Anderson*), лекарке с дипломом медицине из Абердина, која је радила у болници од 8. октобра 1915. до фебруара 1916. У мају су стигле др Едит Холвеј (*Dr. Edith Hollway*) и др Мери Филипс (*Dr. Mary Phillips*) са неколико медицинских сестара, а оне су већ имале лекарско искуство у Србији и говориле су српски језик.

Др Мери Блер је руководила радом болничке јединице Корзика од почетка организовања транспорта српских избеглица (8. октобра 1915) до септембра 1916.

Др Мери Алис Блер (*Dr. Mary Alice Blair*, 1880–1962) (Слика 3) рођена је 27. фебруара 1880. године у старој шкотској породици на Новом Зеланду, у Данидину, где је њен отац Вилијам Њушам Блер радио као виши инжењер за јавне радове од 1863. до 1890. Мери Блер је похађала Колеџ за девојке у Велингтону пре него што је уписала Колеџ Кентербери, 1898. Своје студије започела је на новоотвореном колеџу Викторија у Велингтону, али је универзитетско образовање стекла на Универзитетском колеџу у Окланду (*Auckland University College*), 1902. године. У жељи да се бави медицином, Мери Блер је отишла у Енглеску, где је студирала на Лондонском медицинском факултету за жене (*London School of Medicine for Women*). После добијених квалификација лекара и хирурга на Универзитету у Лондону, 1907. године, провела је више од двадесет година у Краљевској болници у Лондону (*Royal Free Hospital, London*), а од 1908. до 1911. била је асистент на анестезији, болнички хирург и старији асистент на педијатрији. Поред приватне праксе, прво у Кенсингтону, потом у Вестминстеру, држала је предавања и радила на Пројекту за јавну службу (*Civil Service Commision Work*) [6].

За посебне залуге у пожртвованој мисији указаној српском народу у Великом рату, Србија је одликовала др Мери Блер Орденом Светог Саве, IV реда.

Др Кетрин Емсли Андерсон (*Dr Catherine Emslie Anderson*, 1881–1934) родила се у Цејлону, у породици узгајивача чаја. Медицински факултет је завршила 1904. у Абердину (Шкотска). Диплому тропске медицине је стекла 1911. на Одељењу за тропску медицину (*Department of Tropical Medicine*) у Ливерпулу. Највеће искуство је стекла радећи у дечјој болници у Цејлону, где је и предавала дечје болести на Медицинском факултету Цејлона. У току Првог светског рата била је чланица Болнице шкотских жена у Солуну и на Корзици. Њено име се налази на меморијалној плочи Универзитета Абердин. Др Андерсон је 1921. године постала члан Краљевског удружења хирурга (*A Fellow of Royal College of Surgeon – FRCS*).

Др Мери Филипс из Ваљева

Др Мери Елизабет Филипс (*Mary Elizabeth Phillips*, 1875–1956) рођена је у Велсу, у подножју планине

Слика 5. Др Мери Филипс, лекар у Болници шкотских жена у Ваљеву и на Корзици
Figure 5. Dr. Mary Phillips, a physician at the Scottish Women's Hospital in Valjevo and on Corsica

Епинт. Завршила је медицину на Медицинском факултету Универзитета Кардиф (*Cardiff University, Medical College*) 1900. године, а лекарску праксу обавила у Краљевској болници (*Royal Free Hospital*), у Лондону. На почетку Првог светског рата др Филипс се придружила медицинској мисији у саставу Болнице шкотских жена (Слика 4). Прва служба је била у болници на Малти, где је обављала дужност лекарског помоћника др Алис Хачинсон. Била је то јединица Болнице шкотских жена која је указала помоћ великом броју рањених Аустралијанаца и Новозеланђана после битке на Галипољу.

Др Филипс је од јуна 1915. године радила у Другој јединици Болнице шкотских жена у Ваљеву (Слика 5), као лекарски помоћник др Алис Хачинсон. У Ваљеву се разболела па је 1. септембра 1915. године враћена у домовину на опоравак. После опоравка др Филипс је путовала по Великој Британији и држала предавања за промоцију деловања Болнице шкотских жена.

После повлачења српске војске преко Црне Горе и Албаније, др Филипс ће се заједно са неколико милосрдних сестара, које су већ биле у Србији, прикључити Болници шкотских жена у Ајачу, на Корзици. Са Корзике је др Филипс писала како јој је драго што је поново међу Србима, који су је топло дочекали. Српски рањеници и рековалесценти на Корзици били су срећни што је неко могао да их поздрави на матерњем језику. Др Филипс је заслужено добила титулу најпопуларније докторке међу Србима, јер је описана „као савршена лекарка у сваком погледу". Отуда није било ни чудо што је др Филипс постављена да управља Болницом шкотских жена, Јединицом Корзика на Корзици. Др Филипс је руководила Јединицом Корзика у Ајачу на Корзици од 1. маја 1916. до 4. јануара 1917.

У овом периоду др Филипс је имала велику помоћ и подршку др Едит Блејк Холвеј (*Dr. Edith Blake Hollway*, 1874–1948), која је радила у болници од 20. априла 1916. до 16. августа 1916. Др Холвеј је говорила српски јер је као лекарка Прве јединице Болнице шкотских жена радила у Крагујевцу, у време велике епидемије пегавог тифуса. Оснивањем Четврте јединице Болнице шкотских жена постављена је за руководиоца јединице у Лазаревцу. Са доласком окупације, др Холвеј се повукла у Крушевац, где ће радити у Болници „Цар Лазар", са осталим чланицама Болнице шкотских жена, под руководством др Елси Инглис.

Популарност др Мери Филипс потврђује и испраћај, када су младићи из Лазарета приредили позоришну представу и концерт. У њену част, у Ајачу, јануара 1917. године, приказана је српска верзија Молијера. Одласком није престала њена љубав према Србима. Др Филипс је као лекар асистент (*Assistant Medical Officer of Health in Merthyr Tydfil*) покренула обуку српских девојака за медицинске сестре, која је успешно обављена.

Др Елизабет Кортолд

Др Елизабет Кортолд (*Dr. Elizabeth Courtauld*, 1867–1947) рођена је као трећа ћерка Џорџа Кортолда (*George Courtauld*). Квалификовала се за медицинску сестру, али је имала јаку жељу да постане лекар. То није било лако, јер у је то време лекарска професија била привилеговано мушка професија и девојке нису имале приступ студијама медицине. Тако је Елизабет Кортолд студирала и завршила медицину на универзитету у Брислу. Пошто је обавила лекарски стаж у Краљевској болници у Лондону (*Royal Free Hospital*), добила је лиценцу лекара 1901. Након дугогодишњег боравка у Индији др Кортолд се вратила у Енглеску пре почетка Првог светског рата. Комитет Болнице шкотских жена поставио је др Кортолд за руководиоца Јединице Корзика. Запамћена је као особа која је упркос страхотама и трагедијама рата уносила оптимизам. Једном је рекла да она, као и остатак света, никад неће заборавити те године, те бројне тешко рањене војнике и уништене младости. Др Кортолд је руководила Јединицом Корзика у Ајачу највероватније од 13. јануара 1916. до краја јула 1917. По одласку са Корзике радила је у Болници шкотских жена у Рејмону, у Француској, од почетка августа 1917. до 6. марта 1919.

У болници на Корзици са др Кортолд радиле су др Хелена Џонс (*Dr. Helena G. Jones*, од 16. фебруара 1916. до 16. маја 1916) и др Софи Џексон (*Dr. Sophie Bangham Jackson*, од 30. септембра 1916. до 25. марта 1917). Др Софи Џексон је 1902. завршила медицину на Медицинском факултету у Њукаслу (*College of Medicine, Newcastle-upon-Tyne*).

Др Кортолд је носилац српских и француских одликовања *Croix de Guerre* и *Legion d'Honneur*. Носилац је два висока француска одликовања као знак признања за своју храброст да настави операцију под свећом у време непрекидне непријатељске паљбе. Као великодушан ктитор Болнице Халстед у Халстеду (Есекс), др Кортолд је 1920. поклонила 4.000 фунти, за изградњу новог амбулантног блока у знак сећања на свог оца Џорџа Кортолда. Доцније је живела у Персесу, у Гринстед Грину, где је преминула 26. децембра 1947. Хируршки блок Халстеда је недавно пресељен у новоизграђен комплекс зграда, који је понео име „Др Елизабет Кортолд" [7].

Др Матилда Макфејл

Др Александрина Матилда Макфејл (*Dr. Alexandrina Matilda MacPhail*, 1860–1946) рођена је у Шкотској на острву Скај. Медицину је студирала на Лондонском медицинском факултету за жене (*London School of Medicine for Women*), где је успешно дипломирала 1887. године. После завршених студија медицине, др Макфејл је преузела службу лекарке у медицинској мисији у Индији.

Постављена је 1888. године за првог медицинског мисионара, када се бавила организацијом лечења жена. Др Макфејл је у Мадрасу основала диспанзер за сиромашне жене и децу, потом отворила малу болницу у комплексу бунгалова и ту живела и радила годинама. Прикључила се Болници шкотских жена из Индије и, мада јој је срце остало у Индији, заволела је Србе и била је вољна да ради на Корзици. Дужност управника болнице преузела је августа 1917. У писму комитету Болнице шкотских жена она наводи да је Корзика најлепше место где је радила: „*Corsica is certainly the most beautiful place she ever worked in*". Руководила је Јединицом Корзика у Ајачу од 2. августа 1917. до 26. новембра 1917. Др Макфејл је имала у болници помоћ и подршку др Мери Грант Фергусон (*Dr. Mary Micholina Grant Ferguson*), која је радила у Болници шкотских жена на Корзици од 14. септембра 1917. до 9. новембра 1918.

Проведене године у избеглиштву и последице свих ратних страдања и страдања у повлачењу резултирале су већим бројем оболелих, што је указало на потребу за организованом здравственом заштитом. Српски потпорни фонд је помогао отварање пункта Болнице шкотских жена у Бастији, док је управа болнице поверена др Матилди Макфејл. Убрзо је у Бастији основано и Српско позориште, које је током 1917. године, трудом избеглих уметника и аматера, успешно приказивало популарне комаде из српског живота. Залагањем леди Бојл (*Lady Boyle*), а уз помоћ лорда Бојла (*Lord Boyle*) и других чланова Српског потпорног фонда, у договору са српским свештенством отворена је српска црква, одмах до болнице. У тек отвореној српској цркви у Бастији прва служба је одржана 20. марта 1917. године, када су чинодејствовали прота Божа Николић и ђакон Пешић. „Тихо јецање и плач жена, деце и стараца био је одговор на јектенија тог дана." Истовремено, мисија Српског потпорног фонда имала је своје пододборе у Швајцарској, Италији и Румунији, а сви су радили са заједничким циљем – помоћи српском народу у Србији, у избеглиштву, у заробљеничким логорима [8, 9].

После одласка са Корзике, др Макфејл је преузела дужност лекарке у Болници шкотских жена у Саланшеу, у Француској, која је као санаторијум била намењена српским студентима оболелим од туберкулозе. У Саланшеу је радила од 1. фебруара 1918. до 1. новембра 1918.

После Првог светског рата вратила се у своју вољену Индију, али ће се радо сећати српске младости на Корзици, којој је дала обећање да ће једног дана посетити Србију.

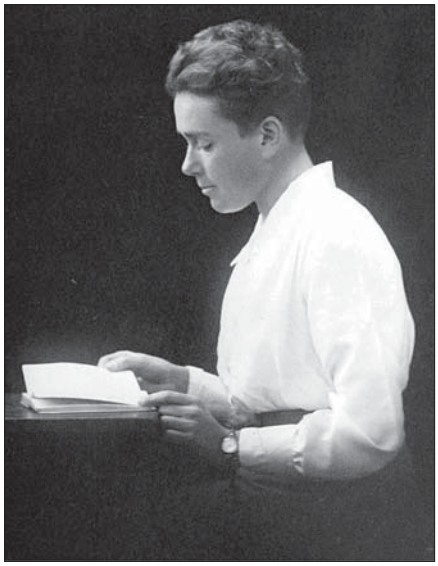
Др Една Гест

Др Една Мери Гест (*Dr. Edna Mary Guest*, 1883–1958) рођена је 1883. у Лондону, у канадској држави Онтарио. Завршила медицину на Универзитету Торонто у Торонту, 1910. године. После постдипломских студија на Универзитету Харвард и лекарског стажа у Болници за жене и децу у Бостону, др Гест се придружила Канадској медицинској мисији у Индији (*Ludheana*), где је радила као професор анатомије и доцент на хирургији на Медицинском факултету за жене (*Women's Medical College*). Мада је на почетку Првог светског рата одбијена да као лекарка буде у саставу санитета, доцније у току рата постала је члан хируршке екипе у чину капетана у болници Нортхемптоншир у Хјустону (Енглеска), где је радила од 1915. до 1917. године. Др Гест, лекарка мисионар с великим медицинским искуством, радо се одазвала позиву Комитета Болнице шкотских жена. Тако је др Гест постављена за руководиоца Јединице Корзика и радила од 31. октобра 1917. до 9. јануара 1918. Одласком са Корзике, др Една Гест је преузела место лекара у Болници шкотских жена у Рејмону, Француска, где је провела мало времена (од 1. јула 1918. до 1. августа 1918) (Слика 6).

Слика 6. Др Една Мери Гест (1883–1958)
Figure 6. Dr. Edna Mary Guest (1883–1958)

После Првог светског рата др Гест се вратила у Канаду и 1919. отворила приватну праксу. Др Гест је била прва жена која је ангажована у новооснованој медицинској служби у Торонту у Болници медицинског факултета (*Women's College Hospital*). У овој болници др Гест је постала шеф Специјалног одељења за венерична обољења (*Special Department of Venereal Disease*).

За посебне заслуге хуманости у медицинској мисији др Една Мери Гест је одликована Орденом Британске империје (*OBE – the Order of British Empire*).



Слика 7. Др Онорија Самервил Кир (1883–1969)
Figure 7. Dr. Honoria Somerville Keer (1883–1969)

Слика 8. Српски ученици и студенти у Француској
Figure 8. Serbian schoolboys and students in France

Слика 9. Српски ученици у Француској
Figure 9. Serbian schoolboys in France

Као велики борац за равноправност жена и положај жена лекара у Канади, бирана је 1940. и 1941. године за председницу Федерације жена лекара Канаде (*Federation of Medical Women of Canada*) [10].

Др Онорија Кир

Др Онорија Самервил Кир (*Dr. Honoria Somerville Keer*, 26. децембар 1883 – 20. март 1969) рођена је у Торонту (Канада) од мајке Елајзе Самервил и оца генерал-мајора Џонатана Кира. Дипломирала је медицину и хирургију на Медицинском факултету за жене у Глазгову, 1910. године. Извесно време радила је као лекарка у Хамилтону, а са почетком Првог светског рата придружила се Болници шкотских жена (Слика 7).

Др Кир је била у саставу Јединице Гиртон и Њунам, која је почела са радом у Француској, потом пребачена у Ђевђелију, а завршила у Солуну, на Солунском фронту. Др Кир је у саставу ове јединице радила од 8. маја 1915. до 21. јануара 1918. Јединица Гиртон и Њунам у Солуну, под управом др Ен Луизе Макилрој (*Dr. Anne Louise Mcllroy*, 1874–1968), одиграла је значајну улогу у лечењу српских рањеника након Горничевске и Кајмакчаланске битке. Касније је јединица постала позната по оснивању Ортопедског центра Калкута (*Calcutta Orthopaedic Centre*), који се бавио лечењем српских рањеника и инвалида. По ослобођењу, др Макилрој је основала Ортопедски центар за српске инвалиде, код Београда, испод Авале.

Др Кир је у Ајачу на Корзици руководила Јединицом Корзика, Болнице шкотских жена, која је лечила и неговала српске избеглице на Корзици. Др Кир је радила на Корзици од 8. маја 1918. до 15. јануара 1919 [7, 10].

У Болници шкотских жена је приређена велика свечаност поводом Божића, на дан 25. децембра 1918. Рањени и болесни војници су добили поклоне од становника Бастије, а после заједничке закуске приређен је концерт. Пригодна свечаност је окупила велики број српских избеглица, чланице Болнице шкотских жена, Српског потпорног фонда, локално становништво Бастије, српско свештенство, наставнике и ученике из Лицеја. Посебно је био запажен хор српских ђака, који је певао патриотске и народне песме из старог краја, о чему су писали и бастијски листови. У Српској цркви у Бастији припадници српске избегле колоније приредили су и свечаности за Видовдан и Петровдан 1918. са свечаним литургијама и благодарењима у част рођендана Њ. В. краља Петра I [6] (слике 8 и 9).

Др Кир је била последња управница болнице у Ајачу, јер је болница затворена у пролеће 1919. Повратком српских избеглица у домовину престала је потреба за овом врстом болничке установе.

После Првог светског рата др Кир је краће време радила у болници у Ланарку, у Шкотској. Године 1924. стекла је диплому тропске медицине и постала лекар у државној болници у Нигерији. Носилац је два висока француска одликовања: *Croix de Guerre* и *Medaille d' Honneur*. Србија је др Онорију Кир одликовала Орденом Светог Саве.

Поред др Онорије Кир на Солунском фронту и Корзици, и др Едне Гест на Корзици, у саставу Болнице

шкотских жена велики број Канађана, лекара и другог медицинског особља пожртвовано је помагао српским војницима у канадским болницама на Солунском фронту [9].

Са Корзике, болничарка Агнес Патерсон (*Agnes Paterson*) писала је својима: „Ајачио је дивно место, палме, наранџе, лешници, и смокве поред путева. Нажалост и врло топло место. Имали смо две болнице, једну велику 'општу' која је исто тако лечила рањене војнике, а служила и као породилиште за Србе... Наша друга болница била је за инфективне болести, грозницу, тифус итд. и увек смо имали неколико тешких болесника... Сви смо били јако сложни и срећни у целој јединици. Често би на крају дана, када је претопло и кад смо сви преморени да се одвучемо на спрат, седели и певали заједно. То подстиче наше расположење и умањује носталгију за домовином“ [3]. „Медицинске сестре и болничко особље су савршено радили и заслужују све похвале“ [3].

Тако су пролазили дани, месеци, године у борби за живот избеглих и прогнаних. А њихови једини погледи наде су били упрти у небо и њихове спасиоце, лекаре и сестре.

Захвалница

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Serbs on Corsica in the Great War – Part 2

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SUMMARY

Historians and historical research of the role of the Serbian nation in the Great War give ample respect and recognition of the great battles and great victories. However, the exodus of the Serbian people and its armies out of Serbia is also not forgotten. Neither are the Salonika Front, nor other battlefronts. Less well known and researched is the fate of 35,000 young Serbian recruits, the young people dispersed to distant lands.

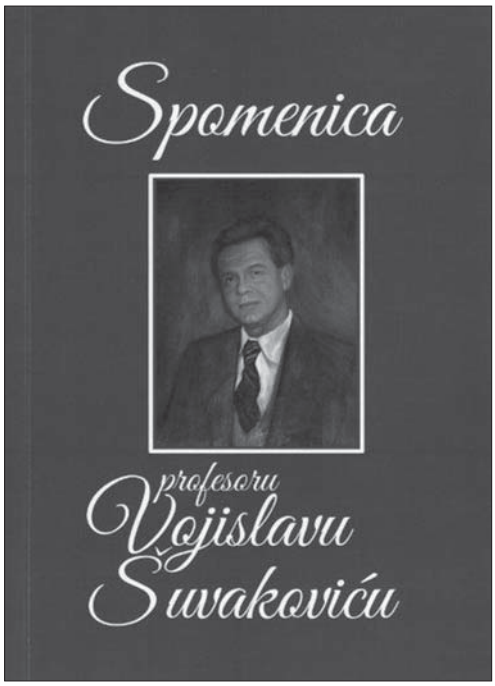
This research is concentrated on the fate of the Serbian refugees in Corsica, on those who helped them, looked after them, and treated them to recovery, and who themselves came there from other parts of the world. Those Serbian refugees in Corsica were looked after by the representatives of diplomatic, humanitarian, and medical missions from Serbia, France, and Great Britain. The life of the Serbian refugee colony in Corsica was organized, financed, and supported by the Royal Serbian Government in exile in France, the French Relief Committee for the wounded, sick, and refugees, the Serbian Relief Fund, the Scottish Women's Hospitals for Foreign Service, the local authorities, and numerous individuals in Corsica.

We have paid particular attention to the Scottish Women's Hospital in Corsica that provided a special hospital unit called "Corsica Unit," situated in Ajaccio, with the isolation ward in Lazaret, and ambulances and dispensaries located in various villages, where the Serbian refugees were billeted. At the time of centennial commemorations of the Great War, we want to express our profound gratitude to the humanitarian and medical assistance from all quarters, and in particular to the Scottish Women's Hospitals, and Dr. Elsie Inglis, the founder and the leader of this medical mission.

Keywords: World War I; French medical help; Serbian Red Cross; Serbian Relief Fund; Scottish Women's Hospitals; Corsica; Serbia; Inglis E

ПРИКАЗ КЊИГЕ / BOOK REVIEW

Споменица професору Војиславу Шуваковићу (A tribute to Professor Vojislav Šuvaković)



Приредили: Стеван Баљошевић и Миодраг Павловић
Аутори: Владимир Кањух, Марија Вукотић, Стеван Баљошевић, Стеван Литвињенко, Миодраг Павловић, Бранко Брмболић, Радослав Катанић, Марија Богдановић (Библиографија радова)
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УВОД

Могућност да напишем приказ књиге као што је „Споменица“ доживљавам као посебну привилегију. Но, то је такође и велика одговорност која се не умањује тиме што ћу имена која помињем само по добру помињати а о личностима говорити онако како су колеге и сарадници говорили.

Како сам наслов „Споменица“ каже, књига је посвећена проф. др Војиславу Шуваковићу.

Иако обухвата шири контекст, то је превасходно књига о једном човеку „који је био и отац и син и муж и лекар, виноградар и илегалац и ратник и професор, а надасве добар човек, који је знао поштовати медицинску традицију, али је показивао и непоколебљиво интересовање за све што је ново у медицини“ (Б. Брмболић, „Споменица“, страна 81)

ОПШТИ ПОДАЦИ О КЊИЗИ

„Споменица“ је штампана на 132 странице у које улази 60 фотографија, као и списак од 260 библиографских јединица чији је аутор проф. др В. Шуваковић (књига, сепарата, чланака, постера, кратких садржаја радова, рецензија и превода).

Тематски се у „Спомениици“ може издвојити пет блокова које у јединствену целину повезује личност и рад проф. Шуваковића. Ти блокови су:

– Проф. др В. Шуваковићу у споменсећање колега и сарадника, укључујући и последње речи опроштаја;
– Инфективне болести, у чије савлађивање је уложено много знања, искуства и самопрегорног рада (текст о маларији);
– Сарадници и пријатељи (текст о проф. др Миомиру Кецмановићу);

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– Земља, народ, политичка ситуација, укупни амбијент у коме се живело и радило.

Наша пажња у даљем приказу биће превасходно усмерна на први блок.

ВОЈИСЛАВУ ШУВАКОВИЋУ У СПОМЕН, СА ПИЈЕТЕТОМ

„Био је изузетно добар, племенит и хуман човек, неустрашиви успешан организатор и борац против смртоносних епидемија у нашој земљи, одличан стручњак-инфектолог, талентовани професор-педагог и признати научник у области инфектологије“ (В. Кањух, „Споменица“, стр. 19).

Основни биографски подаци нам казују да је рођен 1925. године у Београду, где је завршио основну школу и гимназију. Током немачке окупације као члан СКОЈ-а био је хапшен и затваран. Народноослободилачкој војсци Југославије прикључио се 1944. године, а 1945. постаје члан Комунистичке партије.

Медицински факултет у Београду уписао је 1945. године, а завршио 1951. „Био је одличан студент и имао је лепе манире. ... Шуле је био изузетно поштен човек и познато је међу студентима да он лично никада није урадио ништа лоше другима, колико ја знам сви га памте по добру, а за остале комунисте са нашег факултета не би се могло рећи исто“ (М. Вукотић, „Споменица“, стр. 24).

Био је један од најбољих студената своје генерације, демонстратор на физици и патологији који је својим изванредним педагошким способностима приближио материју студентима. Изабран је за асистента на Медицинском факултету у Београду 1959. године, 1969. за доцента, 1975. за ванредног професора и 1981. за редовног професора.

Цивилно је мобилисан и распоређен на Косово 1951. године. Тамошња здравствена ситуација била је веома тешка, а здравственог кадра било је веома мало.

„Др Војислав Шуваковић био је први лекар у Призрену и на Косову и Метохији који је положио специјалистички испит из града где је радио савесно, предано и врло успешно...

Иако млад, др Шуваковић је својом сталном медицинском активношћу постао важна јавна личност у граду, омиљен у свим националним срединама. Био је врло поштован и прихваћен јер је имао слободу да изрази своје виђење ствари и у медицинској професији и уопште о животним питањима тог времена“ (С. Баљошевић, „Споменица“, стр. 31, 32).

У Призрену се бавио проучавањем антракса (из ове области је и докторирао), а 1962. учествује у сузбијању тифуса у Приштини. Био је стипендиста СЗО 1963. године у Индији, где се посебно бавио проучавањем и сузбијањем великих богиња (*Smallpox Control*). Тада је овладао сазнањима која је на највишем професионалном нивоу употребио на Косову 1972. године и дао огроман допринос сузбијању епидемије ове опаке болести.

„Др Војислав Шуваковић и проф. др Миомир Кецмановић су данонoћно опсервирали болеснике и сумњиве случајеве, прописивали терапију, интервенисали у свим компликованим случајевима болести, одржавали контакте са експертима из других земаља и експертима СЗО. Врло често је др Шуле био на терену у кућама лежећих болесника и њиховој околини и својим одлучним ставом храбрио становништво да се вакцинише на време. ... Дежурао је и био у приправности без икаквог ограничења и био пример свим члановима карантинске заједнице у Ђаковици. Добио је значајна државна признања и у то време постао легендарно име у борби против ове тешке болести. ... Истицан је као пример великог хуманисте и експерта који је преносио своје знање, динамику и енергију у лечењу болесника од вариоле вере“ (С. Баљшевић, „Споменица“, стр. 39).

Од 1978. до 1979. године био је директор Клинике за инфективне и тропске болести у Београду. Према М. Павловићу („Споменица“, стр. 100), био је запамћен као директор који је пружао руку младима, стимулисао их да препознају модерне медицинске путеве, поштујући њихове напоре да се радом потврде, не замерајући онима који су његову благонаклоност често заборавили. Одлази у Нигерију 1979. године, где се бави лечењем тропских болести – посебно маларије.

Први је у СФРЈ схватио опасност и комплексност ХИВ инфекције/АИДС-а и написао прву популарну књигу о томе. Оснивач је првог одељења за лечење оболелих. „Посебно смо се дивили Вашој медицинској знатижељи, коју је крунисао пионирски рад на пољу АИДС-а у периоду када су се заплашени том пошашћу сви од ње клонили“ (М. Павловић, „Споменица“, стр. 100).

Био је редовни члан Академије медицинских наука од 1983. године, омиљени и поштовани професор, ментор бројних магистарских и докторских теза.

Умро је фебуара 2010. године.

У ЧЕМУ ЈЕ ЗНАЧАЈ ОВЕ КЊИГЕ

„Споменица“ страну по страну, текст по текст попуњава портрет Војислава Шуваковића, као мозаик састављен од безброј драгоцених коцкица. Многе нисмо поменули, а све их је немогуће приказати.

Тај бард српске инфектологије (М. Павловић, „Споменица“, стр. 100) израста кроз текстове ове књиге, надахнуто и топло написане, у ренесансни лик лекара, педагога, ЧОВЕКА. Говорио је француски, енглески, немачки и италијански језик, био је спортиста-лакоатлетичар, побеђивао на шаховским турнирима, учио студенте медицине и друге здравствене раднике, лечио људе, бавио се експерименталним радом на антраксу, гасио пожаре епидемија свуда где је позиван, бавио се, поред инфективних болести, хепатологијом и тропском медицином, високо поштовао и придржавао се етичких принципа своје професије, остао веран својим младалачким идејама о једнакости и социјалној пра-

вди, знатижељно и са ентузијазмом тежио новинама, волео људе, колеге, пријатеље и своју породицу, био прихваћен, цењен и вољен.

Велико и прелепо за један људски век.

Све је то „Споменица“ сачувала на страницама књиге: сећања на људе, догађаје, лепоту земље Србије, истрајност у борби за боље здравље људи и за савремену медицинску науку, упркос бројним препрекама. Сачувала је, такође, значајне информације о развоју српске (југословенске) инфектологије у другој половини XX века, те тиме представља допринос развоју историје медицине у нас.

Сећања су подстрек за младе на факултетима и школама као и за све здравствене раднике, јер садрже практичне примере живота и рада који су били и остали у складу са тековинама медицинске науке и принципима етике лекарског позива. Странице књиге „Споменица“ остају да подсећају будуће генерације на те вредности.

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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 (научни и стручни) радови, метаанализе, прегледни радови, претходна и кратка саопштења, прикази болесника и случајева, слике из клиничке медицине, видео-чланци, радови за праксу, актуелне теме, радови из историје медицине и језика медицине, лични ставови, наручени коментари, писма уреднику, прикази књига и други прилози. Оригинални радови, претходна и кратка саопштења и прикази болесника и случајева 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.

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, метаанализу, 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, претходна и кратка саопштења и метаанализе сажетак треба да има следећу структуру: Увод/Циљ, Методе, 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 (нпр. рад из историје медицине, језика медицине и др.), потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик. Сажетке и радове који су у целости на српском језику аутори из Србије треба да пишу ћирилицом.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад, метаанализа, претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор метаанализе и прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (*°C*), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада – који чине насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, претходно и кратко саопштење, рад из

историје медицине и преглед литературе до 5.000 речи, а за приказ болесника, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3.000 речи; радови за остале рубрике могу имати највише 1.500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату avi, *mp4 (flv)*. У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

ТАБЕЛЕ. 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. 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. 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.

СХЕМЕ (ЦРТЕЖИ). 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, а у метаанализи 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 публикације 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. Примери 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.

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