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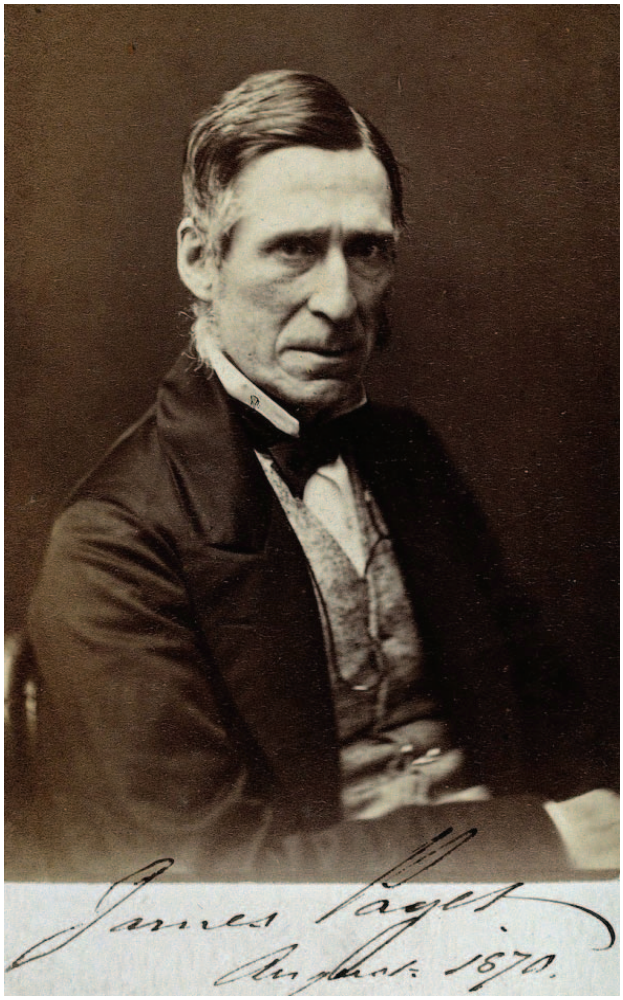

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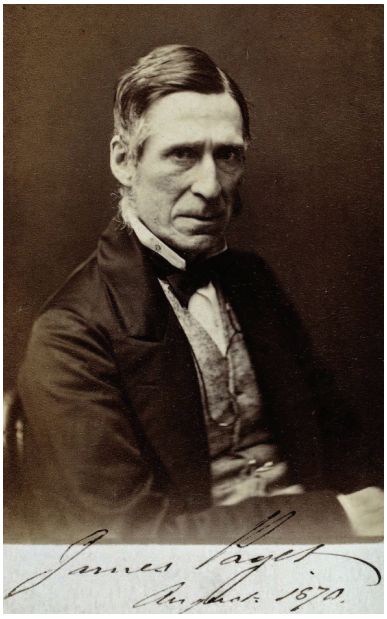

Sir James Paget (January 11, 1814 – December 30, 1899) was a fameous English surgeon and pathologist who is considered as one of the founders of scientific medical pathology. He is best remembered for describing two conditions named after him: Paget's disease of the bone (osteitis deformans), and Paget's disease of the nipple (a form of intraductal breast cancer spreading into the skin around the nipple), but there are several medical conditions which were described and later named after Paget, too: Extramammary Paget's disease (a group of similar, more rare skin lesions which affect male and female genitalia), Paget-Schroetter disease (a form of upper extremity deep vein thrombosis) and Paget's abscess (an abscess that recurs at the site of a former abscess which had resolved).
This year, on January 11th, it would be 205 years since he was born, and at the end of the same year, on December 30th, it would be 120 years since he died.

Sir James Paget (11. januar 1814 – 30. decembar 1899) bio je slavni engleski hirurg i patolog koji se smatra jednim od osnivača naučne medicinske patologije. Najviše je poznat po opisu dva stanja koja nose njegovo ime: Paget-ova bolest kostiju (*osteitis deformans*) i Paget-ova bolest bradavice dojke (oblik intraduktalnog raka dojke koji se širi na kožu oko bradavice), ali postoje i druga stanja koji je on takođe opisao i koja su kasnije nazvana po njemu: ektramamarna Paget-ova bolest (grupa sličnih, retkih kožnih lezija na muškim i ženskim genitalijama), Paget-Schroetter-ova bolest (oblik duboke venske tromboze gornjih ekstremiteta) i Paget-ov apsces (apsces koji se ponovo javlja na mestu bivšeg, prethodno rešenog apscesa).
Ove godine, 11. januara, navršava se 205 godina od njegovog rođenja, a krajem godine, 30. decembra, 120 godina od njegove smrti.

E D I T O R I A L

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The *Vojnosanitetski Pregled* in 2019 – continuing a tradition of quality

Vojnosanitetski pregled u 2019 – nastavak tradicije kvaliteta

Silva Dobrić

University of Defence, Institute for Scientific Information, Belgrade, Serbia

In 2019, the *Vojnosanitetski Pregled* (VSP) will celebrate the great jubilee – 75 years of continuous release. During that period, the VSP underwent many changes. Having been, the journal, whose primary goal was to inform members of the military medical care about novelties from the field of medicine, pharmacy and dentistry as well as to familiarize the wider professional public with the work of military physicians and pharmacists, it developed into the leading national medical journal, and, when it was admitted to the Science Citation Index Expanded (SCIe) database in 2008, it became an international journal. This is, undoubtedly, the result of the continuous work of the Editorial Staff and the Editorial Board of the Journal on raising its quality and ensuring the highest possible visibility in domestic and foreign scientific and professional community. Today, it is considered prestigious to publish a paper in the VSP, so it has been long since it ceased to be only a journal for military doctors and pharmacists. Moreover, in recent years, the papers of the authors from so-called civil medical and academic institutions from the country and abroad have manly been published in it. Their number particularly increased after the inclusion of the VSP into the list of journals indexing in the SCIe database and obtaining an impact factor. As its value grows from year to year, it is not surprising that the number of papers submitted to the VSP Editorial Office for consideration for publication keeps on increasing. Over the past few years, this number has been in the range of 300 to 400 per year, which means that almost every day, at least one manuscript is submitted to the VSP Editorial Office.

In 2018 (till December, 20th) a total of 332 manuscripts were received, of which 75% were from the authors from domestic civil institutions, 14.75% from the authors working at military institutions (mainly at the Military Medical Academy in Belgrade) and 14.75% from the authors from abroad. This is in line with the data from previous years, with the exception of somewhat higher inflow of papers from abroad which is an indicator of increasing influence of the Journal on the international scientific community. Of the received papers, slightly more than 35% were rejected, 33% were accepted for publication while the remaining one third is still in the review process. As in previous years, the largest number of submitted manuscripts belonged to the category of Orginal Articles (71.4%) and Case reports (22%), followed by those from the General Review category (2.4%), History of Medicine (1.5%), Letter to the Editor (1.2%), Practical Advices for Physicians (0.6%), Meta-analysis (0.3%) and Book Review (0.3%).

Similarly, the number and structure of papers published in the VSP in 2018 did not differ significantly from those published in the previous years. As it can be seen from Table 1, a total of 179 different articles were published in 12 issues last year, of which, again, most of them were Original Articles (57%) and Case reports (20.7%). Also, in the last year, 202 articles were published in the electronic version, as Online first with a DOI number in the so-called "raw" form meaning that they were not professionally, linguistically and technically edited. These papers will subsequently be published in some of the printed issues of the Journal in accordance with the established order, but they are presently available to readers and can be cited with reference to the DOI number.

Table 1

Categories and the number of articles published in the Vojnosanitetski Pregled in 2018

Category	Articles	
	n	%
Editorial	2	1.1
Original Article	102	57
General Review	6	3.3
Current Topic	4	2.2
Practical Advice for Physicians	1	0.6
Case Report	37	20.7
Short Communication	17	9.4
In Focus	1	0.6
History of Medicine	1	2.8
Letter to the Editor	4	2.2
Meeting Report	1	0.6
Book Review	3	1.7
Total	179	100.0

Correspondence to: Silva Dobrić, University of Defence, Institute for Scientific Information, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: vsp@vma.mod.gov.rs

Table 2

Reviewers of the *Vojnosanitetski pregled* in 2018

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Zeba Snježana

Živković Solavoljub
Živković Vladimir
Životić Vanović Mirjana

The highest number of published papers in 2018, as in the previous years, was from the authors working at civil institutions (68.2%), including the authors from abroad (14.5%) while 7.8% of the papers was written by the authors from military medical institutions. The remaining papers were co-written by the authors from civil and military medical institutions. The number of published articles by the authors from abroad increases every year, and, hopefully, this trend will continue in the years to come.

In 2019, it will be continued with the already established practice that from the submitted manuscripts in the further review process will be forwarded, exclusively those ones that bring something new, which are technically well-prepared and have previously passed the check on (auto)plagiarism. Experience shows that such papers are more cited which is the best indicator of their value. This has always been the practice of the VSP Editoril Board, so there is no wonder that we are now getting requests from readers to send them articles from some of the earlier issues of the Journal that were not yet in the open access to the Internet. Therefore, this year we will begin scanning the previous volumes of the VSP to make them available to interested readers.

At the end, as always, I would like to express my deep gratitude to all members of the Editorial Board, Editorial Staff and our respected authors and peer reviewers who, every year, make a great effort in increasing the quality of the Journal. This specially refers to the peer reviewers – having in mind that without a good review, there are no quality papers, and therefore no quality journals. Therefore, I would like to thank all the reviewers who participated in the review process for the VSP in 2018 (Table 2) with the hope that we would continue this cooperation in 2019, too. On this occasion, I would particularly thank Prof. Slobodan Obradović, Prof. Ljubomir Todorović and Prof. Gordana Dedić who carried out most reviews for our Journal in 2018.

ORIGINALS ARTICLES

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Laser hemorrhoidoplasty versus Milligan-Morgan hemorrhoidectomy – short-term outcome

Poređenje hemoroidektomije laserom i hemoroidektomije metodom Milligan-Morgan – kratkoročni rezultati

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Abstract

Background/Aim. According to the "vascular" theory, arterial inflow into the upper hemorrhoidal artery leads to venous dilatation of the hemorrhoidal plexus. Laser hemorrhoidoplasty (LHP) is a new treatment applied to outpatients in whom the hemorrhoid arterial blood flow is coagulated (nourishes by hemorrhoidal plexus) by laser. The aim of this study was to compare two groups of patients treated by two different methods: by laser (LHP) and with open surgical procedure – the Milligan Morgan (MM) method. **Methods.** This study included 200 patients with grade 3 hemorrhoidal disease older than 18 years, divided into two groups: 100 patients treated with the LHP, while the other 100 patients with the MM hemorrhoidectomy. Parameters used to compare two applied surgical methods were: duration of hospitalization, postoperative pain, the presence of bleeding and time needed to return to normal life. **Results.** The results reveal a statistically significant difference between these two methods. The level of postoperative pain was lower in the group of patients treated with the LHP compared to the group of patients treated with the MM method ($p < 0.0001$). The group treated with the LHP manifested less bleeding in comparison with the group treated with the open surgical method (MM). Length of hospitalization and duration of surgery were significantly shorter in the group treated with the LHP method than in the group treated by the MM method. **Conclusion.** According to our results, it is clear that the LHP method has many advantages over the MM hemorrhoidectomy in patients with grade 3 hemorrhoidal disease.

Key words:
hemorrhoids; laser therapy; surgical procedures, operative; postoperative period; postoperative complications.

Apstrakt

Uvod/Cilj. Prema "vaskularnoj" teoriji arterijski priliv u gornjoj hemoroidalnoj arteriji dovodi do dilatacije hemoroidalnog venskog pleksusa. Laser hemoroidoplastika (LHP) je novi postupak primenjen u ambulantnom lečenju hemoroida u kojem se hemoroidalni arterijski protok krvi koji ishranjuje hemoroidalni pleksus zaustavlja laserskom koagulacijom. Cilj ove studije bio je poređenje između grupa bolesnika lečenih sa dve različite metode, laserom (LHP) i sa otvorenom hirurškom metodom – Milligan Morgan (MM). **Metode**. U ovu studiju bilo je uključeno 200 bolesnika sa hemoroidima trećeg stepena, starijih od 18 godina, od kojih je 100 bilo tretirano LHP metodom, dok je ostalih 100 bolesnika tretirano Milligan-Morgan hemoroidiektomijom. Parametri koji su se koristili za poređenje dve hirurške metode bili su: dužina hospitalizacije, postoperativni bol, prisustvo krvarenja i vreme potrebno da se bolesnici vrate normalnom životu. **Rezultati.** Rezutati su pokazali statistički značajnu razliku među metodama. Nivo postoperativnog bola bio je niži kod bolesnika u grupi lečenih LHP u odnosu na grupu bolesnika lečenih MM metodom ($p < 0{,}0001$). U grupi tretiranoj metodom LHP, krvarenje je bilo manje u odnosu na grupu koja je tretirana otvorenom hirurškom metodom (MM). Trajanje operacije, kao i dužina hospitalizacije bili su znatno kraći u grupi sa hemoroidoplastikom (LHP) u odnosu na grupu sa hemoroidektomijom (MM metoda). **Zaključak.** Dobijeni rezultati upućuju na značajne prednosti LHP metode u odnosu na metodu Milligan Morgan kod bolesnika sa hemoroidima trećeg stepena.

Ključne reči:
hemoroidi; hirurgija laserom; hirurgija, operativne procedure; postoperativni period; postoperativne komplikacije.

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Introduction

Hemorrhoidal disease is ranked much higher than the rectum and colon diseases. Today, the presence of hemorrhoidal disease is evaluated to be between 2.9%–27.9% among the worldwide population and 4% are symptomatic. One third of the total number of patients ask for medical advice [1, 2].

Based on the Gauss method the highest incidence rate of the disease is found among patients aged between 45 and 65 years, while the incidence rate of the disease decrease after 65 years of age [3, 4]. Men are more often affected than women [5].

Anorectum vascular cushions together with the internal anal sphincter are essential in maintaining continence by supporting the soft tissue in the closure of the anal canal [6, 7]. Different options for the treatment of symptomatic hemorrhoids varied over the time. The measures include a variety of conservative medical procedures, non-surgical treatment and various surgical methods. Various non-surgical procedures include rubber band ligation (RBL), sclerosing injection, cryotherapy, infrared coagulation, laser therapy and coagulation by diathermy as well as a therapeutic procedure that can be applied without anesthesia. The non-surgical methods mentioned above are considered as primary option in hemorrhoids level I–III treatment [8]. If conservative methods are not successful, patients are treated surgically. Significant factors in setting the indications for surgical treatment are: papilla hypertrophy, associated fissure, thrombotic enlargements and recurrent symptoms after RBL. The Milligan-Morgan (MM) hemorrhoid ectomy is the gold standard and often applied procedure in the United Kingdom [9].

Hemorrhoidectomy is an extremely painful procedure. Pain is caused by damaging the tissue of the anal region which is richly innervated by nerve endings. Postoperative pain is the most common problem in surgical treatment.

The aim of this study was to compare the postoperative results: pain, bleeding, infection, recidive, urinary retention, hospitalization period, return to normal life and satisfaction of patients after treatment with the laser hemorrhoidoplasty (LHP) or MM methods.

Methods

This comparative and prospective study included 200 patients with grade 3 hemorrhoidal disease where 100 patients were treated with the LHP while the other 100 patients were treated with the MM hemorrhoidectomy method.

The study was done at the Surgical Clinic ALOKA, Pristina, from June 2014 to May 2015. Control and follow-up of the patients was done during week 1, 2, 3, 4 and after 8 weeks (60 days).

All operations were performed by one surgeon. General anesthesia was applied on a patient's request. Preoperative treatment such as proctoscopy and sigmoidoscopy followed by the laser procedure using Bio-Litec equipment were included in all cases treated bz the LHP method.

Exclusion criteria were applied in case when a patient was younger than 18 years as well as when a patient had hemorrhoids and another condition in the anus (fissure, fistula, perianal abscess).

The perianal area was shaved and patients from both groups recived cleansing with bisocodyl supp. 1 × 2. The patients were treated in gynecological position. Anoscop was applied and followed by the laser procedure using Bio-Litec equipment with a diode (Bonn, Germany), which operates at a wavelength of 980 ± 30 nm with optical power of 8–15W (Pulse Mode) that is sufficient for the denaturation and reduction of hemorrhoidal plexus (Figure 1).

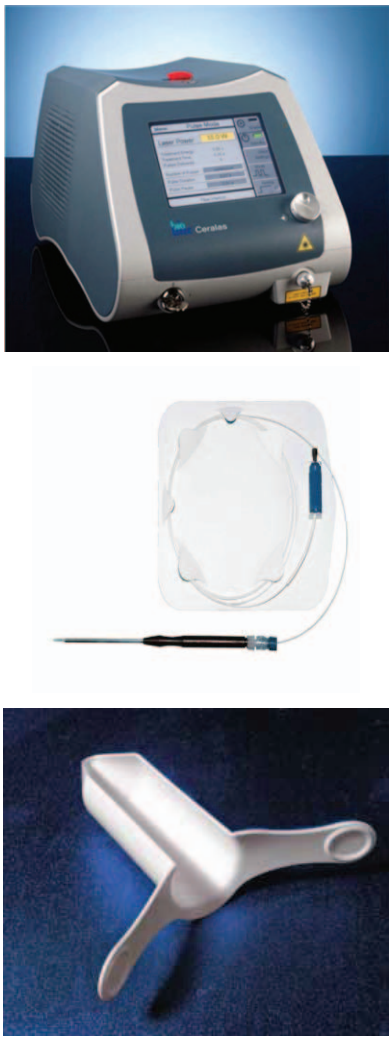


Fig. 1 – Laser, diode 980-nm and anoscope.

In the LHP technique, the energy created by the laser was transmitted to the place we wanted to treat through the optical fiber. LED lighting equipment can help to determine the diameter of the shape and the length of the treatment as well as the duration of the procedure. First, we provided a small skin incision about 1 to 1.5 cm distance from the anal edge concentrically for about 4 to 5 mm and performed the perianal skin/anodermis, tunneling with scissors to the edge of the internus. The pointed laser probe was then quickly driven subanodermally/ submucosally until it reached the area underneath the distal rectal mucosa. This was followed by about six pulses (adjusted to respective dimensions of the piles) of approx. 30 joule per node; a half of which was

highly submucosal and the other half highly intranodal. The tissue response could be clearly discerned by the light reduction: contraction was occasionally observed immediately (Figure 2). Hemorrhoidal nodes were not treated with the LHP method since this method was applied only to the hemorrhoidal plexus without ligature or any other procedure.

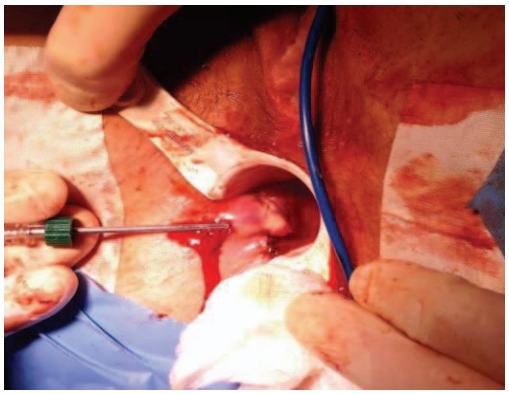


Fig. 2 – Laser hemorrhoidoplasty procedure.

In the MM technique all the patients were operated on in the lithotomy (prone) position and general anesthesia.

A V-shaped incision by the scalpel in the skin around the base of the hemorrhoid was made using scissors dissection in the submucous space to strip the entire hemorrhoid from its bed (Figure 3). The dissection was carried cranially to the pedicle which was ligated with a strong catgut and the distal part excised. Other hemorrhoids were similarly treated, leaving a skin bridge amid to avoid stenosis (Figure 3). The wound was left open and a hemostatic gauze pad was left in the anal canal.

Postoperative pain, bleeding, delayed healing and acute urine retention were common complications.

Both the LHP and MM hemorrhoidectomy were performed under general anestesia.

Assessment of postoperative pain

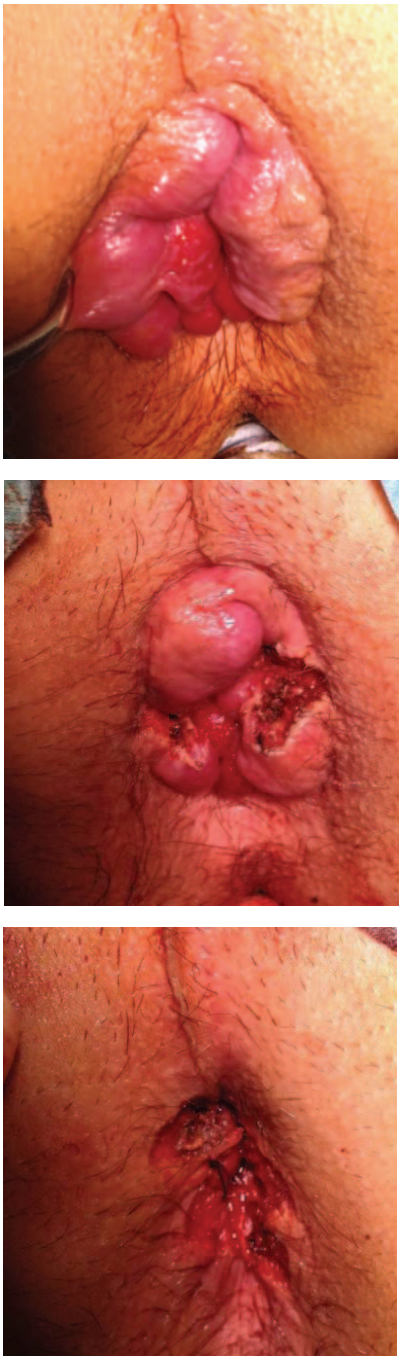
Postoperative pain was evaluated using the visual analogue scale (VAS 0-10) where 0–1 represented no pain, 1.1–3 less pain intensity, 3.1–7 pain of medium intensity, 7.1–9 pain of high intensity and 9.1–10 strong, unbearable pain. The VAS protocol was performed on the days 1, 7, 14, 21, 30, and 60 after surgery.

All the patients recieved analgesics - diclofenac 75 mg 2 × 1 intravenously (*iv*) if needed. In case of persisting pain, trodnadol 50 mg 3 × 1 *iv* were used as needed. Control of the patients for bleeding was carried out in weeks 1, 2, 3 and 4, and during the following first and second month after treatment as well as at any time in case of major bleeding.

Statistical analysis was performed by the χ^2 test and Mann-Whitney test.

Results

This prospective study was based on 200 patients where 121 (60.5%) were males and 79 (39.5%) were females. There were two different methods used in their treatment – the LHP and MM hemorrhoidectomy From the overall number of patients (200) with grade 3 hemorrhoids, a half (100) was treated with the LHP method. The average age of the patients was 47 ± 12.6 years (range 24–70 years). The procedure was performed in 57 males and 43 females. The MM procedure was applied on other 100 patients out of whom 64 were males and 36 females aged 49 ± 12.3 years. There was no difference between these two groups of patients regarding age. Also, we found homogeneity in the groups regarding gender where the χ^2 test showed 0.88 value.



a)

b)

c)

Fig. 3 – Hemorroids: a) before the operation; b) during the operation; c) after the operation.

Figure 4 shows in detail the results of postoperative pain development in two groups treated with two different methods: the LHP and the MM method.

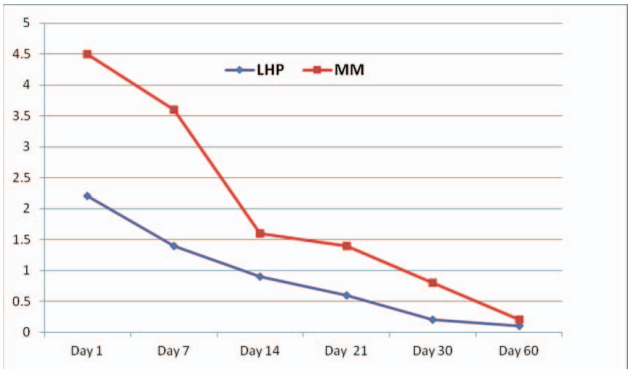


Fig. 4 – Results of postoperative pain in the laser hemorrhoidoplasty (LHP) and Milligan Morgan (MM) groups according to VAS during 60 days after the intervention ($p < 0.0001$).

As we can see, after hemorrhoidal intervention with the LHP method, the level of postoperative pain on the day 1 was on average 2.2 (SD ± 0.3) (VAS). On the other hand, after hemorrhoidal intervention with the MM method, the average pain level was 4.5 (SD ± 0.8). On the day 30, in the LHP group, the average level of pain or VAS was 0.2 (SD ± 0.1) while in the MM group it was 0.8 (± 0.2 SD). The same values were after 60 days. Postoperative pain was significantly lower in the LHP group than in the MM group ($p < 0.0001$).

During the first days after the intervention, 13% of the patients in the LHP group and 77% of the patients in the MM group had small scale bleeding which was statistically significant ($p < 0.0001$). Bleeding was present with statistically significant difference ($p < 0.001$) on the day 7 (10% of the patients in the LHP group and 33% of the patients in the MM group).

On the day 60 after the intervention, there was no bleeding in any of the groups (Figure 5).

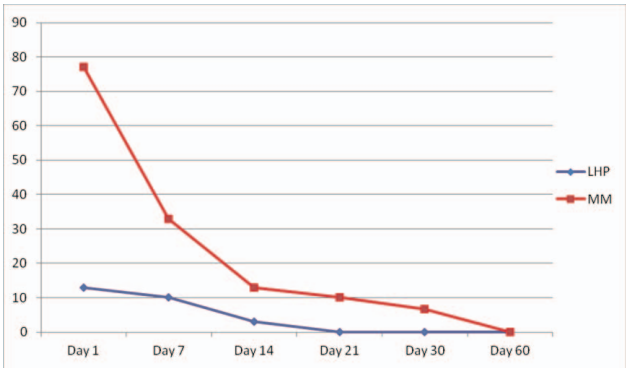


Fig. 5 – Mean bleeding during 60 days after hemorrhoidal treatment by laser hemorrhodoplasty (LHP) and hemorrhoidectomy (Milligan Morgan method – MM).

Using the Mann-Whitney test, we got a statistically significant difference in length of hospitalization by the groups ($U = 2545.0$, $p < 0.0001$).

The average recovery time for the patients treated with the LHP procedure was 17.2 days (SD ± 4.9 days), ranging from 5 to 30 days, while for the patients treated with the MM haemorrhoidectomy, the average recovery time was 19.2 days (SD ± 2.9 days), ranging from 14 to 35 days. The Mann-Whitney test showed a statistically significant difference regarding the time needed for patients per group to return to normal life ($U = 1829.4$; $p < 0.003$).

The average duration of hemorrhoidectomy with the LHP was 15.9 minutes (SD ± 1.9 minutes), in the range of 10–20 minutes and with the MM procedure, it was 27.2 minutes (SD ± 6.5 minutes), ranging from 12 to 60 minutes. The results showed a statistically significant difference ($p < 0.0001$) between the groups regarding the duration of the surgery.

The costs of the treatment with the LHP were higher than that of the MM method because the fiber optic LED is used only once which is required for this type of treatment, is used.

Discussion

The LHP is used for a delicate treatment of advanced hemorrhoids, in conditions of adequate anesthesia where endoluminal laser coagulation („welding") was made in hemorrhoidal vessels. Since the energy of the laser beam is applied solely only in hemorrhoidal vessels, no damage was done to anoderma and mucosa (the surrounding healthy tissue) [10–13]. In the treatment with this method, no foreign materials (buckles and surgical sutures) are used, which greatly contributes to elimination of postoperative pain and a risk of postoperative stenosis (narrowing) of the anal canal [14, 15]. Healing and recovery are excellent and fast, practically imperceptible, due to the absence of cuts, open wounds and stitches [3, 16–18].

After the MM hemorrhoidectomy, patients usually remain in hospital for 3–5 days and leave with considerable discomfort [19]. After the treatment with the LHP hemorrhoidectomy, typically, a patient can return to home the same day. After 3 or 4 days he/she are very comfortable without pain or any difficulty with their bowels**,** and they can return to their normal routine in 7–10 days after the intervention [20]. Simply, painless hemorrhoidectomy results in satisfaction of both the patients and surgeons [16, 21, 22]. Open surgical hemorrhoidectomy is the most widely used procedure in the surgical management of hemorrhoids. However, the MM method is associated with considerable complications including pain, bleeding and infection which can result in longer hospitalization [3, 16, 19, 23]. Our results showed significantly lower pain in the group after the LHP than in the group after the MM procedure. Postoperative pain is the most important complication that bothers patients and makes them reluctant to undergo surgical treatment. Our study showed that postoperative pain in the first month was significantly lower after the LHP than after the open hemorrhoidectomy which is similar to the results of some other studies [3, 16, 18, 24]. We found that the LHP procedure caused minor bleeding, which stopped in a much shorter period when compared to hemorrhage

after the MM method [22]. According to relevant literature [21], in 71% of the cases bleeding lasted less than a week. None of the patients required surgical intervention nor blood transfusions which is in agreement with our results [21, 22]. According to literature sources [25] infection occurs in 5%–15% of patients, and relapse in 5%–30% [16, 17, 24, 25, 26]. Not a single case of urinary retention and no need to set a urinary catheter were registered in comparison to some literature data showing 0%–16% of cases with urinary retention and catheterization [21, 27]. Average hospitalizations was 2.1 days in case of the MM method and 1 day after the LHP. According to Voigtsberger et al. [20], hospitalization lasted for 3 days. Financial costs are higher for the LHP treatment than for the MM procedure [28]. Crea et al. [16] suggest that ambulatory treatment by the LHP lowers the cost of anesthesia and enables treatment in hospitals which have no equipment required for general anesthesia [28]. According to our analysis of the cases in both groups, none of the patients accepted the treatment in local anesthesia, which means that general anesthesia was preferred. This confirms the fact that patients chose a painless method.

Conclusion

Our results show that the LHP as a minimally invasive method is more preferable than the MM procedure because of significantly lower postoperative pain, bleeding, and the duration of surgery.

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The relation of stress coping strategies and self-handicapping strategies to the process of opiate addicts behavior changes

Povezanost strategija za prevazilaženje stresa i samohendikepirajućih strategija sa procesom promena ponašanja opijatskih zavisnika

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Abstract

Background/Aim. During a progress of addictive behavior treatment, the strategies of coping with stress are engaged, but addicts may continue with self-handicapping behavior which is opposite to changing a problematic behavior. The aim of this study was to examine the stress coping (CS) strategies and self-handicapping (SH) strategies in relation to the process of addictive behavior change. **Methods.** In the descriptive clinical study, the sample of 200 consecutively recruited inpatient opiate addicts were explored. They underwent methadone therapy. The general information questionnaire, the Indicator of coping strategies (CSI), SH-questionnaire for assessing self-handicapping behavior (SH) and the University Rhode Island Change Assessment (URICA) questionnaire for the assessment of process of change were completed. The Student *t*-test, Pearson's correlation coefficient and multiple regression analysis were applied. The SPSS for Windows was used and the $p \leq 0.05$ defined as statistically significant. **Results.** Among the CS, there were significant correlations between avoiding problems strategy and all SH strategies ($p \leq 0.02$). The social support was directly proportionate to the process of change ($p = 0.03$, $\beta = 0.35$). However, the process of change inversely correlated to internal handicaps in interpersonal relationships strategy (IHI) ($p = 0.02$; $\beta = -0.54$) and strategy of focusing to the problem ($p = 0.00$, $\beta = -0.44$). **Conclusion.** The significant positive predictor for the process of addictive behavior change was a strategy of social support, but focusing on the problem and the strategy of internal handicaps in achievement situations were significant negative predictors. The evaluation of motivation process and stress coping strategies could be useful for creation of improved tailored treatment of opiate addiction.

Key words:
opioid-related disorders; therapeutics; stress, psychological; mental disorders; surveys and questionnaires.

Apstrakt

Uvod/Cilj. U tretmanu adiktivnog ponašanja koriste se strategije za prevazilaženje stresa – *stress coping* (SC), mada zavisnici često nastave sa samohendikepirajućim – *self-hendikeping* (SH) obrascem ponašanja, koji je u suprotnosti sa promenama problematičnog ponašanja. Cilj ove studije bio je da se ispitaju SC i SH strategije u odnosu na proces promene adiktivnog ponašanja. **Metode.** U deskriptivnoj kliničkoj studiji ispitan je uzorak od 200 konsekutivno regrutovanih bolesnika koji se nalaze na bolničkom tretmanu zbog opijatske zavisnosti. Za prikupljanje podataka primenjeni su: Opšti informativni upitnik, CSI- indikator *coping* strategija, SH- upitnik za procenu *self-handicapping* ponašanja i *University Rhode Island Change Assessment* (URICA) – upitnik za procenu procesa promena. Primenjen je Studentov *t*-test, koeficijent Pearsonove korelacije i multipla regresiona analiza. Korišćen je SPSS za Windows; vrednost $p \leq 0.05$ je definisana kao statistički značajna. **Rezultati.** Zavisnici su najviše koristili strategiju izbegavanja, a manje socijalnu podršku i fokusiranje na problem. Od CS značajna povezanost je bila utvrđena samo između ponašanja izbegavanja i svih SH strategija ($p \leq 0.02$). Sa procesom promene ponašanja jedino je socijalna podrška bila pozitivno povezana ($p = 0.03$; $\beta = 0.35$), dok su sa procesom promene obrnuto proporcionalno bili povezani fokusiranje na problem ($p = 0.00$, $\beta = -0.44$) i strategija internalizovanog hendikepa u sagledavanju sutuacije – IHI ($p = 0.02$; $\beta = -0.54$).

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Zaključak. Značajan pozitivan prediktor u procesu promena lečenih opijatskih zavisnika bila je strategija mobilizacije socijalne podrške, dok su negativni prediktori bili fokusiranje na problem i strategija internalizovanog hendikepa u sagledavanju situacije. Procena motivacije i prevazilaženje stresa bile bi veoma korisna u kreiranju poboljšanog tretmana zavisnika.

Ključne reči:
poremećaji izazvani opioidima; lečenje; stres, psihički; ponašanje, poremećaji; ankete i upitnici.

Introduction

Substance use and drug and behavior addictions have recurrent characters that are multiply determined and lead to a significant impairment of quality of life [1, 2]. In order to reach changes, special efforts are required, but the addicts are often motivated by short-term goals and their treatment acceptance may be the first step towards change [3]. Miller and Rollnick [4] indicate that it is necessary to observe the motivation for the change as a multidimensional phenomenon. It may be eventually developed in different directions by increasing or reducing the likelihood of change [5]. Motivation is considered as a key component for starting change, reducing risky behavior and confidence in the treatment outcome. Motivation includes both a willingness to change and treatment resistance (lack of treatment confidence) [6].

The researchers gathered around Prochaska et al. [7], conducted a series of researches and came up with several key constructs which may explain the nature of change which they called the Transtheoretical Model of change. In this model, there are few basic stages of Change: temporal dimension of change and processes of change, all the activities that people carry out or experiences that they used to change some of their thinking, behavior and assumption experience. Stages of change in this model are: precontemplation, contemplation, preparation, action maintenance and termination [5–8].

However, there is a series of behavior that people persist on in order to keep self-image and public image which are opposed to a change of problematic behavior. At the end of the 70s, Jones and Berglas [9] called such persons the self-handicapping. When failure is expected in an activity, a person is actively seeking or creating factors that may interfere the performance of these activities, which may serve as a justification for the potential failure [10]. In these situations, the person suspects in self-efficacy which is defined as an individual's belief in his/her own ability to perform and execute a specific action [11]. Many psychopathological symptoms are interpreted in the light of self-handicapping strategies and included even the use of alcohol or drugs [10]. Obstacles are further created in a way that can be linked to failure and this does not realistically represent the major obstacle to a success [12]. In addition to such behavior, in the process of change, an addictive behavior and maintaining achievement, changes may be affected by the strategies because stress is often cited as the cause of addiction [13]. The addicts, with extreme levels of stress, show higher expectations from treatment [9, 14]. Twoy et al. [15] believes that drug abuse can be interpreted as a learned pattern of dealing with the frustrations and the anticipated failure. These strategies of coping with stress allow the adequate adaptation to circumstances and require significant efforts to problems solutions which, eventually, leads to psychological well-being [16, 17]. In a case of addictions, particularly important strategy is mobilizing social support because people with more social support less perceive the stress and deal with it more successfully [18].

The aim of this study was to explore the stress coping strategies (CS) and self-handicapping (SH) strategies in relation to the process of addictive behaviour change.

Methods

Subjects

The sample consisted of 200 opiate addicts who were consecutively hospitalized at the Clinic for Psychiatry, Clinical Center of Vojvodina, Department of Addictions, in Novi Sad. The subjects involved in the study met the International Classification of Diseases (ICD-10) criteria for opiate addiction. There were 160 male (80%) and 40 (20%) female subjects. The average age of respondents was 35.6 years. The history of opiate use showed that the 68 (34%) respondents had no recidive, 64 (32%) patients had between 1 and 3 recidives and 68 (34%) patients had more than three recidives.

The study was conducted in the period from 01 December 2013 to 01 April 2014. The study protocol was approved by the Ethics Committee of the Clinical Center of Vojvodina and prior to the investigation the written informed consents from all the subjects were obtained. The self-questionnaires were anonymous, in accordance with the ethical principles of scientific research.

Instruments

The study participants filled out anonymously four questionnaires: the questionnaire of general information (age, gender, job status, lifestyle, etc), the CSI –Indicator coping strategies, the SH assessment questionnaire for self-handicapping and the University Rhode Island Change Assessment (URICA) questionnaire for the assessment stage of the change process which is the current process of personal change. The general information questionnaire was designed for this study and contained 10 questions that included basic socio-demographic data (gender, age, education, employment status, marital status, current living conditions, socio-economic status) as well as questions related to the consumption of psychoactive substances , the family support and number of relapses in the previous period.

The CSI questionnaire demands that respondents recall and describe in a few sentences on a particular situation from personal experience in the past 6 months which represented a

problem for them and answer why they were concerned [19]. After that, the subjects answer on how they used each of the 33 individually listed strategies to overcome the stress caused by mentioned problem. The questionnaire is designed to measure 3 independent dimensions: focus on the problem, seeking social support and avoiding problems. Each dimension has 11 items with three-point Likert scale which indicats how often the subjects use them [20].

The SH questionnaire consistes of four scales containing 34 items with a five-point Likert scale for answers [21]. Each item is a combination of external or internal causes which a person use to justify a potential failure in interpersonal relationships or situations achievements. The first scale includes items related to self-handicapping external causes in interpersonal relationships and the second one contains indicators of self-handicapping internal causes in interpersonal relationships. The third scale implies self-handicapping internal causes in situations of achievement while the fourth scale refers to self-handicapping external causes in situations of achievement. The scales and the total SH questionnaire have adequate representativeness, reliability and homogeneity [12].

The URICA questionnaire is 32-items scale which assessess the stages of change [22]. The questionnaire includes four scales obtained after performing the analysis components: the precontemplation, contemplation, action and maintenance changes. With this questionnaire, it is possible to calculate the scores for the individual stages of the change process as well as the total score obtained by adding up the scores on the stages of contemplation, action and maintenance, and their sum is subtracted score for the precontemplation stage.

Statistical analysis

Statistical analysis was performed in the program Statistica 0.7 and SPSS for Windows, for the following analyses: descriptive analysis, correlation coefficients, hierarchical regression analysis, linear regression, analysis of variance and Student *t*-test. The *p* values of 0.05 or below were defined as statistically significant.

Results

There was a statistically significant difference in the SH strategies used among addicts ($p = 0.02$; $F = 3.33$). The internal handicaps strategy in achievement situations (arithmetic mean 2.77) and external handicaps in achievement situations (arithmetic mean 2.60) were the most used. The external handicaps in interpersonal relations (arithmetic mean 2.31), and internal handicaps in interpersonal relations (arithmetic mean 2.27) were less used (Figure 1).

The SH strategies were borderline and significantly associated with the process of change ($p = 0.05$; $R = 0.425$). Among the SH strategies, there was a statistically significant correlation only between internal handicaps in the interpersonal relationships strategy (IHI) and processes of change ($p = 0.02$). The beta correlation coefficient was -0.54 which showed that more intensive use of this strategy slowed the progression of the process of change (Table 1).

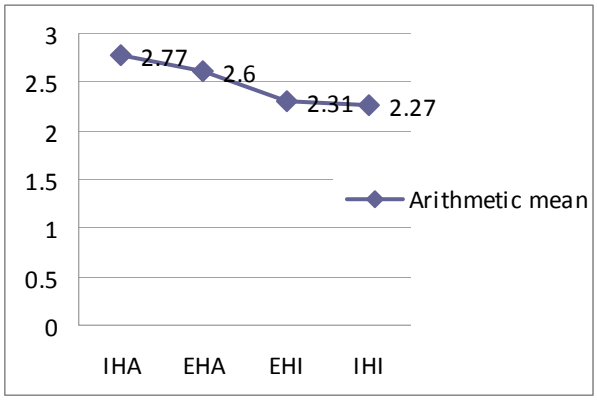

Fig. 1 – The self-handicapping strategies among opiate addicts.
EHI – external handicaps in interpersonal relationships; IHI – internal handicaps in interpersonal relationships; IHA – internal handicaps in achievement situations; EHA – external handicaps in achievement situations.

Table 1
The self-handicapping strategies in the prediction of progression through the process of change

The self-handicapping strategies	Process of change		
	β	*t*	*p*
EHI	-0.05	-0.30	0.76
IHI	-0.54	-2.28	0.02
IHA	0.02	0.12	0.90
EHA	0.23	1.13	0.26

EHI – external handicaps in interpersonal relationships; IHI – internal handicaps in interpersonal relationships; IHA – internal handicaps in achievement situations; EHA – external handicaps in achievement situations.

Besides the SH strategies, the impact of SC strategies on the process of addictive behavior change was examined. There was a significant difference in the intensity of use of different coping strategies ($F = 7.007$; $p = 0.00$). The addicts mostly used avoidance strategy (arithmetic mean 9.64), then the social support (arithmetic mean 8.90) and the least used strategy was focus on the problem (arithmetic mean 5.90) (Figure 2).

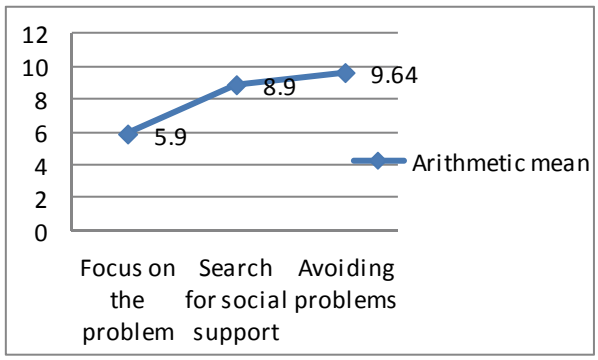

Fig. 2 – The stress coping strategies among opiate addicts.

The correlation between the SC strategies and progress in the process of change was of borderline significant (p = 0.05; R = 0.39).

The avoiding problems strategy was not significantly associated with the process of change, but focus on the problem ($p = 0.00$) and social support ($p = 0.03$) were found to be statistically significantly associated (Table 2).

Table 2

The coping strategies in the prediction of progression through the process of change

The coping strategies	Process of change		
	β	*t*	*p*
Focus on the problem	-0.44	-2.76	0.00
Social support	0.35	2.16	0.03
Avoiding problems	-0.04	-0.35	0.72

The strategy of focusing on the problem was inversely proportional to the change process, the beta coefficient of correlation was -0.44 showing that focusing on the problem led to less progress in the process of change. The social support was directly proportional to the process of change, beta coefficient of correlation was 0.35, indicating that more social support had impact on greater advancement in the process of change.

We found that there were the significant correlations between the avoiding problems strategy and external handicaps in interpersonal relationships ($p = 0.02$), internal handicaps in interpersonal relationships ($p = 0.00$), internal handicaps in achievement situations ($p = 0.00$) and external handicaps in achievement situations ($p = 0.02$). These correlations were inversely proportional, more used avoiding strategy led to less SH behavior used (Table 3).

Table 3

Correlations between self-handicapping strategies and stress coping strategies

Caping strategies		EHI	IHI	IHA	EHA
Focus on the problem	R	-0.08	-0.81	0.29	0.24
	p	0.56	0.57	0.84	0.86
Social support	R	-0.84	-0.06	0.10	0.82
	p	0.56	0.65	0.94	0.57
Avoiding problems	R	-0.31	-0.38	-0.49	-0.32
	p	0.02	0.00	0.00	0.02

EHA – external handicaps in situations of achievement; IHI – internal handicaps in interpersonal relationships; IHA – internal handicaps in achievement situations; EHI – external handicaps in interpersonal relationships.

Discussion

Changing an addictive behavior is a long process and requires maximum engagement of addicts to solve problems. Among the SH strategies in this study, the addicts mostly used a strategy of internal handicaps in achievement situations. It could be explained that an addict usually experienced the intrapersonal problem in the situations of possible success or failure. This result was in concordance with results from other researches which demonstrated the negative association of authenticity with self-handicapping. The few studies analyzed by Uysal and Knee [23] suggested that low trait self-control predicted self –handicapping, independent of self-esteem, self-doubt, social desirability or gender. The Turkish study from 2014 indicated that self-handicapping was positively predicted by self-alienation and acceptance of external influence, and negatively by authentic living [24]. There was suggested that the addicts tended to see in advance their own failure without attempting any action [9]. This could be linked with a number of unsuccessful attempts of treatment, so work on motivation and rewriting irrational beliefs are imposed on as the most important. The conclusions of the study which was dealing with the coping strategies of Vietnam veterans who were treated for posttraumatic stress disorder and substance use disorder suggested that: "…substance abuse is associated with less efficient, avoidant ways of coping with problems in living; and two, that substance abusers with a background of traumatic and stressful experiences are readily distinguishable by even more avoidant coping styles" [25]. If we consider self-handicapping strategies used in the interpersonal relationships of the addicts, the strategy of external handicaps in interpersonal relationships was used prominent one. It indicates that, as the culprits in the failure of achieving adequate interpersonal relationships, see other people, not themselves. This may be due to the prejudice and discrimination they face daily.

Among the SH strategies, there was a statistically significant correlation only between internal handicaps in interpersonal relationships strategy and processes of change. This correlation was inverse, indicating that this strategy led to less progression in the process of change. We could explain it by the clinical observations that the addicts often do not believe in the treatment success and the possibilities of addictive behavior change with doubting themselves and their own capacities. This data indicates the necessity of working on the addicts´ motivation to change and to increase their self-confidence.

The results showed that among SC strategies, the avoiding problems strategy was the most prominent among the addicts. This is consistent with previous findings that young

people who abuse psychoactive substances predominantly used a strategy of avoiding problems [26]. The strategy of avoiding problems can instantly help the addict to escape from the current problems, but its long-term use disturbs addicts to make progress in the process of change. Other authors also found that treated opiate-dependent patients experienced higher level of stress and reported less use of adaptive coping strategies when compared to the controls [27]. Our study showed that the strategy of focusing on the problem was inversely proportional to the change process, which indicated that this SC strategy led to less progress in the process of change. However, the social support was directly proportional to the process of change and led to greater advancement in the process of change. Some recent biological studies also indicated that the social attachments protect against addiction and health consequences of stress, whereas drug abuse and chronic stress can undermine them [28, 29]. These findings suggest that novel treatment approaches and improved social support could be important aspects of decreasing stress during early recovery from opiate addiction. This means that addicts on admission are seeking treatment mostly when they are forced by others, family or judicial authority [1], and they still do not see the problem which they found themselves in, and are most likely in the precontemplation stage. Then, they use social support, which includes seeking informal support from the people in their environment, but also professional help. The other researches indicated that it was necessary to work on practicing different problem solving strategies that would contribute to the maintenance of the achieved changes [16]. Mobilizing social support is therefore in the proportional correlation with the progress in the process of change [17].

Obtained data from this study showed that more used the focus on the problem strategies lead to less progress in the process of change. This data can be linked to the fact that the search for possible solutions and actively coping is a characteristic of the stage action which is advancing higher; when it comes to the maintenance stage, then more pronounced is search for social support, both formal and informal, in order to maintain the changes achieved. These results are in concordance with the setting of the Transtheoretical Model of Change. It is believed that every addict pass, on average, three times through the stages of change until it reaches the stage of maintenance. The person more often passes through these stages progressively spirally than linearly [30]. This means that addicts go through the stages of change and each relapse does not mean a return to the very beginning of the fight, but every relapse is seen as a mistake to learn from, and each recurrence is a step closer to the maintenance changes. The spiral motion means that the relapse is a rule, but upon returning to the previous stages, an addict gets closer, but still maintains the changes [5–8, 20, 30]. It is in concordance with our results which showed that the two-thirds of addicts relapsed during past year, one-third more than three times. It confirmed that the relapse could be expected during the treatment.

Despite treatment chalenges, the cognitive behavioral therapy (CBT) for substance use disorders demonstrated efficacy as part of combination treatment strategies and consisted of heterogeneous treatment elements, such as operant learning strategies, cognitive and motivational elements and skills building interventions [31]. In this study, results showed that there was a statistically significant correlation between strategy of avoiding problems and SH strategies. This correlation was inversely proportional, which means that the more the strategy of avoiding problems was used, the less the SH strategy was applied [26]. We could assume that if the addicts do not face the problem, there is no need to rationalize their dysfunctional behavior. The SH strategies were used in situations where a person was expecting failure of the taken action.

Limitations

There are several limitations in generalization of the findings in this study. The observational descriptive study was used for relatively small sample, thus the observed characteristics and relations of the coping and SH strategies among the treated opiate addicts do not provide explanation whether they are the causes or consequences of addiction. Furthermore, the inpatients are likely to have more severe psychopathology when compared to the addicts from general population. Also, the patient's assessments were not premorbid, and chronic opiate use may modify the assessment of these strategies. A larger prospective study is needed for further study of complex interplay between addiction, the coping and self-handicapping strategies among treated opiate addicts. In this sense, the strategies that addicts use in coping with stress are important as well as SH strategies that can slow down the process of change. Thus, these findings might inform early interventions and treatments that target opiate addicts at a risk in the early dependence recovery.

Conclusion

The results suggested that opiate addicts most significantly used the internal and external SH strategies in the achievement situations. Among coping strategies the avoidance strategy was the most prominent and inversely correlated with all SH strategies. The social support significantly positively correlated and could predict the process of change among the addicts. The change process inversely correlated to focus on the problem and to internal handicapping interpersonal relations.

The assessment of coping and SH strategies and early motivational interventions could improve behavioral change and treatment of opiate addicts.

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Evaluation of odontometric methods in immature permanent teeth: research for a better practice

Evaluacija odontometrijskih metoda kod stalnih zuba nedovršenog razvoja: istraživanje u cilju bolje prakse

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Abstract

Background/Aim. Determination of correct working length is one of the keys to success in root canal treatment. It provides efficient canal cleaning and shaping, a three-dimensional chermetic obturation and an optimal healing procees following root apex formation. The aim of this work was to evaluate and compare the accuracy and applicability of working lengths determined in permanent immature teeth *in vivo* using different clinical methods. **Methods.** The research was conducted at the Dental Clinic of Vojvodina in Novi Sad, the Department of Pediatric and Preventive Dentistry. A sample of 30 canals of young permanent teeth were selected for the research. Inclusion criteria were: a need for endodontic treatmant, young permanent teeth, teeth with incomplete apex formation according to Demirijans stages F and G determined on radiography. Exclusion criteria: more than 3 years from eruption, pathological and iatrogenic resorption of the apex. The canal lenght was measured first on the initial radiograph used later as the parameter for comparison with various clinical methods. **Results.** The greatest average difference of measured working lengths was found by using electroodontometry and the paper point method afterwards. Regarding individual measurements, the most unprecise reading was with electroodontometry and tactile method up to 5 mm difference, and 4.6 mm was the maximal deviation for radiographic method. A deviation was defined by matching the measurements with a canal length measured on the initial radiograph. Our results showed that there was a difference between observed methods, although there was no statistical significance. **Conclusion.** The radiographic method and tactile method stand out as dominant methods for odontometry in permanent immature teeth, thanks to highly accurate readings, while the electroodontometry is considered the most unreliable method for determining working length in immature permanent teeth.

Key words:
endodontics; root canal preparation; odontometry.

Apstrakt

Uvod/Cilj. Određivanje tačnih radnih dužina je ključno u lečenju kanala korena zuba. Preciznim određivanjem radnih dužina korena se omogućuje efikasno čišćenje i oblikovanje, kao i trodimenzionalno hermetičko zatvaranje uz optimizaciju procesa lečenja. Cilj ove studije je evaluacija i upoređivanje primenjivosti i tačnosti određenih radnih dužina kod stalnih zuba nezavršenog razvoja korena dobijenih *in vivo* različitim kliničkim metodama. **Metode.** Istraživanje je sprovedeno na Klinici za stomatologiju Vojvodine, na odeljenju Dečje i preventivne stomatologije. Uzorak je činilo 30 kanala mladih stalnih zuba. Kriterijumi za uključivanje u istraživanje bili su: potreba za endodontskim tretmanom, mladi stalni zubi sa nezavršenim razvojem korena, F i G stadijum, po Demirijanu određeno na radiogramu. Kriterijumi za isključivanje bili su: ako je prošlo više od tri godine nakon nicanja zuba, patološka ili jatrogena resorpscija vrha korena. Dužina kanala je najpre izmerena na inicijalnom radiogramu, a zatim je ova vrednost uzeta kao parametar za upoređivanje radnih dužina dobijenih različitim kliničkim metodama. **Rezultati.** Najveće prosečno odstupanje određenih radnih dužina dobijeno je elektrodontometrijskom metodom, zatim papirnim poenom. Najmanje precizno indvidiualno merenje dobijeno je elektroodontometrijom i taktilnom metodom sa zabeleženim odstupanjem i do 5 mm, dok je maksimalna devijacija za radiografsku metodu bila 4.6 mm. Devijacija je određivana merenjem poklapanja sa dužinom određenom na inicijalnoj radiografiji. Rezultati pokazuju da postoje razlike u merenjima pomoću ispitivanih metoda, ali bez statistički značajnih razlika. **Zaključak.** Zahvaljujući vrlo preciznim merenjima, radiografska i taktilna metoda izdvajaju se kao dominantne metode za odontometriju kod mladih stalnih zuba, dok je elektroodontometrija najmanje pouzdana za određivanje radne dužine kod zuba sa nezavršenim rastom korena.

Ključne reči:
endodoncija; zub, lečenje korenskog kanala; odontometrija.

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Introduction

Determination of correct working length is one of the keys to success in root canal treatment. It provides efficient canal cleaning and shaping, a three-dimensional chermetic obturation and an optimal healing procees following root apex formation. In clinical practice the presence of a wide apex may provide challenges in endodontic treatment. A routine root canal procedure cannot be performed in these cases and the success of the treatmant is unpredictable [1].

Immature permanent teeth have open or wide apices at the time of their erruption as a physiologic phase during root development. Apical closure occurs approximately 3 years after eruption [1]. Open apices can also be present as a consequence of trauma, caries, or pathological resorption. They can also be iatrogenic as a result of overinstrumentation or root resection [2]. An open apex may develop in a previously mature apex owing to extensive resorption after orthodontic treatment or severe periapical inflammation [1]. An open apex and thin dentinal walls make the endodontic treatment difficult and there is a higher risk of post-treatment root fracture under occlusal or traumatic forces [1, 3, 4]. The walls of the apex may diverge, converge, or be parallel depending on the stage of root development [5].

The aim of determining the working length is to enable the root canal to be prepared as close to the apical constriction as possible. There is a general agreement that the apical constriction is appropriate for termination of canal preparation and opturation [6].The location of the apical constriction normally varies between 0.5 and 2 mm from the radiographic apex in fully developed permanent teeth [6]. However, in cases of wide apices, the apical constriction is not formed and, consequently, this guideline cannot be followed. A lack of research in this field and no defined protocol nor golden standard test for working lenght determination in immature teeth has led to variable methods and rendered the question of working lenght determination a controversy.

Long-term medication with calcium hydroxide is widely used to induce the apexification of immature teeth with pulpal necrosis before a definitive obturation [7]. The success rate of apexification with calcium hydroxide is about 95%. With Mineral Trioxide Aggregate (MTA), the success rate of apexification is comparable or higher [3]. The advantages of MTA are fewer visits and faster development of a calcific barrier, even though the long-term success rate of the MTA apexification is yet to be determined [8]. Calcium hydroxide and also MTA should be placed in the soft tissue region at the apex in order to promote apexification [3]. In contrast to using calcium hydroxide or MTA, relevant literature highlights the benefits and a better long-term prognosis with regenerative endodontic therapy, even though there are no standardized protocols for its application as well.

Given the lack of clinical research in the field of odontometry in immature permanent teeth and precise clinical protocols for determining working length, the study aimed to evaluate and compare the accuracy and applicability of working lengths determined in permanent immature teeth *in vivo* using different clinical methods: electroodontometry, radiographic method, tactile method and paper point method.

Methods

The research was conducted at the Dental Clinic of Vojvodina in Novi Sad, the Department of Pediatric and Preventive Dentistry. The study protocol was approved by the local Ethics Committee, and patients/parents gave their informed consent. The selection of patients was made by two experienced clinicians, one pedodotistand, one general dentist with 15 years of experience. The endodontic procedures and measurments were performed after the dentists were calibrated, with a kappa intra-examiner concordance index score of 0.84. Inclusion criteria were: a need for endodontic treatmant, young permanent teeth and teeth with incomplete apex formation according to Demirijan's stages F and G determined with radiography [5]. Exclusion criteria were: more than 3 years from eruption, and pathological and iatrogenic resorption of the apex. All patients had endodontic treatmants throughout multiple visits. The treatmants were done with calcium hydroxide or MTA. For the purpose of this research paper, the clinical protocol remained unchanged and additional diagnostic procedures were not included.

The clinical examination began with thorough history of subjective symptoms, following the diagnostic tests and the radiographic examination. The diagnosis of pulpal status was irreversible pulpitis or pulpal necrosis. The canal lenght was measured firstly on the initial radiograph, which was later used as the parameter for comparison between various clinical methods. The retroalveolar radiograph was made with a digital X ray (SironaHeliodentVario, Sirona Dental Systems GmbH) using bisecting angle method. The lenght was measured on the X ray between a reference point on a cusp or incisal edge 1 mm shorter than the visible edge of the rooth on the radiograph. The estimated canal lenght was measured with a mm ruler and 2x magnification with two clicks (1 click at the reference point and the second click 1 mm shorter than the apex).

Local anaesthesia was used if pain was expected regarding the diagnosis, or if a patient requested it and patients/parental consent was gained. If not approved, anaesthesia was not given. After isolating the tooth with a rubber dam, an access cavity was prepared to allow removal of all inflamed or necrotic pulp tissue. Next, a nerve file was inserted. At this point some of the pulp tissue was removed by rotating and withdrawing a nerve file. Irrigation was done with NaOCl 0.5%.

The tactile measurements were completed firstly, using a suitable file. Local anaesthesia was not used when these measurements were performed. The tip of the file was placed against a dentinal wall in the root canal and displaced apically until it reached the edge of dentinal wall at the apex and provoked sensitivity or haemorrhage. The length was adjusted and measured. This procedure was repeated to circumferentially probe all dentinal walls; if a shorter length was determined, the ring on the file was readjusted, thus representing the tactile working length.

Electronic measurements were done after that, by using the Raypex 5 electronic apex locator (VDWGmbH, Munich, Germany), the fourth generation apex locator. After a copi-

ous irrigation with NaOCl 0.5%, a file was chosen; it was four degrees smaller than the file which was earlier defined as suitable for the tactile method. After slightly drying the canals, the chosen file was introduced until a constant beep (around 5 seconds) was evoked. This was repeated and the correct lenght noted.

The next step was to record radiographic measurements with a file placed in the canal, in length which corresponds to the lenght on the initial radiograph. The steps of radiographic imaging were standardized. If the obtained results differed more than 3 mm, the X ray was repeated. If the difference was less than 3 mm, the lenght of the instrument was measured again and the working length was corrected adding or subtracting for adequate length. The measuring was done with a mm ruler and x2 magnification with 2 clicks (1 click at the reference point and the second click at the file tip).

Odontometry using paper points was done next. An initial paper point was placed 0.5 mm short of the indicated length determined by the tactile method done earlier. The point advanced apically until some fluid was noticed on the tip. Another paper point was used just short of this point. The working length was then determined as the maximum length that a paper point could be placed into the canal and remained dry after brief contact [9].

The working length measured by apex locator, tactile method, paper point and radiographic method was compared to the canal lenght measured on the initial radiograph. Data was collected and statistical analysis was carried out with the use of Statistical Package for the Social Sciences (SPSS) Windows version 12.0. Statistical analysis included standard descriptive statistical analysis; the differences between investigated groups were compared using one-way analysis of variance (ANOVA) test [absolute values and standard deviation (SD) in mm were compared for all determined working lengths] with the level of significance set at $p < 0.05$. Average differences, maximal and minimal deviations and SD were determined for each individual measurment method. The deviations from the average values (both positive and negative) were calculated for all measurements as well as the correlation coefficient between employed clinical methods.

Results

The sample consisted of 21 patients (9 females, 12 males), mean age 8.3 ± 1.7 years. The sample of 22 immature permanent teeth including 13 upper central incisors, 2 upper lateral incisors, 2 upper premolars and 2 upper and 3 lower molars with a total of 30 canals were selected for the research. The results of this study are shown in Table 1. The greatest average difference of measured working lengths was found using electroodontometry, then the paper point method. Regarding individual measurements, the most unprecise reading was with electroodontometry and tactile method with 5 mm difference while 4.6 mm was the maximal deviation for radiographic method. The minimal deviation meant that the single measurements corresponded to the parameter measured on the initial radiograph. Our results showed that there was a difference among observed methods, although there was no statistical significance. In two cases, there was a problem in defining the correct canal length with paper point method, when repeatedly a dry canal could not be obtained while some uncertainties were present in one case when using the tactile method, where the mean value of four measurements was applied. In Figure 1, each method and all measurements of working lengths are shown. The correlation between the deviations in all clinical methods was 0.79.

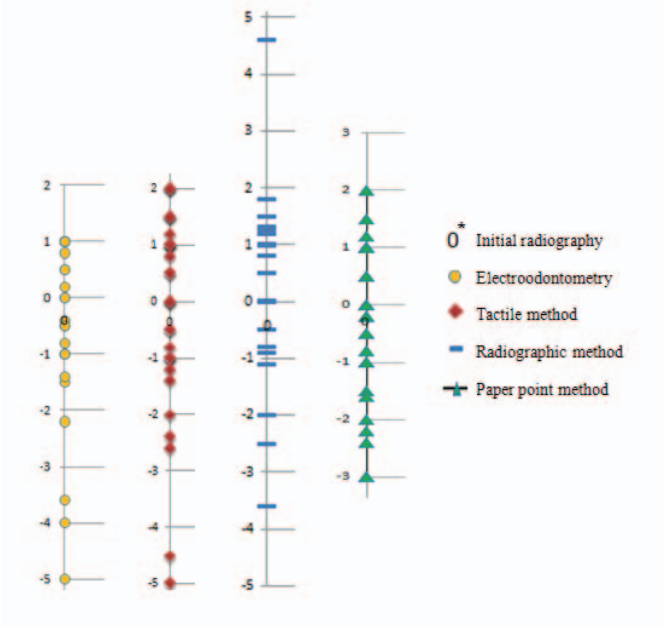

Fig. 1 – Differences between working lenghts measured (mm) on the initial radiograph and by various clinical odontometric methods.
***lenghts measured on the initial radiograph were taken as zero in order to display differences among various methods.**
Note: the negative values were shorter and positive values were longer working lenghts obtained.

Table 1

Statystical analysis of measured working lengths using different clinical methods

Parameters	Electroodontometry	Tactile method	Radiographic method	Paper point method
Average difference	0.597	0.213	0.16	0.373
Maximal deviation	5	5	4.6	3
Minimal deviation	0	0	0	0
Standard deviation	1.689	1.793	1.5	1.434
		$p = 0.322$		

Discussion

To the best of the authors' knowlegde, no prospective clinical studies of working length determination in immature teeth have been published. By its design, this was prevailingly *in vivo* study aimed to clarify the dillema of odontometry in teeth with the incomplete root formation.

There are many experimental *in vitro* studies about working lenght determination in immature teeth. The time taken to process an *in vitro* research and its conclusions versus an *in vivo*, clinical research is significantly shorter. The results from *in vitro* studies should be interpreted with caution; as in clinical situations, there is often a lack of ideal circumstances and controlled enviroment for precise measurment [10–12]. Nevertheless, for a comprehensive understanding of this matter, knowledge of odontometry about permanent immature teeth should be validated through both *in vitro* and *in vivo* studies.

Apex locators have been shown to be highly accurate in locating the apical foramen and constriction in fully developed teeth [8]. Their performance can be influenced by several factors: the diameter of apical foramen, the size of file in use, electrolytes, pulp tissue and blood. The third and later generation apex locators were constructed to overcome some of these limitations [1]. Even though, various authors determined that as the diameter of the apical foramen increased, the measured lenghts with apex locators became shorter than the actual canal lenght [13]. A laboratory study showed that file size was irrelevant for apical size of 60, whereas, better fitting files were recommended to use for apical sizes over 70 [1]. It has been found that apex locators had an accuracy rate of only 62.7% in cases of teeth with wide apices, often showing shorter working length as incorrect measurements [9]. Our results mainly correspond to these findings meaning that electroodontometry can be suprisingly unprecise in immature teeth with a tendency to record shorter working lenghts. Various studies indicated that a difference of ± 0.5 mm in electroodontometry measurements was clinically acceptable [13–15]. In our research, the average difference of working lenghts determined with electroodontometry was within this range, even though it varied mostly in the initial working lenght in comparison to other methods.

In the teeth with open apices, the radiographic interpretation of canal length can be difficult due to a different apical structure and the missing periodontal ligament space at the root apex [16]. Although the radiography is the main method of determining working lenght during endodontic treatment of immature permanent teeth, variations are frequent among the imaging tehniques used [1]. With a correct imaging technique magnification and image distortion can be minimized, but a certain amount of these phenomena is unavoidable [17]. The radiographic methods may lead to overinstrumentation due to showing a longer canal length [14]. The main reason is the fact that the apical foramen is frequently (92%) located short of the apex and the length of the measuring file appears radiographically shorter than its actual length [15]. In our study measurements with the radiographic method were the most precise. This can be due to the fact that the parameter for defining the deviations was the canal lenght measured on the initial radiograph. In the literature there are statements that the success rate of the endodontic treatment using the Raypex5 electronic apex locator and radiographic measurement are quite similar [1]. The benefits of electroodontometry, in addition to eliminating radiation exposure, is that apex locators are superior in reducing overestimation during odontometry compared to radiographic canal lenght determination [18]. In our study, we concluded that, when comparing single measurements, the radiographic odontometric method was more precise, but there was no statistically significant difference comparing all the results gained from applying electroodontometry and radiographic methods.

The accuracy of the Tactile Method, measured in the teeth with open apices was found to be high (over 97%) [13, 14, 16]. ElAyouti et al. [19] described a tactile method using a size 25 file with a bent tip. Their results showed that this method may offer an alternative to other methods, as 97.7% of measurements were in the range of ± 0.5 mm to actual canal lenght. Our results are in accordance with these findings since the average difference for tactile method was 0.213 mm, also within the clinically acceptable range. During measuring by the tactile method, there were some unscertainties in one case with 5 mm deviations observed in multiple working lenght determination attempts.

While using paper point method, there were some issues with defining the correct length in two first molars, when repeatedly a dry canal could not be obtained. The control of moisture is difficult because the contact area to the periapical tissues is wide, especially in cases with periapical inflammation when an excess moisture is inevitable [19, 20]. Also, to determine precise measurements, the periapical tissue must be located at the same level of the apical foramen, a requirement which may not be present in immature permanent teeth since periapical tissues can extend in the canal up to 3 mm [21].

Our results are in line with earlier published statements by ElAyouti et al. [19] and Gurtu et al. [22] who noted difficulties in the usage of tactile and paper point method in curved and narrow canals, contrary to expected success in anterior teeth with wide canals with obtained moisture control.

The study limitations include the possible risk of error in reproducibility during measuring and relatively small sample sizes. The study also reflects a single center experience. In two cases, there was a problem in defining the correct lenght with paper point method, when repeatedly a dry canal could not be obtained. With the tactile method there were some unscertainties in one case when the examiner decided to use the mean value of four measurements.

Conclusion

Thanks to highly accurate readings, the radiographic method and tactile method stand out as dominant methods for odontometry in permanent immature teeth. On the other hand, electroodontometry is the most unreliable method for determining working length in immature permanent teeth.

Defining a precise protocol and golden standard method for working lenght determination in permanent immature teeth remains necessary to be an objective in the field of endodontics.

Conflict of interest

All authors declare that they have no conflict of interest.

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Awareness of HIV/AIDS and other sexually transmitted infections among the Montenegrin seafarers

Svest o HIV/AIDS i drugim infekcijama prenosivim seksualnim putem među crnogorskim pomorcima

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Abstract

Background/Aim. Human immunodeficiency virus (HIV) continues to be a major global public health issue having claimed more than 35 million lives so far. Seafarers belong to a group of migrant workers whose working and living conditions are confined for a long time. Their way of life put them at a high risk of HIV infection and other sexually transmitted infections (STIs). The aim of this study was to assess the level of knowledge about HIV and other STIs among Montenegrin sailors. **Methods.** A research was carried out from October 2014 to April 2015 as a cross-sectional study. The research included 543 examinees. A research instrument was a particularly structured closed-type questionnaire created by the Joint United Nations Programme on HIV/acquired immune deficiency syndrome (AIDS) (UNAIDS) and used in international and national researches. For data analysis, we used the SPSS for Windows 20.0. **Results.** The result that only 42.9% of the examinees knew that HIV and STI transmission could be prevented by a proper and frequent use of condoms was alarming. More than a third of the examinees (38.9%) were aware of the fact that HIV could be transmitted by having sexual intercourse with a person who looked healthy, while 25.6% of them thought that HIV could not be transmitted in this way. Considering the level of education, there was a statistically significant difference related to the awareness of HIV transmission by sharing a meal with a person was HIV positive ($p = 0.001$). There was also found a statistically significant difference related to the awareness of the examinees about HIV transmission by using public toilets ($p = 0.004$). **Conclusion.** The results of this research showed that beside the fact that awareness level of HIV and STIs among the sailors was heightened in comparison to 2008, the level of awareness is still not satisfactory.

Key words:
hiv infections; attitude to health; humans; military personnel; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Virus humane imunodeficijencije (HIV) i dalje je jedan od najvažnijih problema javnog zdravstva i do sada je odneo više od 35 miliona života. Pomorci spadaju u grupu radnika migranata čiji su radni i životni uslovi skučeni na duže vreme. Način života koji vode stavlja pomorce u visok rizik od infekcije prouzrokovane HIV-om i drugim seksualno prenosivim infekcijama. Cilj rada bio je procena nivoa znanja o HIV-u i drugim polno prenosivim infekcijama među pomorcima u Crnoj Gori. **Metode.** Istraživanje je sprovedeno od oktobra 2014. do aprila 2015. godine kao studija preseka i obuhvatalo je 543 ispitanika. Instrument istraživanja bio je posebno strukturisan upitnik zatvorenog tipa, kreiran prema programu Ujedinjenih nacija za HIV/sindrom stečene imunodeficijencije (AIDS) (UNAIDS) koji se koristio u međunarodnim i domaćim istraživanjima. Za statističku obradu podataka korišćen je SPSS 20.0. **Rezultati**. Rezultati ukazuju na to da je samo 42,9% ispitanika znalo da se od HIV-a i drugih polno prenosivih infekcija može zaštititi pravilnom i redovnom upotrebom kondoma. Više od jedne trećine ispitanika (38,9%) nije znalo da se HIV može preneti seksualnim odnosom sa osobom koja izgleda zdravo, dok je 25,6% smatralo da se HIV ne može preneti na taj način. S obzirom na stepen obrazovanja, statistički značajna razlika utvrđena je u odnosu na znanje o prenošenju HIV-a deljenjem obroka sa osobom koja je inficirana HIV-om ($p = 0.001$). Statistički značajna razlika utvrđena je i informisanost ispitanika u odnosu na prenošenju HIV-a korišćenjem javnih toaleta ($p = 0.004$). **Zaključak.** Rezultati ovog istraživanja pokazali su da i pored toga što je unapređen nivo znanja pomoraca u Crnoj Gori o HIV in-

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fekciji i drugim polno prenosivim bolestima u odnosu na 2008. godinu, sedam godina kasnije znanje pomoraca još uvek nije na zadovoljavajućem nivou.

Ključne reči:
hiv; stav prema zdravlju; ljudi; kadar, vojni; ankete i upitnici.

Introduction

Human immunodeficiency virus (HIV) continues to be a major global public health issue having claimed more than 35 million lives so far [1]. Strategic plans for responding to HIV/acquired immune deficiency syndrome (AIDS) at the global level recognized a greater vulnerability of some population groups in transmitting this and other sexually transmitted infections (STIs) [2]. Prevention programs focused on specific populations still remain the best approach to combating the HIV/AIDS pandemic [2–4].

The World Health Organization (WHO) estimates that in 2014 there were 35.3 million people in the world who lived with HIV infection [1]. The largest number of HIV/AIDS infections and the increasing trend in the number of the infected people was recorded in Sub-Saharan African countries. In Europe, North America and Australia, the number of the infected does not show a pronounced upward trend and the infection was kept mainly within so-called „risk groups" which include migrant workers, too. The "Risk groups" cause such status due to economic and social circumstances and their proneness to behaviour and habits which may result in HIV infection [1].

Seafarers belong to a group of migrant workers whose working and living conditions are confined for a long time [5]. Their way of life put them at a high risk of HIV infection and other STIs [5, 6]. The sense of isolation and solitude caused by separation from family, friends and homeland and a high degree of routinization of everyday tasks and hierarchical organization of work on board also increase sensitivity of this population [7]. According to the data of the Maritime Union in Montenegro, there are around five thousand people who identify themselves as professional sailors [8].

According to the data of the National HIV/AIDS Registry, participation of seafarers in the total incidence of HIV infections in Montenegro ranged from 16% in 2008 [9] to 9% in 2014 [10, 11].

Epidemiological data and the results of researches that have been conducted in recent years among the sailors in Montenegro [11–13], have contributed to the national strategic response to HIV/AIDS in Montenegro since 2005 when the first strategy for the fight against HIV/AIDS was adopted in Montenegro till the last one for the period from 2015–2020; special emphasis is placed on prevention of HIV and other STIs among seafarers [14–16].

Initial studies that examined the association of labour migration and seafarers with HIV infection were carried out in the countries where seafaring is a traditional profession (Croatia, Germany, Turkey, etc.) [17–19].

The results of the studies [7, 12, 13, 18–20], available in foreign and domestic professional literature, unambiguously showed a lack of information of seafarers about HIV and other STIs, and indicated the need for continued public health interventions with the goal to prevent the spread of HIV and other STIs among this population.

The aim of this research was to assess the level of awareness, attitudes and behaviour about HIV/AIDS and other STIs among seafarers in Montenegro.

Methods

The survey was conducted from October 2014 to April 2015 as a cross-sectional study. For the selection of examinees, a two-stage proportional stratified sample was used. Sample frame was a list of all mariners boarding agencies, mariners educational institutions, marinerstraining centres and health care institutions in which seafarers perform mandatory health checks. The examinees were randomly selected from each agency proportionally to the number of seafarers available at the time of the survey (periods between two sailings). The criteria for the examinees to be included in the study were: not to be younger than 18 years old, to have an on board experience as seafarers at least one month, and to have no more than two years gap from the last navigation.

The research preceded the approval of the Centre for Training of Seafarers (BMV) from Bar. The methodology and study design was approved by the Ethics Committee of Faculty of Medicine, University of Priština/Kosovska Mitrovica, Serbia in accordance with the established procedure after which the research began.

The survey included the seafarers from all coastal municipalities as well as those coming from other municipalities in Montenegro and neighbouring countries in order to load on ships.

The estimated number of seafarers in Montenegro was 5,000. The survey included 543 examinees who represented slightly more than 10% of this population.

Prior to entering the research, all subjects were informed in detail about the study, the research aims and the method of collecting the necessary data. It was explained to them that the questionnaires guaranteed confidentiality by encrypting the data. Participation in the survey was voluntary and the examinees could give up at any time.

The survey instrument was a specifically structured questionnaire created by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and used in the international and domestic research [21]. A survey instrument consisting of 40 multi-part questions included the following: sociodemographic characteristics, knowledge of HIV/AIDS and STIs, attitudes towards HIV/AIDS and STIs, condom use behaviour and health-seeking behaviour. The participants in the study were offered three options in responding: "Yes", "No" and "I don't know".

The results were analyzed by descriptive and inferential statistics. For the data analysis, we used the SPSS for Win-

dows 20.0. In determining a statistically significant differences between the different variables, we used non-parametric χ^2 test. The value of $p < 0.005$ was considered to be statistically significant.

Results

The study included 543 seafarers aged 18 to 65 years. The youngest participant was 18 and the oldest one was 65 and the average age was 37.3 ± 11.6 (Table 1).

Table 1
Social demographic characteristics of examinees

Parameters	Examinees (n = 593)
	n (%)
Gender	
male	501 (92.3)
female	42 (7.7)
Age (years)	
18–27	135 (24.9)
28–37	159 (29.3)
38–47	121 (22.3)
48–57	110 (20.3)
58 and more	18 (3.3)
Education	
primary	29 (5.3)
secondary	197 (36.3)
college or university	317 (58.4)
Marital status	
married	237 (43.6)
single	263 (48.3)
widowed or divorced	43 (8.1)
Rank	
officers	196 (36.1)
interns	30 (5.5)
crew members	173 (31.9)
ship crew (cooks, waiters, stewards, etc.)	120 (22.1)
students	12 (2.2)
other	12 (2.2)

The women were engaged mostly as "white staff" (food servers, maids, waitresses, hostesses, entertainers, beauticians and hairdressers). The majority of the examinees were from Bar (33.5%), but also there were the examinees from Ulcinj (15.3%), Budva (12.4%), Kotor (9.5%), Tivat (8.7%) and Herceg Novi (8.5%). There was 9.5% of the examinees residing in the continental part of Montenegro (Cetinje, Nikšić, Podgorica) while 2.6% of the examinees were residing outside of Montenegro. Over 85% of the examinees lived in a town while the rest of them lived in a village.

The minimal number of years spent on voyages is 1 year and a maximum 47 years. The average number of years spent on voyages is 12.4 ± 9.9. When asked about the length of absence from home, 541 sailors answered that question. The sailors are usually absent from home for a period of 3–6 months (54.2%). Eighty-one (15%) sailors were absent from home less than 3 months, 150 (27.7%) for a period of 7–10 months and 17 (3.1%) for more than 10 months.

Media were dominant information sources (63.1%), as shown in Table 2.

Table 2
Distribution of the examinees in relation to the source of information on HIV/AIDS and other sexually transmitted infections

Source of information	Examinees
	n (%)
Media	343 (63.1)
Family	35 (6.4)
School/college	41 (7.6)
Ship	65 (12.0)
HIV counselling service	20 (3.7)
From friends	32 (5.9)
Other	7 (1.3)
Total	543 (100.0)

HIV – human immunodeficency virus; AIDS – acquired immune deficiency syndrome.

Slightly less than a half of the examinees, 255 (47.0%), knew that there was a counselling office for HIV/AIDS and STIs in their city. The research showed that more than two-thirds (71.8%) of the examinees had no sexual education or any form of education on sexually transmitted infections.

Slightly more than two-thirds (72%) of examinees knew that HIV could not be transmitted by a mosquito bite, while 67.4% of them knew that HIV could not be transmitted by sharing a meal with a HIV positive person. Slightly more than a third (35.5%) of the examinees knew that HIV could be transmitted by unprotected sexual intercourse with a person who looked healthy, 17.9% of them thought that HIV could be transmitted using a public toilet, 44% knew that HIV could be transmitted from an infected mother to a baby while 39.6% knew that HIV was transmitted by the used needles and syringes (Table 3).

Table 4 shows the knowledge of seafarers on the ways HIV was transmitted and the age group, education level and occupation.

Considering the age groups, there was no statistically significant difference related to the awareness of the ways in which HIV could be transmitted. Considering the level of education, a statistically significant difference existed regarding the knowledge about HIV transmission by sharing a meal with a person who was HIV-positive ($\chi^2 = 17.602$, df = 4, $p = 0.001$). The examinees who finished primary school only, showed a lower level of awareness. A statistically significant difference was noted in awareness of the examinees of HIV transmission by using public toilets ($\chi^2 = 15.206$, df = 4, $p = 0.004$).

Considering the profession of the mariners, there was a very important statistical difference regarding awareness that HIV could be transmitted through a sexual intercourse with a person who looked healthy ($\chi^2 = 39.393$, df = 10, $p = 0.000$). Lower level of awareness was perceived among the officers,

slightly more than one-fifth (26.5%) knew that this was a way of HIV transmission, while the highest level of awareness was showed by students.

When it comes to ways of protection against the HIV and STIs, the mariners did not have sufficient information on protection against HIV and other STIs. Slightly less than a half (42.9%) of the examinees thought that a proper usage of condoms prevented the infection; slightly more than a third (38.3%) thought that they could protect themselves by having sexual intercourse with one uninfected and faithful partner. Abstinence, as a way of protection, was chosen by 35.5%, while only one-fifth of the examinees were familiar with vaccine against certain STIs (Table 5).

Table 3

Questions and answers of the respondents regarding the HIV transmission

Ways of HIV transmission	Yes	No	I don't know	Total
	n (%)	n (%)	n (%)	n (%)
Sting of mosquito	83 (15.3)	391 (72.0)	69 (12.7)	543 (100.0)
Sharing food with HIV-positive person	99 (18.2)	366 (67.4)	78 (14.2)	543 (100.0)
Sexual intercourse with a person who looks healthy	193 (35.5)	139 (25.6)	211 (38.9)	543 (100.0)
Usage of public toilets	97 (17.9)	363 (66.9)	83 (15.1)	543 (100.0)
Usage of a glass that HIV-positive person have previously used	138 (25.4)	290 (53.4)	115 (21.2)	543 (100.0)
From infected mother to a child (during the pregnancy, labour and breastfeeding)	239 (44.0)	20 (3.7)	284 (52.3)	543 (100.0)
Usage of needles and syringe that have previously been used	215 (39.6)	15 (2.8)	313 (57.6)	543 (100.0)

HIV – human immunodeficency virus

Table 4

The knowledge of seafarers in relation to the age group, education level and occupation

Ways of HIV transmission	Age groups	Educational level	Rank
Sting of mosquito	$\chi^2 = 13.488$	$\chi^2 = 11.342$	$\chi^2 = 19{,}251$
	df = 8	df = 4	df = 10
	$p = 0.96$	$p = 0.023$	$p = 0.037$
Sharing food with HIV positive person	$\chi^2 = 14.356$	$\chi^2 = 17.602$	$\chi^2 = 12.812$
	df = 8	df = 4	df = 10
	$p = 0.073$	$p = 0.001$	$p = 0.234$
Sexual intercourse with a person who looks healthy	$\chi^2 = 36.434$	$\chi^2 = 9.756$	$\chi^2 = 39.393$
	df = 8	df = 4	df = 10
	$p = 0.000$	$p = 0.045$	$p = 0.000$
Usage of public toilets	$\chi^2 = 17.765$	$\chi^2 = 15.206$	$\chi^2 = 8.844$
	df = 8	df = 4	df = 10
	$p = 0.023$	$p = 0.004$	$p = 0.547$
Usage of a glass that HIV positive person have previously used	$\chi^2 = 15.313$	$\chi^2 = 7.114$	$\chi^2 = 21.078$
	df = 8	df = 4	df = 10
	$p = 0.053$	$p = 0.130$	$p = 0.021$
From infected mother to a child (during the pregnancy, labour and breastfeeding)	$\chi^2 = 19.845$	$\chi^2 = 7.114$	$\chi^2 = 25.986$
	df = 8	df = 4	df = 10
	$p = 0.011$	$p = 0.130$	$p = 0.004$

HIV – human immunodeficency virus

Table 5

Protection against HIV and STIs

Made of protection	Yes	No	I don't know	Total
	n (%)	n (%)	n (%)	n (%)
Proper usage of condoms	233 (42.9)	40 (7.4)	270 (49.7)	543 (100.0)
Having sexual intercourse with one uninfected and loyal partner	208 (38.3)	69 (12.7)	266 (49.0)	543 (100.0)
Avoiding sexual intercourse (abstinence)	193 (35.5)	122 (22.5)	228 (42.0)	543 (100.0)
Vaccination against STIs	139 (25.6)	286 (52.7)	115 (21.2)	543 (100.0)

HIV – human immunodeficency virus; STIs – sexually transmitted infections.

Next, we investigated the respondents' knowledge about protection against HIV and STIs. There was a statistical significance in terms of the frequent presence of proper usage of condoms and having sexual intercourse with one uninfected and loyal partner ($\chi^2 = 25.321$, df = 10, $p = 0.005$).

The sailors also showed a different level of knowledge concerning the existence of vaccines against certain STIs ($\chi^2 = 27.853$, df = 10, $p = 0.002$).

Discussion

The examinees participated in research between two sailings. The average age of the examinees was 37.3 ± 11.6 which correlated with the age of the examinees in the previously conducted research in Montenegro [11].

The length of service among the sailors was about one to 47 years with the average of 12.4 ± 9.8 years. Our research showed that the sailors were mostly absent for 3 to 6 months (54.2%). Data on the length of separation from the family are highly important because the longer the sailor is absent from home the greater the possibility is to have risky sexual intercourse with random partners or with commercial sex workers which is directly connected with HIV transmission. Similar results were obtained in research conducted among Montenegrin sailors in 2008 [12] and 2013 [13].

The results showed that the largest number of the examinees learnt about HIV and STIs from the media (63.1%). The percentage of the examinees who got information via media is slightly lower in relation to the results of previous research in Montenegro. The reason for this is the great availability of information about HIV and other STIs on ship (12%). The access to prevention of HIV transmission among the sailors, which was applied by nongovernmental department/sector in Montenegro through consultation and distribution of educational material (leaflets and brochures) before boarding, set up the constant availability of information and possibility of education for those who did not have sailor counselling. Similar results of the most common ways of getting information on HIV and other STIs were obtained in the research conducted among Turkish sailors in 2007. The majority of the sailors who participated in this research got information about HIV via media (68%) [19]. A research that was conducted 2011 in Italy about the perception of the risk and sexual behaviour of the sailors provided data that showed that the sailors mostly got information about HIV from medical workers [22].

This research showed that only 7.6% of the examinees got information about HIV from their family. This can be explained by traditionalism that is very common in this area [4, 8, 20].

The most common fallacy is the belief that HIV can be transmitted by a sting of a mosquito, by sharing food with infected person or by using public toilets. The results of this research showed that more than two-thirds of the examinees denied making the most common mistake in HIV transmission. The results showed that the examinees were better informed about the most common mistakes than the ones in the previously conducted research in Montenegro [12, 13].

What is alarming is the fact that more than a third of the examinees (38.9%) were aware of the fact that HIV could be transmitted by having sexual intercourse with a person who looked healthy while 25.6% of them thought that HIV could not be transmitted in this way, which is consistent with the data from other studies [4, 13, 22]. The result that only 42.9% of the examinees knew that HIV and STIs transmission can be prevented by proper and frequent usage of condoms is very alarming, but that is almost more than double when compared to the results of the research conducted in Montenegro in 2013. Only 25.6% of the examinees showed insufficient knowledge [13].

Only 38.3% of the examinees thought that they could protect themselves from HIV and STIs by having sexual intercourse with one uninfected and loyal partner. A little bit more than a third of the examinees (35.5%) knew that they could protect themselves from HIV and STIs by avoiding sexual intercourse (abstinence). The examinees showed insufficient knowledge on vaccination, namely, 52.7% of them knew that vaccination could not protect them from HIV and similar results were obtained in a research in Croatia [23] and Italy [22] as well as in the previously conducted research in Montenegro [12, 13].

Only 8.5% of the examinees perceived a personal risk of being infected by HIV as an important reason for a change in behaviour. Similar results were obtained in a research conducted among the sailors in Croatia in 2006 [5], while almost a half of the examinees of research conducted in Turkey in 2007 [19] thought that they were at a risk of being infected by HIV.

The majority of the above mentioned researces conducted not only among sailors but other populations that involve mobility and migrations with insufficient awareness of STIs and unavailability of the protection resources (condoms), showed a higher level of vulnerability to HIV of this population in comparison to those who had better living conditions [24, 25].

Out of the total number of the examinees who participated in this research, 22.3% of them were tested on HIV, 8.1% on hepatitis B and only 6.8% on hepatitis C. The examinees mainly decided to get tested on some of the STIs because they were obliged by the employer (36.9%). This fact points out that when sailors decide to get tested, this distorts the basic concept of HIV testing. The sailors decide to get tested because they are under the pressure by a growing number of foreign campaigns which is direct violation of the human rights and basic principle of testing on HIV being voluntary and confidential testing. More than a half of the examinees confirmed that they knew where they could be tested on HIV with maintained confidentiality and for free. This is the result of numerous promotion campaigns for voluntary and confidential testing on HIV that has been conducted in recent years in Montenegro.

Conclusion

The results of this research showed that beside the fact that awareness level about HIV and STIs among the sailors

was heightened in comparison to 2008, the level of awareness is still not satisfactory.

Due to increasing popularity of this profession among young people, it is necessary to establish an education program involving both sailors and managers.

R E F E R E N C E S

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Impact of surgical treatment of benign prostate hyperplasia on lower urinary tract symptoms and quality of life

Procena efekata operativnog lečenja benignog uvećanja prostate na simptome donjeg urinarnog trakta i kvalitet života

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Abstract

Background/Aim. Benign prostatic hyperplasia (BPH) is a pathological process, which is one of the most common causes of so-called lower urinary tract symptoms (LUTS). LUTS affect many aspects of daily activities and almost all domains of health-related quality of life (HRQoL). The objective of this study was to evaluate the effects of operative treatment of BPH using standard clinical diagnostic procedures and effects on LUTS using the symptom-score validated to Serbian language as well as implications on HRQoL. **Methods.** Seventy-four patients underwent surgical treatment for BPH. The study protocol included objective and subjective parameters of the following sets of variables measured before and after the surgery: voiding and incontinence symptoms were measured using the International Continence Society male Short Form (ICS male SF) questionnaire, HRQoL was measured using the SF-36 questionnaire along with standard clinical measurement of residual urine and urine flow. **Results.** After the surgery, all patients had decrease of voiding scores (13.5 ± 3.3 before and 1.5 ± 1.4 after surgery) and incontinence symptoms (5.7 ± 3.9 before and 0.6 ± 0.8 after surgery) in comparison to period before operative treatment. Significant improvements in all dimensions of HRQoL were noticed, particularly in emotional health. Although mental and physical total scores were significantly better than prior to the surgery, the level of improvement of voiding and incontinence scores were significantly correlated only with the level of improvement of mental score. **Conclusion.** After BPH surgery, patients are likely to have normal voiding symptoms, barely some involuntary control over urination and overll better HRQoL, particularly in emotional domain.

Key words:
prostatic hyperplasia; urologic surgical procedures; preoperative care; postoperative period; quality of life; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Benigno uvećanje prostate ili benigna hiperplazija prostate (BPH) je patološki proces koji vrlo često uzrokuje brojne simptome donjeg urinarnog trakta (*Lower Urinary Tract Symptoms* – LUTS) i posredno ometa obavljanje dnevnih aktivnosti, umanjuje kvalitet života (*Health-Related Quality of Life* – HRQoL) muškaraca. Cilj ovog istraživanja bio je procena efekata operativnog lečenja BPH na LUTS i na HRQoL koja je izvršena uz pomoć standardnih kliničkih dijagnostičkih procedura kao i primenom simptom-skora validiranog na srpski jezik. **Metode.** Sedamdeset četiri bolesnika podvrgnuta su operativnom lečenju zbog BPH. Simptomi mokrenja i inkontinencije mereni su upitnikom Internacionalnog udruženja muške inkontinencije – skraćena forma [*International Continence Society Male Short Form* (ICS male SF)], a kvalitet života upitnikom SF-36, i to pre i šest meseci nakon operacije. Procena kliničkih efekata operativnog lečenja je utvrđena merenjem toka i jačine mlaza urina tokom uriniranja i količine rezidualnog urina pre i posle operacije. **Rezultati.** U odnosu na period pre operacije, posle operacije svi bolesnici imali su devetostruko smanjenje učestalosti mokrenja i simptoma inkontinencije. Njihov kvalitet života bio je značajno poboljšan, izrazito u domenu emocionalnog zdravlja. Iako su bili značajno ukupno poboljšani skorovi mentalne i fizičke komponente kvaliteta života i zdravlja, nivo promene vrednosti skora mokrenja i skora inkontinencije jedino je korelisao sa nivoom promene vrednosti skora mentalnog aspekta kvaliteta života. **Zaključak.** Posle operacije zbog BPH, bolesnici će vrlo verovatno

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mokriti uobičajeno, skoro bez nevoljnog mokrenja, imaće značajno bolji kvalitet života, a posebno poboljšanje će biti u domenu emocionalnog zdravlja.

Ključne reči:
prostata, hipertrofija; hirurgija urološka, procedure; preoperativna priprema; postoperativni period; kvalitet života; ankete i upitnici.

Introduction

Benign enlargement of prostate, or benign prostatic hyperplasia (BPH) is a pathological process, which is one of the most common causes of the so-called lower urinary tract symptoms (LUTS) [1]. A multinational population-based survey points to the high prevalence of LUTS in older population [1], suggesting that focus should be on finding treatment strategies of LUTS and BPH that are efficacious, safe and manageable solution which also improves quality of life of patients [2] having in mind an increasing likelihood that a male will seek help for LUTS attributable by BPH along with a prolonged life expectancy [3]. LUTS affect many aspects of daily activities, and almost all health dimensions: Physical Function (PF), Role Physical (RP), Body Pain (BP), Global Health (GH), Vitality (Vit), Social Function (SF), Role Emotional (RE), Mental Health (MH) 4. Among many factors attributable to LUTS 2, benign enlargement of prostate is a major clinical and public health problem [5]. Recent attempts to improve diagnosing of LUTS attributable by BPH include a number of questionnaires for patients in addition to standard clinical examination and diagnostic procedures to document how LUTS affects in particular a quality of patient's life. These surveys became an indispensable part of the algorithm tests prior decision-making about the treatment and are common element of every assessment of the treatment effects [6, 7]. Although the International Prostate Symptom Score (IPSS) is the most famous [8], its variations are used in practice [9, 10]; their biggest drawback is that they do not examine the symptoms of incontinence, since it was thought that incontinence is primarily a female issue. In recent years evidence have shown that men also suffer from urination difficulties and incontinence leading to the deterioration of health-related quality of life (HRQoL) [11]. A short form of the questionnaire of the International Association for Incontinence thoroughly and accurately defines the urinary symptoms and incontinence [9, 10, 12]. Additionally, it is important to measure the patient's quality of life appropriately and to provide a valid and psychometrically proper patient's opinion and experience in an efficient way [13].

To evaluate the effects of operative treatment of BPH on LUTS and on HRQoL in this study, apart from the standard clinical diagnostic procedures, the new symptom-score standardized instruments were applied: 36-item short-form health survery (SF-36) [13] for self-assessment of HRQoL of patients with various chronic diseases, and a short form of the questionnaire of the International Association for Incontinence that is culturally adapted to the Serbian context[10].

Methods

Study design and participants

This prospective study was conducted at the Clinic of Urology, University Clinical Centre of Serbia in Belgrade in the period from December 2015 to August 2016. The sample size of the study participants was calculated based on the formula for calculating the sample size for the error level $\alpha = 0.05$ and power of the study $1\beta = 0.8$. The required sample size to detect a statistically significant difference in LUTS and HRQoL was projected to 41 patients [13]. The study included 74 patients. All of them underwent endoscopic transurethral prostatectomy (TURP) or classic transvesical prostatectomy (PTV). The criteria for inclusion into the study were patients with informed consent and a diagnosed subvesical obstruction due to BPH, previously treated pharmacologically (alpha blockers and 5-alpha reductase inhibitors), and age of 40 years and above. The criteria for exclusion from the study were: mental inability of the patient to fill out the questionnaire, depression (established by Beck's Depression Scale the day before surgery) and patients who refused to participate in the study.

Study instruments and variables

The study included both subjective and objective approach for measurement of the outcomes of surgical treatment of BPH with regard to the LUTS and HRQoL. On admission to the Clinic, patients filled two Serbian version questionnaires of ICS male SF questionnaire, and then the SF-36, a general questionnaire used for assessing the quality of life. After that, they underwent ultrasound examination with measurement of prostate volume, residual urine and uroflowmetry. The patients with urinary catheter did not take the uroflow preoperative testing (Qmax – maximum flow rate), average flow rate and residual urine. For comparison with the original condition of the patient, the study protocol and clinical measurements were repeated 6 months after the date of the operation.

Statistical analysis

Data are presented as means ± standard deviations. The preoperative and postoperative values were compared using *t*-test and Wilcoxon Signed Ranks Test. Correlation analysis was used to assess the relationship between voiding and incontinence delta scores and quality of life delta scores. The Delta score was calculated as difference between the first and the second measurement of examined variable. The first measurement was obtained during hospital admission and the second measurement was obtained 6 months after the surgery. All *p* values less than 0.05 were taken as the values for the rejection of the null hypothesis. All data were analyzed in the SPSS 20.0 (IBM Corporation) software package.

Results

Mean age of patients was 66.7 ± 10.1 years and 37 (50%) patients had urinary catheter at hospital admission. All patients had prostate volume measured and average volume was 55.6 ± 30.8 mL.

According to the results in Table 1, a significant decrease of voiding and incontinence symptoms was observed in all patients. At the same time, all dimensions of quality of life revealed a significant increase of the scores, except mental health. The highest change was observed in the emotional health dimension.

Table 1

New system-score measurements of LUTS and HRQoL: ICS-male SF and SF-36 results before and after the surgery of BPH (n = 75)

Tests	Before surgery (mean ± SD)	After surgery (mean ± SD)	*p* value
ICS-male SF			
Voiding	13.49 ± 3.30	1.50 ± 1.37	< 0.001[a]
Incontinence	5.74 ± 3.97	0.57 ± 0.79	< 0.001[a]
SF-36			
Physical function	60.34 ± 27.11	66.92 ± 24,10	< 0.001[a]
Role Physical	44.18 ± 40.07	61.30 ± 31.74	< 0.001[a]
Body pain	47.64 ± 26.46	60.73 ± 22.72	< 0.001[a]
Global health	42.78 ± 15.72	45.37 ± 14.28	0.008[a]
Vitality	51.64 ± 10.99	57.12 ± 11.21	< 0.001[b]
Social function	49.88 ± 21.01	62.53 ± 18.55	< 0.001[b]
Emotional	29.64 ± 36.27	65.36 ± 34.05	< 0.001[b]
Mental health	53.59 ± 6.76	52.82 ± 6.32	0.305[a]

[a]Paired samples *t*-test; [b]Wilcoxon Signed ranks test.
LUTS – lower urinary tract symptoms; ICS-male SF – International Continence Society male Short Form; SF – 36 item short- form survey; BPH – benign prostatic hyperplasia; SD – standard deviation.

Clinical parameters measured before and after surgery revealed an objective improvement (Table 2). While Qmax and flow rate revealed 2 and 6 times higher values, respectively, residual urine decreased 6 times.

The level of change of the voiding and incontinence parameters correlated with levels of change of the HRQoL parameters. According to results of correlation analysis, only significant correlation was observed between Role Emotional change and voiding and incontinence change (Table 3). Other correlation coefficients that were near conventional significance level were between incontinence change and Bodily Pain and Social Function change. Since those coefficients were near conventional level of significance (0.05), they were taken in further consideration.

Discussion

Benign prostatic hyperplasia and subsequent LUTS are very frequent pathology in Europe [1, 5, 14] . Global predictions are that by 2018, nearly 1,6 billion people will suffer from the symptoms of urine storage, and over 540 million people will suffer from symptoms of overactive bladder [2]. As well as globally, aging of the population in Serbia is also contributing factor to the growth of incidence and prevalence. This study found that a majority of the patients with LUTS was in the seventh and eighth decade of life. BPH is a progressive disease and untreated enlargement of the prostate leads over time to LUTS and may be further complicated by acute or chronic infections. LUTS compromises everyday functionality and affects all HRQoL domains causing numerous psycho-physical disorders [4].

Table 2

Clinical parameters used for evaluation of surgical procedure

Clinical parameters of the patients (n = 75)	Before surgical procedure (mean ± SD)	After surgical procedure (mean ± SD)	*p* value
Qmax	8.82 ± 3.05	22.76 ± 4.08	< 0.001
Average flow rate	4.21 ± 1.59	10.55 ± 3.58	< 0.001
Residual urine	87.50 ± 44.47	12.63 ± 18.69	< 0.001

[a]Paired samples *t*-test.
SD – standard deviation; Qmax – maximum flow rate.

Table 3

Correlation of voiding and incontinence scores changes and HRQoL score changes, n = 75 patients

Health dimensions	Delta voiding		Delta incontinence	
	Correlation coefficient.	*p* value*	Correlation coefficient	*p* value*
ΔPF	0.027	0.824	-0.149	0.208
ΔRP	-0.049	0.679	-0.129	0.278
ΔBP	-0.197	0.095	-0.210	0.074
ΔGH	-0.187	0.113	-0.013	0.914
ΔVit	-0.149	0.210	0.012	0.918
ΔSF	-0.145	0.220	-0.208	0.078
ΔRE	-0.229	0.049	-0.237	0.043
ΔMH	-0.057	0.631	0.113	0.341

PF – physical function; RP – role physical; BP – body pain; GH – global health; Vit – vitality; SF – social function; RE – role emotional; MH – mental health.
***Pearson's correlation analysis.**

An urgent condition in urology and one of the major complications and unambiguous sign of BPH disease progression is acute urinary retention (AUR) [15]. Progression of the disease is rarely linear and an acute detrusor decompensation of bladder may be the reason for the occurrence of AUR, and the other way is a chronic, weakening of the detrusor, RU accumulation and retention. Verhamme et al. [16] stated that in almost a half of the patients included in their study, AUR was the first reason for reporting to the urologist.

The volume of the prostate as a risk for the AUR occurrence and surgical treatment is the most studied entity. Studies affirm the assumption that patients with the prostate volume greater than 30 mL are in a higher risk of BPH complications, or progress to a stage when the surgical treatment becomes a modality of choice [17, 18]. Measurement of residual urine in the bladder after urination is a common diagnostic procedure for patients with LUTS. Finding larger quantities of RU along with weak Qmax is often considered as a sufficient indication for surgical treatment [6]. Large quantities of RU, especially with hydronephrosis, are an indication for a urinary catheter placement. Kolman et al. [19] indicated that the patients with RU greater than 50 mL were in a high risk of developing AUR. Mochtar et al. [20] suggested that the patients with RU larger than 300 mL were in prospective likely candidates for surgical treatment. The RU values in the present study ranged from 40 to 300 mL. In the postoperative follow-up of the treated patients in our study, similarly to a study by Varkarakis et al. [21] , a drastic reduction (almost as much as seven-times) in the average values of residual urine occured. Uroflowmetry is an essential part of the diagnostic algorithm, and, despite all the constraints, uroflow is a significant indicator of urination disorders. Crawford et al. [18] found that the value of Qmax below 10 mL per second represents a probable disease progression in prospective. Uroflowmetry was done preoperatively for the patients who did not have a catheter and postoperatively for all the patients. The low values of Qmax, from 4 to a maximum of 14 mL/s were recorded preoperatively. A drastic increase in Qmax was determined postoperatively. This finding is similar to the findings in the study by Varkarakisa et al. [21], or Hakenberg et al. [22] as well as the meta-analysis of Lee et al. [23], who agreed that surgical treatment of BPH, among other things, lead to an increase in Qmax. When conservative treatment does not produce satisfactory results, a surgical treatment is becoming the treatment of choice. TURP is the gold standard in the treatment of BPH, but for prostate of greater volume PTV is the method of choice. In the United States, this operation is applied to only 3% of patients surgically treated for BPH [24]. In our study, 23% of patients underwent transvesical prostatectomy. There is a generalized belief that this traditional, open surgical technique is represented only in the economically less developed countries, however, studies suggest somewhat a greater representation of these operations, so that in Sweden, almost 12% of the patients are operated on by this technique [25], and 14% in France [26]. Some studies suggest an even larger share of PTV of the total number of the operated, so Serretta et al. [27] in the Italian study stated that 32% of the total number of patients were subjected to PTV, and 40% in the study by Mozes et al. [28] conducted in Israel.

The change of summary scores of voiding and incontinences on discharge was analyzed subsequently and 6 months after the date of surgery. The values obtained before and after surgery were significantly different in terms of reduction of the voiding scores during the second measurement. These results are complementary with the results of different studies dealing with similar comparative analysis of pre- and postoperative treatment both for TURP and PTV [21, 29, 30]. The intervention drastically reduces the detrimental impact of voiding on quality of life of all patients and this finding is consistent to other studies [21,29,30]. Namely, a large number of patients who had a deteriorating quality of life prior the surgery due to frequent voiding, after the surgery reported “it does not affect” or “little”.

Physical Function (PF) is one of the domains of quality of life of SF 36 scale affected by LUTS. Incontinence rather than voidance significantly reduces the PF [2, 5, 31]. Slight, but statistically significant increase of the score of PF was determined 6 months after the surgery. Engstrom et al. [32] reported that difficulties related to urination, especially waiting for the voiding, straining during voiding and incomplete emptying of the bladder lowered the physical score. In our study, the surgical treatment statistically significantly increased the ability of patient’s physical role approximately for 20%. According to Speakman et al. [14] the quality of overall health was affected by symptoms of LUTS, though insignificantly. Our study found a little, but a statistically significant improvement of the overall health score and vitality 6 months after the treatment.

According to the available literature, the Social Function (SF) score is most deteriorated by incontinence, particularly among elderly patients [32]. In our study, surgical treatment yielded an evident, a statistically significant improvement in the score of the SF. Welch et al. [33] in their study showed that LUTS significantly and negatively affect the Role Emotional (RE) due to diseases such as gout, hypertension, angina pectoris, and diabetes mellitus. Our testing showed that surgical treatment lead to a statistically significant improvement in this score. The impact of LUTS on Mental Health (MH) is one of many variables that we examined. Hunter et al. [31] stated that LUTS affected mental health significantly more negatively than back pain, varicose veins or ulcers. In our study, only patients with good or satisfactory mental status were included, since all patients with a score over 20 at Beck depression test were excluded from the study. That may explain why differences in the average mental health values before and after the surgery in our study were small and statistically insignificant. However, a comparative analysis of the total physical and mental scores before and after surgery undoubtedly indicated their significant increase after the surgery, which supports the justification and appropriateness of the operative treatment to solve LUTS caused by BHP.

Welch et al. [33] emphasized the impact of surgical treatment on the following domains: physical role, vitality, emo-

tional role, the total physical score, PF, bodily pain, social functioning and mental health. At the same time, they indicated a deterioration of HRQoL that was directly proportional to deterioration of LUTS. Welch et al. [33], Hunter et al. [31] and Engstrom et al. [32] recognized that LUTS, and especially incontinence, disturbed most of the domains of quality of life. The total score of quality of life was of significantly higher value after the intervention compared to the value before the intervention. The lowered total score of quality of life caused by severe LUTS was also present in the study by Quek [34] and the study by Haltbakk et al. [35], which especially emphasized the population of advanced age but also in a population study conducted in Serbia [2]. Meta analysis made by Ahyai et al. [29] showed that TURP reduced the IPSS QoL score ($p > 0.3$), similar to bipolar TURP and the HoLEP laser's resection of the prostate. Varkarakis et al. [21] showed the chronology of statistically significant improvement in the IPSS QoL score after the PTV in the immediate postoperative period, then 8 and 12 months after surgery.

This is a pioneer study in Serbia, which assessed the effects of operative treatment of BPH on LUTS and HRQoL by applying the new system-score instruments, but it had some limitations. Although the sample was representative to detect statistically significant results, the study findings are specific to the Serbian patients and should not be generalised prior verifying them on a larger sample. In addition, it represents the work results of one clinic, which is the tertiary level one and the university based inpatient care facility, therefore service differences should be considered in a comparative analysis. Though both system-score instruments, the SF-36 questionnaire and ICS male SF, are standardised questionnaires and culturally adapted, they are self-administered and may contain a portion of under- or overestimation of some aspects of quality of life and LUTS, due to the patients' cognitive abilities, such as memory, or willingness to report private issues. Finally, this study showed results of 6 months follow-up after surgery which is a short-term effect rather than impact assessment which requires recording 12 months and more after the surgical treatment.

Conclusion

After the surgery, almost all dimensions of quality of life keep changing significantly towards greater score, which clearly suggests the positive impact of the intervention on patient's quality of life, including very large (e.g. emotional role) and small (e.g. overall health) improvements. After the BPH surgery, the patients are likely to have normal voiding symptoms, almost annulated involuntary control over voiding and better all HRQoL dimensions.

The surgical treatment of BPH either as classic or endoscopic surgery, leads to the improvement of the objective clinical parameters, to the release from catheter as well as to a reduction of residual urine and increase in Qmax. The operation significantly reduces the subjective parameters in voiding symptom score and incontinence measured by the ICS male SF questionnaire, in contrast to the most famous IPSS score. This approach precisely measure difficulties in voiding and incontinence and is a reliable diagnostic tool, highly recommended as complementary measurement of the subjective and objective parameters of LUTS and HRQoL prior and after the treatment of BPH.

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Surgical treatment of unstable pelvic ring fractures

Hirurško liječenje nestabilnih preloma karličnog prstena

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Abstract

Background/Aim. Pelvic ring fractures are complex injuries and are often associated with internal organs injuries. These injuries require rapid and accurate diagnosis and in some cases one or more surgical interventions. The aim of this retrospective study is to describe the indications and outcomes of surgical treatment of pelvic ring injuries with the emphasis on anatomical reconstruction and stable osteosynthesis as a prerequisite for early mobilization and more favorable functional outcomes. **Methods.** In the period from 2006 to 2012, fifty-five patients with pelvic ring injuries with or without acetabular fractures were analyzed. The average age of all patients was 36 years. Forty-one patients were treated with operational open reduction and internal fixation (ORIF) while nine of them were treated nonoperatively (bed rest, skeletal traction and external fixation). **Results.** All operated patients were treated within 3-24 days with ORIF, stable osteosynthesis and early mobilization which resulted in avascular necrosis (AVN) of the femoral head in two cases. AVN of the femoral head was noted in five cases in combined and isolated pelvic ring injuries and acetabulum which were treated with skeletal traction. Neurological deficit was recorded in three patients treated with conservative methods while two patients underwent ORIF. Deep vein thrombosis (DVT) was noted in two patients and pulmonary thromboembolism appeared in one patient 23 days after surgical intervention. Two infections occurred around Steinman pins in the patients who had the definitive treatment performed with external fixator. In one patient treated with ORIF a superficial infection occurred and was treated with antibiotics. The functional results were evaluated based on Merle d'Aubigné score. The results of the radiography treatment were analyzed according to Slatis. **Conclusion.** Strict application of rational criteria and surgical technique with stable internal fixation with early mobilization provide significantly better outcomes of these injuries in relation to non surgical treatment or treatment with definitive external fixation.

Key words:
pelvic bones; fractures, bone; orthopedic procedures; open fracture reduction; fracture fixation, internal; treatment outcome.

Apstrakt

Uvod/Cilj. Povrede karličnog prstena su kompleksne povrede udružena sa povredama unutrašnjih organa. Ove povrede zahtevaju brzu i tačnu dijagnozu i u nekim slučajevima jednu ili više hirurških intervencija. Cilj ove retrospektivne studije je bio da opiše indikacije i ishode hirurškog lečenja povreda karličnog prstena sa akcentom na anatomsku rekonstrukciju i stabilnu osteosintezu, kao preduslov za ranu mobilizaciju i povoljniji funkcionalni rezultat. **Metode.** U periodu od 2006. do 2012. god. analizirano je 55 bolesnika sa povredom karličnog prstena, sa i bez preloma acetabuluma. Prosečna starost svih bolesnika je bila 36 godina. Operativno otvorenom repozicijom i internom fiksacijom (ORIF) lečen je 41 bolesnik, a devetoro njih neoperativno (lečeni su mirovanjem, skeletnom ekstenzijom i spoljašnjom fiksacijom). **Rezultati.** Svi operisani bolesnici tretirani su unutar 3–24 dana ORIF stabilnom osteosintezom i ranom mobilizacijom. Kao posledica, pojavila se avaskularna nekroza (AVN) glave femura kod dva slučaja. AVN glave femura je zabeležena kod pet slučajeva kod kombinovanih i izolovanih povreda karličnog prstena i acetabuluma, koji su lečeni skeletnom ekstenzijom. Neurološki deficit je zabeležen kod trojice lečenih konzervativnim metodama i kod dvojice operisanih ORIF. Duboka venska tromboza (DVT) je konstatovana kod dva bolesnika, a plućna tromboembolija kod jednog operisanog i to 23 dana posle hirurške intervencije. Desile su se dve infekcije oko Stajmanovih klinova kod bolesnika kod kojih je definitivno lečenje provedeno spoljašnjim fiksatorom. Kod jednog bolesnika tretiranog ORIF nađena je površna infekcija koja je sanirana primenom antibiotika. Funkcionalni rezultati su procenjeni na osnovu M. d'Aubigné skora. Rezultati lečenja putem radiografije analizirani su prema Slatis-u. **Zaključak.** Striktna primena racionalnih kriterijuma i hirurška tehnika sa stabilnim internim fiksacijama uz ranu mobilizaciju daju značajno bolje ishode ovih povreda u odnosu na neoperativni tretman ili tretman sa definitivnom spoljašnjom fiksacijom.

Ključne reči:
karlica; prelomi; ortopedske procedure; prelom, otvorena redukcija; osteosinteza; lečenje, ishod.

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Introduction

Pelvic ring fractures are complex injuries and are often associated with internal organs injuries. These fractures are among the most severe injuries which often happen in traffic accidents, sometimes with significant consequences. These injuries require rapid and accurate diagnosis, and in some cases, one or more surgical interventions [1].

Good estimate of general life threat and classification of injury is very important in these patients as well as the acute treatment of injuries. At this stage of treatment, the first priority is to save the life of a patient by applying appropriate reanimation procedures with a temporary stabilization of the pelvic ring (external fixator, C - ram, etc.), and appropriate surgical interventions of other system, if necessary (head, abdomen, chest, etc.). After stabilizing the general and hemodynamic status, it is necessary to pass on to the definitive treatment of these injuries in the period up to 4 weeks [2].

Stability of all articulations is given through three factors: bone stability, stability of capsular ligaments soft tissue and dynamic stability of muscle structures (minimum contribution). The sacrum is the "cornerstone" for bone stability of the pelvic ring when the ligament apparatus is intact. Sacroiliac ligaments are the most important for the stability of the posterior segment. There are various opinions (classifications) on defining zones of pelvic ring instability. Some are focused on the instability and some on the cause of injury: classifications by Tile [3] and March et al. [4].

The decision on operative treatment is made only after quality and adequate diagnosis. When admitting a patient to the emergency services, it is important to determine the mechanism and severity of the injury. That primarily refers to the assessment of pelvic ring deformity, length and rotation of extremities as well as the assessment of soft tissue condition when physical examination of the patient is performed. Radiographic examination includes standard imaging of the pelvic ring (antero-posterior – AP profile, inlet and outlet), and in the case when acetabulum injury is suspected, two semi-angled images are also made [5].

For preoperative planning, timing is very important. Due to associated injuries, a good coordination of more specialties is necessary: the extremities, neurosurgical, abdominal, urological, etc. For stabilization of hemodynamic instability a C-clamp/ external fixator, sheet or pelvic binder must be applied, and must be removed for definitive treatment, usually within a period of 5-7 days after the injury [5, 6].

The choice of surgical approach also includes an adequate selection of the position of a patient, a repositioning technique and fixation of fractures in accordance with all biomechanics osteosynthesis principles. For reduction and fixation of fractures of the pelvic ring, the specific instrumentation and the appropriate set of osteosynthetic material is necessary (osteosynthetic material adequate for the injury – reconstruction plates and titanium material are used; they provide firmness to external and internal forces of rotation and movement) [7].

Pelvic ring injuries with dislocations and signs of instability are treated surgically since conservative treatment gives poor results in these cases. Surgery can be performed openly, percutaneously or can be combined. Open techniques provide better visualization and easier fixation, but their disadvantages are the risk of infection, blood loss, possible surgical soft tissue injuries and large scars [7]. Percutaneous techniques are increasingly applied due to less surgical traumatization of tissue and blood loss, having as a disadvantage the increasing radiation exposure to both patients and health care personnel. The combination of the open and percutaneous approach is a good choice, especially if a stabilization of the pelvic ring in more places is needed [8, 9].

In preventing complications, it is most important to recognize soft tissue injuries, to avoid incisions through compromised tissue, to use the appropriate osteosynthetic material and be careful when placing implants [10, 11].

In the end, the outcome of the treatment will be significantly more favorable.

Methods

In the period from 2006 to 2012, fifty-five patients with pelvic ring injuries with or without acetabular fractures were analyzed. The average age of all patients was 36 years. Forty-one (74.5%) patients were operationally treated and fourteen (25.5%) non-operatively. Fourty-one patients who underwent open reduction and internal fixation (ORIF), stable osteosynthesis and early mobilization constituted the first group (Figure 1), and fourteen patients who were only treated with bed rest, skeletal traction and external fixation are classified in the second group (Group II).

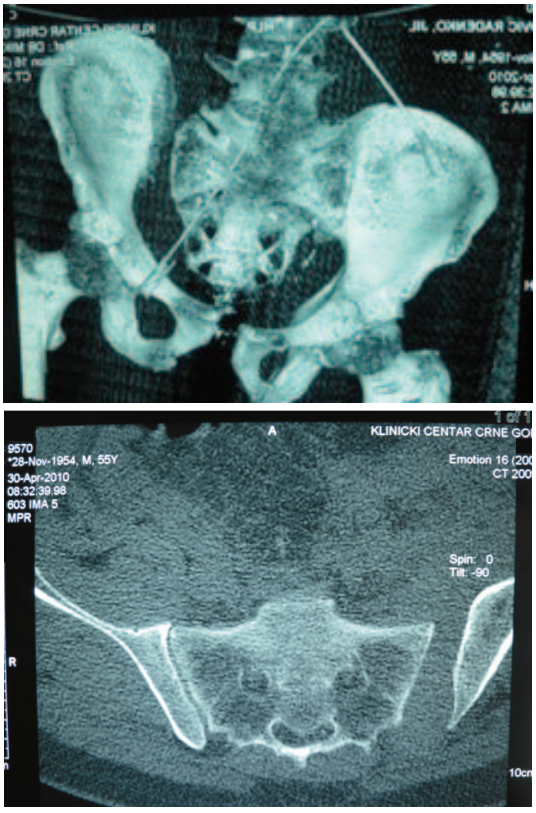


Fig.1 – Vertical and rotational instability of the pelvic ring [computed tomography (CT)].

In all cases computed tomography 3D (CT 3D) reconstruction was performed which significantly helped us in defining the instability of the pelvic ring. The indication for surgery was given based on the degree of pelvic ring instability determined according to Marvin Tile classification [3]. According to this classification, the representation of patients was: type A – 26%, type B – 44% and type C – 30%.

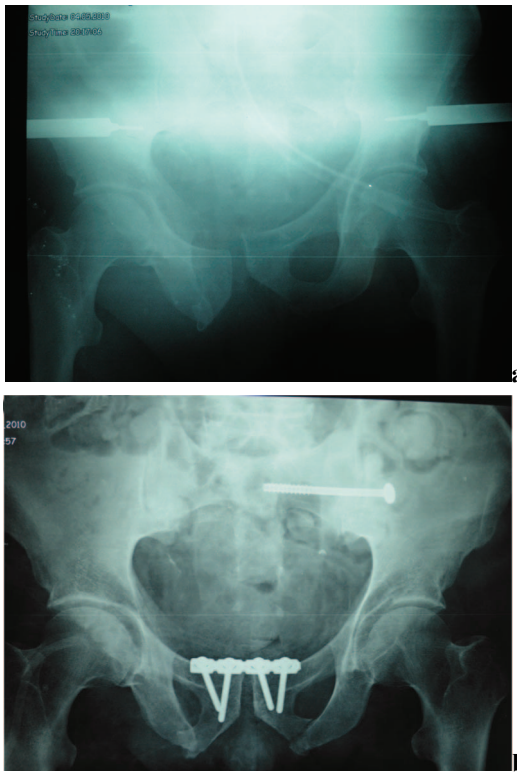
Regarding a form of associated injuries with other systems, it could be seen that there were 19.2% head injuries, 14.8 % abdominal injuries, 11.4% thorax injuries, 5.6% spine injuries and 49.0% extremity injuries.

Preoperatively, all patients were given a low dose anticoagulant therapy to prevent blood clotting. Sometimes, magnetic resonance venography (MRV) was performed in order to determine the existence of a possible blood clot in the veins of the injured pelvic ring or extremities.

Stabilization of the pelvic ring with a C-clamp or external fixator must be performed before eventual laparotomy, or other surgical procedures of any region. After stabilizing the hemodynamic status in the period of up to 4 weeks, we made a decision on definitive open reduction and internal fixation of the injured pelvic ring.

There were 27 (49.1%) isolated pelvic ring injuries. According to the gender structure, 19 were in men and 8 in women of the average age of 35 years. The average number of operations per patient was 1.3.

According to the definitive treatment method, ORIF with one or more plates was performed in twenty-one patients, stabilization was definitely completed by external fixator in four patients and two patients were definitely treated with skeletal traction (Case 1: Figures 1 and 2).



a)

b)

Fig. 2 – a) Primarily fixed C – clamp; b) Definitive osteosynthesis.

There were 28 (50.9%) combined pelvic ring and acetabulum injuries of which 19 in the male patients, 9 in the female patients of the average age of 37 years. The average number of surgeries in this group of patients was 1.8. According to the method of treatment, three patients were definitely treated with skeletal traction, only two with bed rest, while twenty-three patients were definitely internally stabilized with one or more plates and free screws. The patients who were not treated surgically had comorbidities or refused surgery (Case 2: Figures 3 and 4), (Case 3: Figures 5–8).

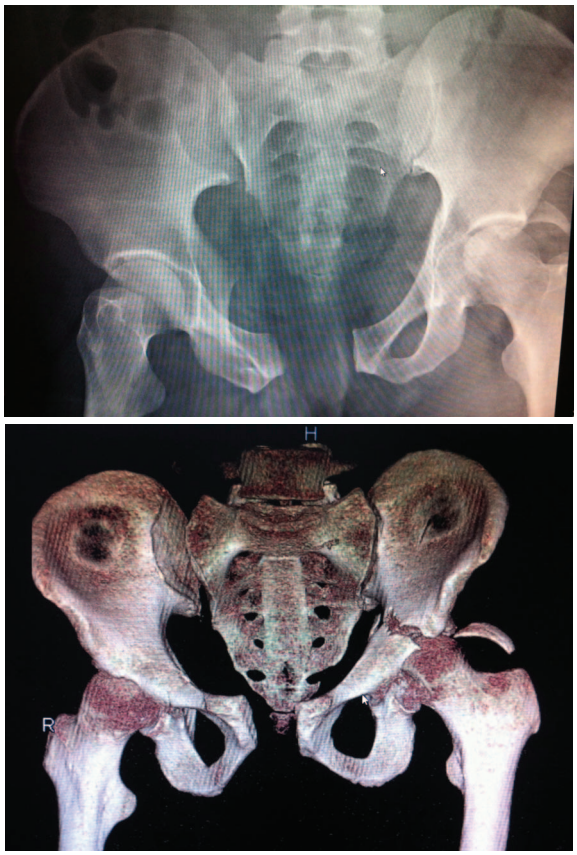


Fig. 3 – The instability of the anterior and posterior segment of the pelvic ring associated with an acetabular fracture and the lower part of the femoral head (Pipkin fracture – Type IV).

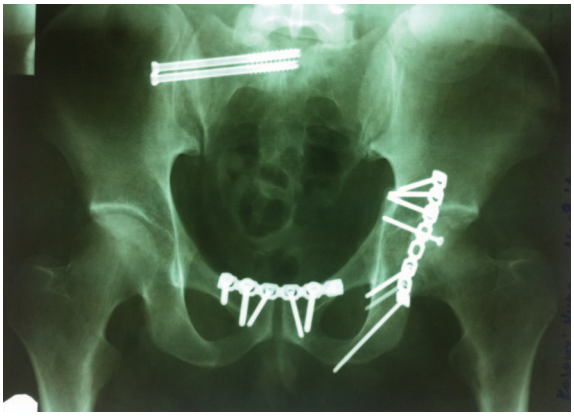


Fig. 4 – Definitive osteosynthesis open reduction and internal fixation (ORIF) combined with the percutaneous technique.

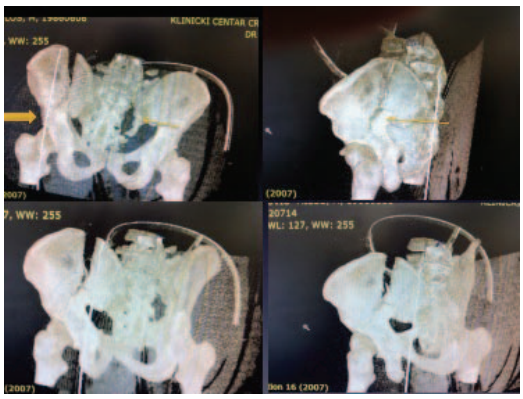


Fig. 5 – Posterior pelvic ring segment instability [computed tomography-3D (CT – 3D)].

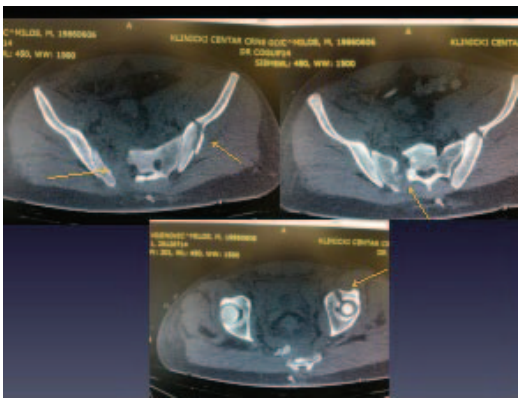


Fig. 6 – Denis II sacral fracture with acetabular fracture.

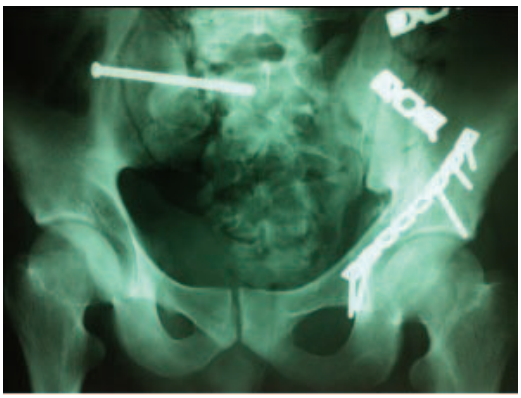


Fig. 7 – Definitive osteosynthesis.

Fig. 8 – Functional outcomes 8 months after injury.

Postoperatively, all patients received anticoagulation therapy for the period of up to 6 weeks. In the beginning, pain management includes analgesics. In severe cases, the patient-controlled analgesia (PCA) pump was used, and therefore there was no danger that the patient receives too much pain medication. The average period of postoperative follow-up in the patients was 16 months (range of 6–36 months). For more objective assessment of functional clinical results of our patients, the following scoring was used: pain, daily life activities, a range of motion, power (PARP) – according to the Modified Merle d'Aubigné and Postel scoring system. The outcomes of treating the patients by using radiography were analyzed according to Slatis [6, 12].

Results

Analyzing the outcomes of isolated pelvic ring fractures, treatment in those who, in our series of patients, besides the unstable pelvic fracture had an acetabular injury, the assessment of the clinical functional status was made by using the Merle d'Aubigne and Postel scoring system (Table 1) [6]. According to the methods of medical treatment, the patients were divided into two groups: the first group comprised the patients treated by stable osteosynthesis with 1, 2 or more reconstruction plates and free screws. The second group comprised the patients treated by bed rest, skeletal traction or external fixator (Tables 2 and 3).

Table 1

Numerical strength of isolated pelvic ring injuries and combined acetabulum and pelvic ring injuries

Injuries	Group I (n)	Group II (n)	Total (n)
Pelvis	18	9	27
Pelvis/acetabulum	23	5	28
Total	41	14	55

Group I – patients treated by stable osteosynthesis
Group II – patients treated by bed rest, skeletal fraction or extenal fixator.

Table 2

Analysis of the functional status outcomes

Outcomes	Group I (%)	Group II (%)
Pain	19	55
Activities	87	40
ROM	63	33
Power	94	61

ROM – range of motion.
For explanation see under Table 1.

Our results in the Table 3 showed that the radiological outcomes were better in the group I ($p < 0.03$). The analysis of radiological outcomes was evaluated based on distance between fragments at an anterior or a posterior pelvic ring segment as follows: excellent from 0–5 mm, good 6–8 mm, satisfactory 9–11 mm and and poor from 12 mm and above.

Table 3

Radiologic outcomes

Group*	Radiologic outcomes			
	Excellent	Good	Satisfactory	Poor
Group I, n (%)	20 (48.8)	12 (29.3)	6 (14.6)	3 (7.7)
Group II, n (%)	2 (13.3)	1 (6.7)	3 (20.0)	9 (60.0)
		$p < 0.03$		

The outcome of radiography treatment – Slatis.
For explanation see under Table 1.

Three patients who were treated with external fixation or traction had a neurological deficit at the L4, L5 and S1 levels, while three of them recovered during the follow-up within the average period of 16–36 months. The sensory deficit in levels S1-S2 roots was isolated in two patients treated by stable osteosynthesis, one at multifragmental sacral fracture, type Denis zone 2 fracture. Two patients treated conventionally and with traction and only one treated with stable osteosynthesis had a deep vein thrombosis (DVT). Poor consolidation and re-dislocation of the fracture was observed in five cases where the treatment included external fixation or skeletal traction. Avascular necrosis (AVN) of the femoral head occurred in two patients with unstable osteosynthesis treated with screw and traction, and in only one treated with stable fixation. Sexual dysfunction was not recorded in any group of the patients. Three patients from the Group I and one from the Group II had ectopic ossification (Table 4).

Table 4

Numerical strength of complications in both groups

Complications	*Group I (n)	*Group II (n)
DVT	1	2
Pulmonar trhomboemboli	1	0
AVN	2	5
Infection	0	2
Ectopic. ossifikation	1	3
Sexual disfunction	0	0
Neurological deficit	2	3
Nonunion	0	1
Malposition	0	3
Symphyseal fusion	1	0
Pelvic obliquity	0	2

AVN – avascular necrosis; DVT – deep vein thrombosis.
***For explantion see under Table 1.**

Discussion

Unstable pelvis and acetabulum fractures require definitive stabilization since the injury itself and the type of surgical procedure directly affect the subsequent quality of patients' lives. Two-thirds of these injuries were from road traffic accidents, primarily involving motorcyclists and pedestrians, and only then involving the other traffic participants. One third was caused by a fall from height, most often to construction workers [2, 13].

Pelvic fractures are the result of the force of high intensity and if associated with the injuries of extremities, head, abdomen, chest - within polytrauma, mortality rate is very high (60% –80%), and if the injury is isolated, the rate amounts to 10% [13, 14]. Four deaths in emergency patients with unstable pelvic ring fractures in polytrauma were not considered in this paper since no temporary pelvic stabilization was performed during reanimation measures (sheet, pelvic binder, external fixation, C-clamp). The reason for such the outcome was the absence, at that time, of the appropriate protocol of unstable pelvic ring fractures treatment in polytraumatized patients in our Clinical Centre.

Unstable pelvic ring and acetabulum injuries treated with the conventional closed methods often result in significant disability, and mortality rate drastically increase [8, 9, 13]. We opted for a non-operative treatment in patients with multiple life-threatening chronic diseases and in patients where their families or they themselves did not agree to suggested surgical interventions, i.e., did not receive the consent of an anesthesiologist and internist for performing stable internal fixations in an adequate period of time, up to 4 weeks after the injury.

Some authors state that the use of external fixation significantly reduces venous and bone bleeding, maintains a good stability of the pelvic and that other interventions are not necessary [6, 14, 15]. Biomechanical studies showed that external fixators could not provide sufficient stability to allow for mobilization without the risk of redislocation of fragments. The use of external fixators or C-clamps in unstable pelvic injuries is applied in urgent cases, and helps in stabilizing the hemodynamic status [16]. External fixators can be used temporarily in unstable injuries as part of emergency treatment to allow the patient to be placed in the upright position to improve ventilation. In our material, external fixator or C–clamp was applied in fourteen cases, and the same were removed within a period of 5–7 days and a definitive internal osteosynthesis was done. Patients with such stable osteosynthesis were earlier mobilized without a greater risk for redislocation of fragments. Early mobilization of patients is affected by whether there are other skeletal injuries which required surgical intervention, i.e., disburdening of that extremity [17, 18].

In sacroiliac joint (SI) injuries, stabilization technique with percutaneous techniques, cannulated screws, is biomechanically superior to other methods of internal fixation. Due to minimal surgical aggression, the bleeding is slight, functional results are satisfactory in 96% of cases while radiological results are satisfactory in 86% of cases [4, 19]. In our patients, 14 percutaneous stabilizations of the SI joint with one or two screws were done. The fixation with 2 cannulated screws gave firmer stabilization without radiological signs of instability, which was noted in single screw fixation. This percutaneous technique is demanding and requires a good knowledge of anatomy and its radiological correlation in order to avoid complications.

A large number of authors agree that functional outcomes depend on whether the patients had associated injuries (open fractures, bladder and urethra injuries, craniovertebral and thoracic injuries ...) accompanied by deep vein thrombosis, pulmonary embolization and neurological outbursts of lumbosacral plexus [17, 20].

Prevalence of primary neurological injuries in this study is 26%. Four patients in the Group I with a combined motor and sensory neurological deficit at the L4, L5, S1 levels nerve fully recovered at the time of follow-up within 16–36 months. In all patients, a stable internal fixation was done, which a large number of authors cited as a reason for more favorable prognosis. Three patients from the Group II were monitored within a period of 36 months and did not have a satisfactory neurological recovery [21–23].

The results of this study (Group I) match with other studies which state a stable fixation of the anterior and/or posterior segment (Type-C) of pelvic ring injury with subsequent reduction of morbidity and mortality [5, 24]. The patients from this study had a rapid improvement in their general condition during their stay and after discharge from the hospital. They were earlier mobilized without a greater risk of redislocation of fragments, despite other skeletal injuries. Functional and radiological results were significantly worse in the Group II.

Conclusion

In pelvic ring injuries, isolated ones and those associated with injuries of other systems, the most important thing is the stabilization of vital parameters followed by a firm internal fixation. All this significantly reduces mortality. Just because of this fact, they represent a challenge for a small number of surgeons, for adequate treatment and guidance of these patients. Strict application of rational criteria and surgical techniques with stable internal fixation with early mobilization provide significantly better outcomes of these injuries than those which were non-operatively treated. Our analysis and the studies on a larger number of patients by other authors show that the rehabilitation period is shorter and that psychological and functional outcomes are significantly more favorable.

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Serum B cell activating factor and interleukin 10 levels in common variable immunodeficiency: relationship with clinical findings

Serumski nivoi B ćelijskog aktivacionog faktora i interleukina 10 u običnoj promenljivoj imunodeficijenciji: povezanost sa kliničkim nalazima

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Abstract

Background/Aim. Common variable immunodeficiency (CVID) is an immunologically and clinically heterogeneous disorder. Disturbed cytokine production is implicated in dysfunctional immune response. The aim of this study was to investigated B-cell activating factor (BAFF) and interleukin (IL)-10 levels in CVID patients. **Methods.** The study included 28 CVID patients diagnosed and followed during a 20-year period (mean follow-up 14.5 years). Control groups consisted of 4 patients with X-linked agammaglobulinemia (XLA) and 21 healthy subjects. According to clinical characteristics, the CVID patients were divided into four groups which partly overlap: chronic pulmonary diseases (n = 21), splenomegaly (n = 13), autoimmune diseases (n = 9) and patients with recurrent infections despite regular intravenous immunoglobulin (IVIg) substitution (n = 4). The serum levels of BAFF and IL-10 were measured by commercial ELISA. **Results.** The BAFF levels were found to be higher in all CVID patients compared to the healthy controls ($p < 0.01$). The most significant differences were observed in the patients with pulmonary diseases and splenomegaly ($p < 0.0001$). Also, concentrations of IL-10 were higher in all CVID patients in comparison with the XLA patients ($p < 0.05$) and healthy subjects ($p < 0.01$). A statistically significant positive correlation ($r = 0.86$; $p < 0.01$) was found between the levels of BAFF and IL-10 in the CVID patients with autoimmune diseases. We demonstrated that the CVID patients with chronic pulmonary diseases had higher levels of IL-10, while the CVID patients with recurrent infections had higher BAFF concentrations in comparison to the patients without these features ($p < 0.05$). **Conclusion.** In spite of the limited number of patients, this is the first report from Serbia, examining the serum levels of BAFF and IL-10 in the CVID patients. Our study showed significantly increased concentrations of serum BAFF and IL-10 in the patients with CVID compared to the healthy subjects. Further studies are needed to confirm our findings that the BAFF levels are more pronounced in patients with recurrent infections while IL-10 levels are higher in patients with chronic pulmonary diseases.

Key words:
common variable immunodeficiency; b-cell activating factor; cytokines; interleukins; lung diseases; splenomegaly; autoimmune diseases.

Apstrakt

Uvod/Cilj. Obična promenljiva imunodeficijencija (CVID) je imunološko i kliničko heterogeno oboljenje. Poremećena citokinska produkcija utiče na disfunkcionalan imunski odgovor. Cilj rada bio je da se ispitaju nivoi faktora aktivacije B-limfocita (BAFF) i interleukina (IL)-10 u serumu kod bolesnika sa CVID. **Metode.** Studijom je bilo obuhvaćeno 28 bolesnika sa CVID-om koji su dijagnostikovani i praćeni tokom 20 godina (srednje vreme praćenja iznosilo je 14,5 godina). Kontrolne grupe činila su: četiri bolesnika sa X vezanom agamaglobulinemijom (XLA) i 21. zdrava osoba. Prema kliničkim karakteristikama bolesnici sa CVID bili su podeljeni u četiri grupe koje su se delimično preklapale: hronična plućna bolest (n = 21), splenomegalija (n = 13), autoimunske bolesti (n = 9) i ponavljajuće infekcije koje su bolesnici imali uprkos redovnoj primeni intravenskih imunoglobulina (IVIg) (n = 4). Serumski nivoi BAFF i IL-10 mereni su standardnom ELISA metodom. **Rezultati.** Nivoi BAFF-a bili su povišeni kod svih bolesnika sa CVID u poređenju sa zdravim ispitanicima ($p < 0.01$). Najznačajnije razlike nađene su kod bolesnika sa plućnim bolestima i splenomegalijom ($p < 0.0001$). Takođe, koncentracije IL-10 u serumu bile su više kod svih bolesnika sa CVID-om u odnosu na bolesnike sa XLA ($p < 0.05$) i zdrave ispitanike ($p < 0.01$). Statistički značajna pozitivna korelacija između koncentracija BAFF i IL-10 nađena je kod bolesnika sa CVID sa autoimunskim bolestima ($r = 0.86$; $p < 0.01$).

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Bolesnici sa CVID sa hroničnim plućnim bolestima imali su značajno više nivoe IL-10, dok su bolesnici sa CVID sa recidivirajućim infekcijama imali povišene koncentracije BAFF u serumu, u poređenju sa ispitanicima bez navedenih komplikacija ($p < 0.05$). **Zaključak.** Uprkos malom broju bolesnika, ovo je prva studija iz Srbije koja je ispitivala nivoe BAFF I IL-10 kod bolesnika sa CVID-om. Bolesnici sa CVID su u našoj studiji imali značajan porast nivoa serumskog BAFF i IL-10 u odnosu na zdrave ispitanike. Za potvrdu naših rezultata o značajno višim serumskim nivoima BAFF kod bolesnika sa recidivirajućim infekcijama, i značajno višim serumskim nivoima IL-10 kod bolesnika sa hroničnim plućnim bolestima, potrebna su dalja ispitivanja.

Ključne reči:
obična promenljiva imunodeficijencija; faktor aktivacije b-ćelija; citokini; interleukini; pluća, bolesti; splenomegalija; autoimunske bolesti.

Introduction

Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency (PID) with the prevalence of 1 : 25,000 to 1 : 50,000 in general population [1]. CVID is characterized by a normal or low number of B-cells, dysregulation of B-cell differentiation and maturation accompanied by low levels of immunoglobulins, impaired response to vaccines and susceptibility to infections, mainly respiratory ones [1, 2]. Moreover, patients with CVID are often affected with various inflammatory, autoimmune, lymphoproliferative diseases, malignancy and granulomas [1, 2]. X-linked agammaglobulinemia (XLA) is inherited PID, characterized by the absence of B cells, profound antibody deficiency and recurrent bacterial infections. However, XLA patients are not prone to a variety of immunoinflammatory conditions characteristic for CVID [3].

Although numerous B and T cell abnormalities have been described in CVID, dysfunctional immune responses might be, at least partially, explained by disturbed cytokine production and dysregulation of a complex cytokines network [4]. Many studies addressed the possibility that disturbed cytokine production of B-cell activating factor (BAFF) and interleukin-10 (IL-10), in conjunction with other factors, might contribute to the creation of certain CVID phenotypes [4]. The BAFF and IL-10 in chronic inflammation, autoimmunity and immune dysregulation had been extensively examined [5, 6]. Single nucleotide polymorphisms in promotor region of several cytokines genes [IL-10, tumor necrosis factor (TNF)-alpha and interferon gamma] are found to be associated with susceptibility to CVID [7, 8].

BAFF and proliferation-inducing ligand (APRIL) are involved in B-cell development, promoting the survival of mature B cell and class-switching [5]. Reduced expression of BAFF receptor (BAFF-R) was found in some CVID patients with severe defect in B-cell development [9]. Mutations affecting BAFF-R genes in a subset of CVID patients were also described [10]. Several studies revealed elevated levels of BAFF in the sera of CVID patients, but until now no obvious association between serum levels of BAFF and clinical complications of CVID has been demonstrated [9–13]. On the other hand, it was shown that mice carrying a BAFF transgene, leading to BAFF overexpression are prone to develop high titer of autoantibodies and a systemic lupus erythematosus (SLE)-like disease [14]. Serum levels of BAFF were found to be elevated in various autoimmune diseases, especially in SLE [14]. Moreover, anti-BAFF monoclonal antibody is now used for the treatment of SLE patients.

IL-10 is an anti-inflammatory cytokine with pleiotropic effects in the immune regulation. It is primarily produced by monocytes and, to a lesser extent, lymphocytes. IL-10 downregulates the expression of Th1 cytokines, costimulatory molecules on macrophages, but enhances B cell survival and proliferation [15, 16]. Similar to BAFF, serum levels of IL-10 were found to be markedly increased in patients with autoimmune diseases and correlate with disease activity [17, 18]. Besides that, numerous studies revealed the heterogeneous secretion of IL-10 profile in CVID patients, but its role in immune dysregulation in the CVID specific subgroups still remains unelucidated [4].

Only a few studies investigated association between the serum levels of BAFF and IL-10 with clinical features of CVID patients up to now [4, 10]. The aim of this study was to evaluate aberrations in cytokine production in a cohort of Serbian patients with CVID divided into four clinical groups in order to examine relationship between BAFF, IL-10 and certain common complications of CVID.

Methods

This study included 28 CVID patients diagnosed and followed during a 20-year period (1995–2015, median follow-up was 14.5 years) at the Clinic of Allergy and Immunology, Clinical Center of Serbia, Belgrade, Serbia. All 28 patients fulfilled the criteria for CVID (decrease of serum IgG < 2 standard deviations below the mean for age and reduced serum IgA and/or IgM; absence of isohemagglutinins or poor response to vaccines; age greater than two years; exclusion of other causes of hypogammaglobulinemia) according to the European Society for Immunodeficiencies (ESID). Four patients with clinical characteristics corresponding with XLA with genetically confirmed mutations in the gene for Bruton's tyrosine kinase were used as a disease control. Twenty-one healthy control (HC) subjects were recruited as gender- and age-matched control group. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade (Protocol Number 29/XI-9) and all participants gave their written informed consent.

All subjects were free from current infections and were not on immunosuppressive therapy when blood samples were collected. Original medical records of the patients were used to obtain laboratory results, clinical signs and duration of symptoms before the diagnosis of CVID. Diagnostic delay was considered as the time between the onset of symptoms and the time when the diagnosis of PID was established. All CVID and XLA pa-

tients were on regular monthly intravenous immunoglobulin (IVIg) therapy. Blood was taken 30 minutes before the regular monthly IVIg substitution. We checked regularly the serum IgG levels to achieve a minimum concentration of 5 g/L.

Clinical groups of the CVID patients

The CVID patients were categorized into four main clinical groups: 21 of 28 patients had chronic pulmonary diseases with clinical characteristics as followed – 12 suffered from bronchiectasis [determined by the high resolution computed tomography (HRCT)], 4 had bronchial asthma, 4 had chronic obstructive bronchitis and 1 had pulmonary fibrosis. Thirteen of 28 patients displayed splenomegaly defined as spleen length more than 11 cm as determined by ultrasound or HRCT. Nine of 28 patients had autoimmune diseases: 4/9 had atrophic gastritis, 3/9 had autoimmune thyroiditis, 1/9 had systemic vitiligo and 1/9 had autoimmune thrombocytopenia (ITP). Four of 28 CVID patients, despite regular IVIg treatment, suffered from recurrent severe infections defined as more than three episodes of elevated numbers of leukocytes and increased level of C-reactive protein (CRP), body temperature higher than 38.5°C in the previous year.

Quantification of cytokines concentrations in serum

The cytokines BAFF and IL-10 were measured by enzyme-linked immunosorbent assay (ELISA) (RnDSystems, Abingdon, UK). Immunoassays were calibrated against a highly purified recombinant human BAFF and IL-10, respectively. Minimum detectable dose (MDD) of BAFF ranged from 1.01-6.44 pg/mL (the mean value 2.68 pg/mL). MDD of IL-10 was less than 3.9 pg/mL. Cytokine concentrations were expressed in pg/mL.

Quantification of immunoglobulins in serum

The serum concentrations of IgM, IgG and IgA classes were measured by nephelometric method (Minineph, The Binding Site, Birmingham, UK) at the time of diagnosis and during follow-up.

Statistical analysis

Descriptive analysis used medians, percentage, range and interquartile ranges. Statistical comparisons were based on the nonparametric Mann–Whitney U test for two groups of continuous variables and the nonparametric one-way analysis of variance (ANOVA) and the Kruskal-Wallis test for more than two groups of continuous variables. Correlations between continuous variables were evaluated by the Spearman's correlation coefficient. The *p*-value less than 0.05 was considered statistically significant in all statistical analyses. Data were analyzed by using GraphPad Prism 6 software (GraphPad Software, La Jolla, CA, USA) and the Statistical Package for Social Science (SPSS) for Windows (version 20, SPSS Inc., Chicago, IL, USA).

Results

Table 1 describes the demographic characteristics of the patients and controls, including age at presentation and the delay in the diagnosis. All XLA patients were males, significantly younger at the time when a diagnose was established comparing to the CVID patients (median: 4 vs. 33 years; $p < 0.05$). In the group of the CVID patients, 43% were males. Delays in the diagnosis of the CVID and XLA patients were similar (median: 5.5 vs. 5 years). Concentrations of all immunoglobulin classes in serum at the time of diagnosis showed no significant differences between the XLA and CVID patients (Table 2).

Clinical characteristics of the CVID patients

The Table 1 reveals demographic characteristics of the total study population, the CVID patients and defined CVID groups. Out of 28 patients with CVID, 75% had pulmonary disease, 46% had splenomegaly, 32% had autoimmune disorders and 14% had severe recurrent infections. Figure 1 indicates the distribution and partially overlapping features in the main clinical groups of our CVID patients.

There were no differences in the age and gender between the main CVID groups (Table 1). The patients with autoimmune diseases were the oldest at the time of diagnosis (43 years) comparing to other groups. The diagnostic delay was longer for the CVID patients with severe recurrent infections and the patients with autoimmune diseases (13.5 and 11 years respectively) comparing to other groups, but without a statistical significance.

Table 1

Demographics and clinical data of the study groups

Variable	Patients (n)	Gender M/F	Age (years) median (range)	Age (years) at Dg median (range)	Delay in Dg (years) median (range)
HC	21	9/12	42 (18–59)	/	/
XLA	4	4/0	29.5 (28–42)	4 (1–16)	5 (0–9)
CVID total	28	12/16	47.5 (17–62)	33 (10–59)	5.5 (0–31)
pulmonary diseases	21	10/11	46.5 (31–61)	30 (10–59)	6.5 (0–31)
splenomegaly	13	6/7	46.5 (17–61)	33 (13–59)	6 (1–12)
autoimmune diseases	9	5/4	51 (29–62)	43 (25–56)	11 (0–24)
recurrent infections	4	1/3	45.5 (38–53)	20 (15–51)	13.5 (2–31)

Median and range are indicated for all groups.
CVID – common variable immunodeficiency; HC – healthy controls; XLA – X-linked agammaglobulinemia; Dg – diagnosis;M – male; F – female.

Table 2

The immunoglobulin levels at the time of the diagnosis of the CVID and XLA patients and the serum cytokine levels of the study groups

Variable	Patients (n)	IgG (g/L) median (range)	IgA (g/L) median (range)	IgM (g/L) median (range)	BAFF (pg/mL) median (range)	IL-10 (pg/mL) median (range)
HC	21	/	/	/	1070 (658–1628)	0 (0–8.56)
XLA	4	2.805 (2.20–3.90)	0.185 (0–0.25)	0.25 (0.08–0.32)	8,024 (6,393–11,400)	0 (0–9.24)
CVID total	28	1.80 (0.29–4.11)	0.20 (0–0.32)	0.18 (0.09–1.04)	3,306 (1,021–11,300)	7.88 (0–26.82)
Pulmonary diseases	21	1.80 (0.53–4.11)	0.20 (0.04–0.27)	0.17 (0.09–1.04)	4,355 (1,021–11300)	9.22 (0–26.82)
Splenomegaly	13	2.28 (0.33–4.11)	0.20 (0.09–0.32)	0.19 (0.09–1.04)	4,157 (1,021–1,1300)	9.24 (2.90–16.18)
Autoimmune diseases	9	1.98 (0.29–3.70)	0.20 (0–0.27)	0.20 (0.10–0.60)	4,355 (1,113–1,0500)	5.06 (0–26.82)
Recurrent infections	4	1.96 (1.80–3.60)	0.175 (0.11–0.25)	0.125 (0.10–0.20)	7,615 (5,074–1,0500)	12.5 (4.34–24.30)
p	/	ns	ns	ns	< 0.0001	< 0.0001

Median and range are indicated for all groups, as well as the results of Kruskal–Wallis test and the one-way analysis of variance (ANOVA).
CVID – common variable immunodeficiency; HC – healthy controls; XLA – X-linked agammaglobulinemia; ns – not significant.

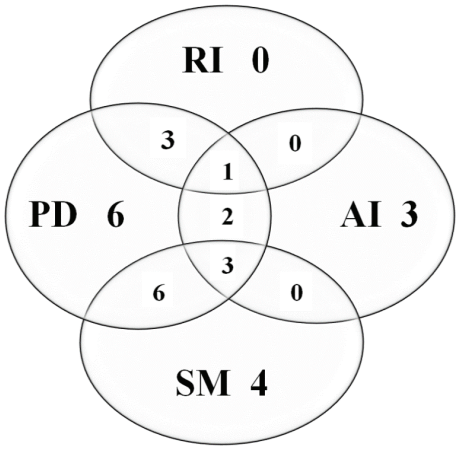

Fig. 1 – Venn diagram illustrating a distribution of the common variable immunodeficiency (CVID) patients into four main clinical groups. Numbers represent the patients in each group. One patient may belong to more than one group, as indicated.
RI: recurrent infections; PD – pulmonary diseases; SM – splenomegaly; AI – autoimmune diseases.

Serum levels of BAFF and IL-10

Median and range of the BAFF and IL-10 levels in sera of the CVID patients and controls are shown in Table 2. The age at diagnosis, the actual age of the patients and the diagnostic delay did not correlate significantly with the concentrations of BAFF and IL-10 in total CVID patients, CVID groups and XLA patients. Also, there were no correlations found between concentrations of immunoglobulins and concentrations of BAFF and IL-10.

The BAFF levels were higher in all CVID patients and CVID groups compared to HC ($p < 0.01$). The most significant differences were found between the patients with pulmonary diseases and splenomegaly ($p < 0.0001$; Figure 2A) and HC. Figure 2A shows that the patients with XLA had higher levels of BAFF than the patients with CVID ($p < 0.05$).

The IL-10 levels were also higher in all CVID patients and all CVID groups compared to HC ($p < 0.01$). The most pronounced differences appeared between the groups of patients with pulmonary diseases, recurrent infections and splenomegaly [$p < 0.0001$; (Figure 2B)]. The patients with CVID were found to have higher levels of IL-10 than the patients with XLA ($p < 0.05$). There was no difference in the IL-10 levels between the XLA patients and HC (Figure 2B).

There were no significant relationships between the BAFF and IL-10 levels in all CVID patients. Further analysis for defined clinical groups of CVID revealed positive correlation between the BAFF and IL-10 levels only for the group of patients with autoimmune diseases [$r = 0.86$; $p = 0.003$; (Figure 3)].

Figures 4A and 4B reveal the differences in concentrations of BAFF and IL-10 among all CVID patients with and without defined clinical complications. The patients with severe recurrent infections, despite regular IVIg therapy, had significantly higher BAFF concentrations than the patients without this complication [$p < 0.05$; (Figure 4A)]. The IL-10 levels were significantly higher in the patients with chronic pulmonary diseases, compared to the patients without these complications [$p < 0.05$; (Figure 4B)]. Also, the patients with bronchiectasis had higher level of IL-10 than the patients without bronchiectasis and other chronic pulmonary diseases ($p < 0.05$).

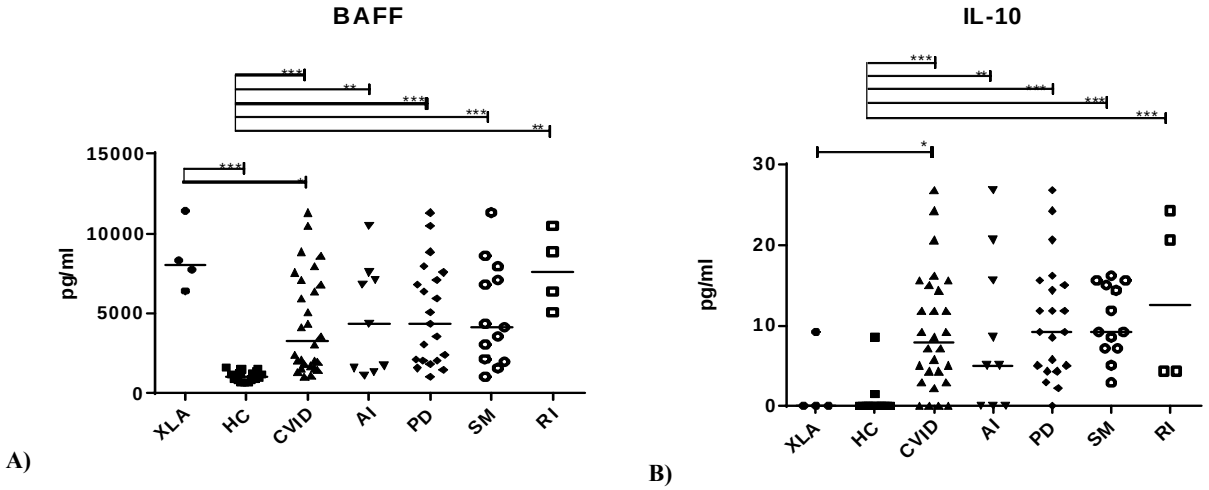

Fig. 2 – Serum levels of A) B-cell activating factor (BAFF) (pg/mL) and B) IL-10 (pg/mL). The common variable immunodeficiency (CVID) patients may appear in more than one group, as indicated in Figure 1 HC: healthy controls; XLA: X-linked agammaglobulinemia; AI: autoimmune diseases; PD: pulmonary diseases; RI: recurrent infections; SM: splenomegaly. Statistics were performed by using the one-way analysis of variance (ANOVA) and Kruskal–Wallis test, with post-hoc test. *$p < 0.05$; **$p<0.01$; ***$p < 0.0001$.

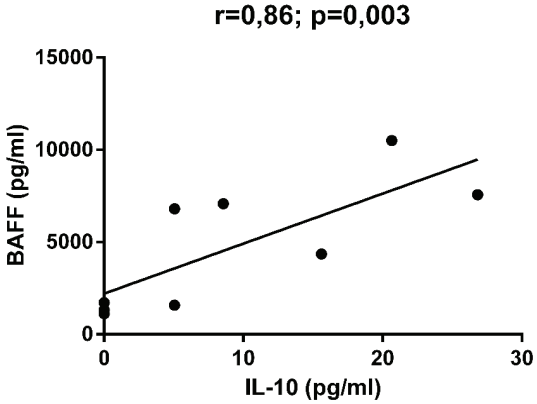

Fig. 3 – A positive correlation between serum levels of B-cell activating factor (BAFF) and interleukin-10 (IL-10) in the group of patients with autoimmune diseases. Statistics were performed by using the Spearman's correlation coefficient.

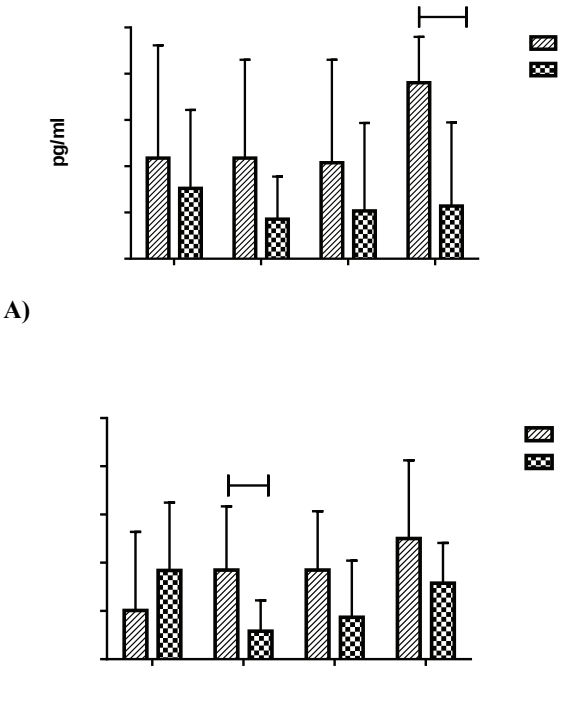

Fig. 4 –Differences in A) B-cell activating factor (BAFF) and B) IL-10 concentrations between the patients with and without particular clinical findings (medians and interquartile ranges). AI – autoimmune diseases; PD – pulmonary diseases; RI – recurrent infections; SM – splenomegaly. Statistics were performed by using the Mann–Whitney U test (*$p < 0.05$).

Discussion

Our study confirmed the heterogeneity of CVID with a wide range of clinical manifestations often with overlapping features (Tables 1 and 2; Figure 1). Symptoms of CVID may appear during the childhood, adolescence or adult life, but the diagnosis is usually established in their thirties, as in our study group (Table 1) [1]. The median diagnostic delay in our center was higher (5.5 years) than the average delay in the greatest cohort of the CVID patients (4.1 years) [1]. The patients with autoimmune diseases had the longest delay in diagnosis in our CVID group (Table 1) in accordance with earlier findings [1].

The large multicenter studies, which primarily analyzed mortality, divided patients with CVID into four main phenotypes: isolated infection, polyclonal lymphoproliferation, autoimmune cytopenias and enteropathy [2].

According to a dominant clinical manifestation, we divided our CVID patients into four main groups (Figure 1). Splenomegaly as a one of the most common features in patients with CVID and its relationship with a variety of im-

munological and cytokine disturbances has been investigated in previous cohort studies [1, 8, 9, 11, 19]. Kutukculer et al. [19] using splenomegaly as the criterion for severe forms of CVID found higher prevalence of splenomegaly and lymphadenopathy in a group of CVID patients lacking switched memory B cells. Also, splenomegaly was more frequent in a group of CVID patients characterized by the absence of memory B cells [20]. Giovannetti et al. [21] showed that the lower numbers of naive CD4+T cells were significantly associated with an increased likelihood of splenomegaly (OR 4,78). Pulmonary involvement is typically found in patients with CVID, and it was showed that up to 90% of patients had abnormalities on chest CT scan [22]. Mortality in CVID was found to be linked to both structural and functional lung impairment [23]. It is very important that some patients, despite the regular IVIg supplementation and antibiotic treatment, had recurrent infections [21, 24]. Moreover, complexity of cellular and cytokine dysregulation in CVID was thought to produce various autoimmune phenomena [1, 25]. Referring to heterogeneity of CVID, different manifestations are often presented either at the same time or during the evolution of the disease in the same patient. Overlapping features, as described in our study (Figure 1), were analogous to previously published investigations in CVID [1, 3, 20].

Identification of the factors governing BAFF-R and transmembrane activator and calcium-modulator and cytophilin ligand interactor (TACI) is crucial for understanding B-cell biology and CVID pathogenesis. BAFF-induced signals are essential for the development of functional B cell compartment. BAFF levels inversely correlate with the numbers and the percentage of circulating B cells and the availability of BAFF receptors [9]. Therefore, the size of the B cell pool and the availability of BAFF receptors seem to be primary factors regulating a steady-state concentrations of soluble BAFF, although a long-term increase in BAFF levels in response to chronic infections and inflammation cannot be excluded [9]. BAFF expression is upregulated by proinflammatory responses, during viral infections and in various autoimmune conditions [9, 14]. We found the highly elevated BAFF levels both in CVID and XLA (Table 2, Figure 2A), diseases that have low numbers of circulating B cells that are blocked in differentiation into switched memory B cells or plasma cells.

Considering different complications in the CVID patients, we found significantly higher levels of BAFF only in the patients with severe recurrent infections despite the regular IVIg treatment (Figure 4A). Quinti et al. [24] recorded that 13.3% of patients continued to have episodes of recurrent pneumonia and *otitis media* despite regular IVIg treatment which is similar to our result of 14.3% [24]. Giovannetti et al. [21] described the strong positive correlation between the number of naive $CD4^+$ lymphocytes and disease severity, including history of severe respiratory tract infections. Our research showed that the patients with severe recurrent infections had significantly higher levels of BAFF, comparing to patients without them (Figure 4A). The limitation of our study was the small number of patients in this group. This finding could be explained by the fact that BAFF is the essential costimulatory factor for humoral immune response to capsular polysaccharides of encapsulated bacteria (*Streptococcus pneumoniae* and *Haemophilus influenzae*), which are the commonest cause of recurrent infections (sinus, lungs, ears) in the CVID patients [26]. Also, Kreuzaler et al. [9] concluded that long-term increase in the BAFF levels in response to chronic infections and inflammation could not be excluded [9]. Contrary to some systemic autoimmune diseases, we did not find elevated concentrations of BAFF in a subset of our CVID patients with autoimmune manifestations. In addition, a significant positive correlation between BAFF and IL-10 was found only for this subset of the CVID patients (Figure 3). Similar data were previously reported for immunoinflammatory and lymphoproliferative diseases such as active sarcoidosis, multiple myeloma and chronic lymphocytic leukemia, possibly through the induction of IL-10 production by transitional B cells [27–29].

We found high levels of IL-10 in all CVID patients and in all CVID groups (Figure 2B). Other authors also showed that CVID was associated with elevated serum levels of IL-10 [15, 30, 31]. Barssoti et al. [32] recently published that IL-10-producing regulatory B cells were decreased in CVID. Since IL-10 in conjunction with anti-CD 40 supports secretion of IgG, IgA, and IgM by B cells, many studies were performed to examine IL-10 production in CVID [4]. Zhou et al. [33] demonstrated that T cell secretion of IL-10 was deficient, but that monocyte-derived high levels of IL-10, plus a relative lack of IL-2 production, contributed to the defects of antigen induced cell proliferation in CVID. Holm et al. [34] found that impaired secretion of IL-10 by T cells from patients with CVID involved preserved function of cAMP/protein kinase A type I. In our investigation the XLA patients had significantly lower levels of serum IL-10 in comparison to the CVID patients (Figure 2B). Schmidt et al. [35] demonstrated that Bruton's tyrosine kinase was required for Toll-like receptor-induced IL-10 production. Barbosa et al. [36] examined monocyte activation in patients with CVID, XLA and healthy controls. They reported elevated markers of monocyte activation in CVID patients, but in contrast to CVID, the patients with XLA and healthy controls did not show increased markers associated with monocyte activation [36]. In this study authors showed that increased monocyte activation with the expansion of activated T cells, irrespective of the lipopolysaccharide levels, might have important role in the inflammation and lymphoproliferation.

In our study, the levels of IL-10 were significantly higher in the patients with chronic pulmonary diseases (Figure 4B) and in the patients with bronchiectasis comparing with HC. It was shown that the IL-10 levels could be affected by a single nucleotide polymorphisms of promoter region of the IL-10 gene [8]. A high production of IL-10 could be explained by a low frequency of low IL-10 producing haplotype in the CVID patients [7, 37]. It is well known that IL-10 is essential for maintaining the integrity of tissue epithelial layers [38]. It down-regulates production of several proinflammatory cytokines in macrophages, monocytes and T-cells [15]. In the CVID patients, IL-10 can limit the damage caused by infection, repress proinflammatory responses and decrease unnecessary tissue damage [37]. Moreover, it was

found that cytokine abnormalities, including IL-10 among other cytokines, were significantly higher in the patients with bronchiectasis [39]. Furthermore, high serum levels of IL-10 can induce some form of B cell "anergy" which is reversible and can be improved by maintenance of B cell in culture [40].

Conclusion

This is the first report from Serbia examining the serum levels of BAFF and IL-10 in the CVID patients. To the best of our knowledge, this is the first report that analyzed BAFF and IL-10 in the CVID patients suffering from severe recurrent infections despite the regular IVIg substitution. We demonstrated that the patients with CVID, in comparison with healthy controls, had higher serum concentrations of BAFF and IL-10. Severe respiratory infections, despite regular IVIG, were associated with higher levels of BAFF, while chronic pulmonary diseases were associated with higher levels of IL-10, compared to the patients without these manifestations. We emphasize that the dysregulation of cytokine production needs to be investigated separately in different subgroups of CVID patients during a long follow-up period.

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Incidence of sensitization to specific inhalatory allergens in patients suffering from allergic rhinitis

Učestalost senzibilizacije na pojedine inhalatorne alergene kod obolelih od alergijskog rinitisa

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Abstract

Backgound/Aim. Allergic rhinitis is the most frequent type of rhinitis affecting more than 600 million people worldwide. As incidence increases, it is important to know about the characteristics, the allergens that exacerbate it as well as effects of allergic rhinitis on population. The aim of this study was to determine among patients with chronic rhinitis the number of patients positive to standard inhaled allergens, their distribution by sex, age and to determine the type and frequency of allergic sensitization to specific inhalatory allergens. **Methods.** Data was collected from 514 patients tested for standard inhalatory allergens via the skin prick test from 01.01.2016 to 31.12. 2016. Age, sex and concomitant diseases as well an analysis of type and frequency of hypersensitivity to different allergens were assessed and recorded. **Results.** Of 514 patients, 307 patients, with an average age of 29.6 ± 8.88 years had a positive skin prick test. The sex ratio was 1.2 : 1 in favor of the females. Outdoor allergens affected 81.2% of all patients while indoor allergens 66.4% of them. Weed pollen (71%), grass pollen (61%) and *Dermatophagoides pteronyssinus* (46%) were the most common allergens. Most patients were sensitized to 1 (22%) or 2 (22%) allergens, while 20% of patients were simultaneously sensitized to 3 allergens. **Conclusion.** Most patients with the symptoms of chronic rhinitis had a positive allergic reaction. Those in their third decade of life were the most commonly affected. Outdoor allergens were the most prevalent allergen group, and weed pollen was the most frequent type of allergen.

Key words:
rhinitis, alleric; allergens; plant weeds; dermatophagoides pteronissinus; incidence; intradermal tests.

Apstrakt

Uvod/Cilj. Alergijski rinitis kao najčešći oblik hroničnog zapaljenja sluznice nosa (rinitisa), nalazi se na četvrtom mestu na listi najčešćih hroničnih oboljenja na svetu, s obzirom da od njega boluje više od od 600 miliona ljudi. Zbog izuzetno brzog porasta incidence oboljenja, značajno je odrediti karakteristike inhalatornih alergena koji ga izazivaju kao i efekte samog oboljenja na populaciju. Cilj studije je bio da se u grupi obolelih od hroničnih rinitisa, koji se podvrgavaju testiranju na alergije, utvrdi broj onih koji su alergični, njihova distribucija po polu, starosti i utvrđivanje vrste i učestalosti alergijske senzibilizacije na specifične inhalatorne alergene. **Metode.** Prospektivo-retrospektivnom studijom analizirani su podaci 514 pacijenata sa hroničnim rinitisom, koji su podvrgnuti testiranju na alergije, supkutanim testom uz upotrebu standardnih inhalatornih alergena, u periodu od godinu dana (od 1.01.2016 do 31.12.2016). Analizirani su starost, pol, pridružene bolesti ispitanika sa alergijskim rinitisom, kao i vrsta i učestalost hipersenzibilizacije na pojedine alergene. **Rezultati.** Od 514 pacijenata sa hroničnim rinitisom, 307 pacijenata prosečne starosti od 29.6 ± 8.88 godina i blagom dominacijom ženskog pola u odnosu na muški (1,2 : 1) je imalo pozitivan test na inhalacione alergene. Na spoljašnje alergene je bilo senzibilisano 81.2% pacijenata, a na unutrašnje alergene 66.4%. Dominantna senzibilizacija bila je na polen korova (71%), polen trava (61%) i na grinje (*Dermatophagoides pteronyssinus*) (46%). Većina pacijenata bila je senzibilisana na 1 (22%) ili 2 (22%) alergena, dok je istovremeno na tri alergena bilo senzibilisano 20% pacijenata. **Zaključak.** Većina pacijenata sa simptomima hroničnog rinitisa je imala pozitivan test na alergije. Najčešće su to pacijenti u trećoj deceniji života. Spoljni alergeni sa najvećom prevalencom uzrokuju alergijski rhinitis, i to dominantno polen korova.

Ključne reči:
rinitis, alerijski; alergeni; korovi; dermatophagoides pteronisssinus; incidenca; intradermalni testovi.

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Introduction

With over 10 million appointments scheduled annually, allergic rhinitis (AR) is a global health problem and one of the most common reasons to visit a doctor. AR is the most frequent type of rhinitis, an inflammation of the nasal pathways initiated by an allergic immune response to inhaled allergens in sensitized individuals. Seasonal allergic rhinitis is caused by outdoor allergens while perennial allergic rhinitis is caused by indoor allergens such as dust mites, pet dander and mould. The signs and symptoms of AR are numerous, often presented with rhinorrhea (excess nasal secretion), itching, nasal congestion and obstruction.

According to the World Health Organization, AR is in the fourth place regarding frequency of chronic disease and more than 600 million people suffer from it - 20%–30% of the population with a steady increase in prevalence. Shockingly enough, 17%–23% of patients do not even know that they have AR. In the EU countries, the prevalence of this disease is 22.7%, according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [1–8].

In 80% of patients, AR develops before 20 years of age. Sometimes symptoms appear in individuals when they reach their third decade of life [8]. Although this is a disease that is not life-threatening, it must be mentioned that it does significantly affect one's quality of life by causing a number of symptoms that are not directly related to AR such as fatigue, agitation, insomnia, hearing loss, anxiety, nausea, feelings of sadness and depression [1–4]. In children especially, symptoms of agitation and hypersensitivity tend to dominate during the day. About 50% of patients report having symptoms of AR more than 4 months out of the year and 20% of sufferers have symptoms more than 9 months throughout the year. This has a significant impact as these disturbances may prevent individuals from being able to do daily necessities such as going to work or school [9].

Approximately 15%–20% of general practitioners do not consider AR as a disease that needs to be treated, however AR provides a "foundation" or risk of developing a number of other conditions and diseases such asthma, rhinitis, chronic rhinosinusitis with nasal polyps (CRSwNP) and inflammation of the middle ear which further increases its medical significance as well as its treatment costs which have been estimated to be around 510 million euros. Patients with AR have more episodes of acute respiratory infections of the upper respiratory tract which in turn last longer and have a graver course of the disease [10, 11].

In turn, early detection and treatment is the key to prevention of the graver course of disease.

The aim of this study was to determine the number of patients with a positive allergic reaction to standard inhalatory allergens, tested by means of the skin prick test as well as their distribution by sex, age and to determine the type and frequency of allergic sensitization to specific inhalatory allergens among those patients.

Methods

This study was designed as a retrospective-prospective investigation. The data was collected in the tertiary level clinic, from medical histories of patients for the period from January 1st, 2016 to December 31st, 2016. In total, 514 patients with the presumptive diagnosis of allergic rhinitis, were sent to do a skin prick test to confirm their atopic status after having undergone a clinical ear, nose and throat (ENT) examination. The skin prick test is performed according to the recommendations of the Subcommittee on Skin Tests of the European Academy of Allergy and Clinical Immunology (EAACI) [1, 2]. The standard solutions of inhalatory allergens from the Institute of Virology, Vaccines and Serums "Torlak" in Belgrade were used (house dust, *Dermatophagoides pteronyssinus*, linen, animal hair, dog hair, cat hair, cockroaches, feathers, cigarette smoke, fungus (mould), bacteria, pollen of trees, grass pollen and weed pollen). Positive skin prick test was marked as the diameter of reaction that is 3 mm higher than the negative control.

After the confirmation of the allergic disease in the total number of patients, an estimate of age, sex and concomitant diseases was done. In the patients with the positive allergy tests, we performed an analysis of type and frequency of hypersensitivity to standard inhalatory allergens.

The data was statistically processed by the Microsoft Excel 2010 software for statistical and tabular calculations. The organized data was then placed into the program STATISTICA 7 for calculation of the descriptive statistical parameters (sum, mean, minimum and maximum and standard deviation) and presented in the results section.

Results

During the 2016, 514 patients with suspected AR underwent the skin prick test for the standard inhalatory allergens. Of 514 patients that exhibited signs and symptoms of AR, 307 (59.7%) had a positive skin prick test, while 207 patients were negative and excluded from further testing. Within the 307 sensitized patients, the average age was 29.6 ± 8.88 years. The youngest patient was 13 years old and the oldest one was 64 years old. Females represented 167/307 (54.4%) and males 140/307 (45.6%) of the patients, with the positive test results to standard inhalatory allergens. The sex ratio was 1.2 : 1 in favour of the females. In this study, we also compared the number of patients that had at least one or more comorbidities along with AR to the positively tested patients who had no other diagnosis. The patients with comorbidities made up 295/307 (96.1%). The most common comorbidities observed were nasal septum deviation, conjunctivitis, acute and chronic rhinosinusitis, bronchial asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and medicamentous chronic rhinitis.

After dividing the standard inhalatory allergens into three groups of indoor, outdoor and combined allergens, sensitization to individual indoor allergens was present in 58/307 (18.8%) patients while the sensitization to collective indoor allergens was present in 66.4% of all patients. Sensitization to individual outdoor allergens was present in 103/307 (33.6%) patients, while sensitization to collective ones was present in 81.2% of all patients. The results of the combined outdoor/indoor allergen group were present in 146/307 (47.6%) patients (Figure 1).

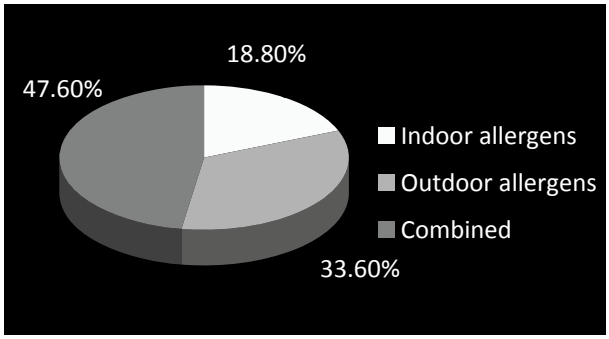

Fig. 1 – Percentage of the patients with indoor, outdoor and combined allergens.

After assessing patients hypersensitivity to each allergen, 222/307 (72%) patients were sensibilized to weed pollen, with grass pollen as the second most common allergen presenting 187/307 (61%) participants while *Dermatophagoides pteronyssinus* was the third most common allergen with a result of 141/307 (46%). Tree pollen also had a significant result in 125/307 (41%) patients as did house dust, affecting 113/307 (37%) patients. The rest of the standard inhalator allergens were considerably less frequent among the participants. Allergy to linen was found in 45 (15%) of the patients, to bacteria in 28 (9%), to cockroaches in 27 (9%), to mould in 25 (8%), to animal hair in 21 (7%), to cigarette smoke in 18 (6%), to feathers in 15 (5%), to cat hair in 12 (4%) and lastly, to dog hair in 9 (3%) of the patients (Figure 2).

When observing hypersensitivity to the number of allergens in each patient, the greatest number of patients were sensitized to one allergen 67/307 (22%), then 67/307 (22%) to two allergens while 62/307 (20%) were sensitized to three allergens. Hypersensitivity was significantly lower in the patients polysensitized to four 43/307 (14%), five 31/307 (10%), six 16/307 (5%), seven 8/307 (3%) and eight 7/307 (2%) allergens. Sensitization to nine, eleven, thirteen and fourteen allergens was the same, 1/307 (0.4%), while there was no patients who were simultanously allergic to twelve allergens (Figure 3).

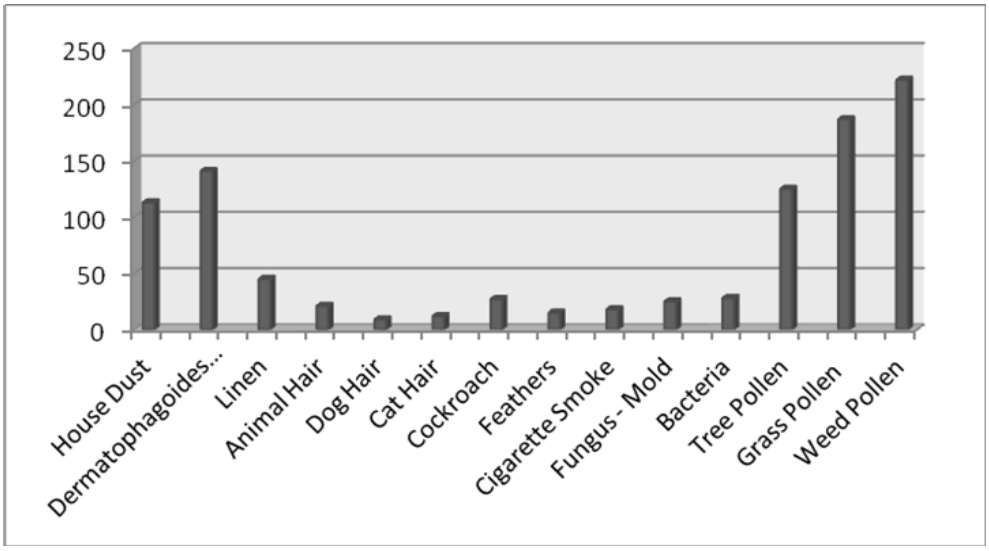

Fig. 2 – Number of patients allergic to each allergen.

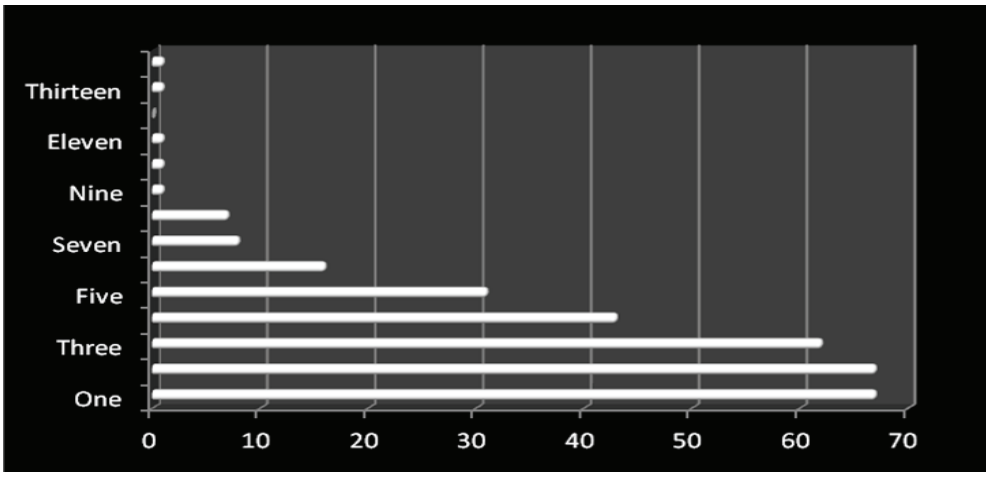

Fig. 3 – Distribution of the patients allergic to one or more allergens.

Discussion

AR is the most common type of allergy in Europe, affecting from 17% to 28% of the European population. That being said, the incidence of AR may vary among as well as within countries themselves. Of the 514 patients who underwent testing for standard inhalatory allergens in 2012, 59.7% of them tested positive, giving a majority. However, it is important to emphasize that a portion of those patients who did not have a positive skin prick test may develop AR over time which is confirmed by studies on the subject of local allergic rhinitis [12–15]. According to a study by Rondon et al. [16], local allergic rhinitis is a newly described type of rhinitis where a local allergic response exists in nasal mucosa, characterized by the production of specific immunoglobulin E (sIgE) antibodies in the absence of atopy (genetic predisposition to increased production of IgE antibodies). It can affect the patients who have been previously diagnosed with non-allergic rhinitis. For the patients with negative results for the skin prick test but symptoms suggestive for AR, an advanced diagnostic approach was proposed with the detection of local sIgE in nasal secretions during natural exposure to inhalatory allergens and a positive allergen provocation test with increased local production of tryptase, eosinophil cationic protein (ECP) and sIgE.

Other studies have proven that gender does seem to have an impact on the prevalence of AR. In childhood, allergic rhinitis is more common in boys than in girls, however, more interestingly, the prevalence is approximately equal between men and women. This information correlates with our results that determined that the women make up 54.4% of positive patients while the men make up 45.6%, giving the ratio of 1.2: 1.

The results of our study demonstrated that the average age was 29.7 years with a standard deviation of ± 8.88 years. Other studies showed that the mean age of onset in childhood was 8–11 yearsof age, but AR may occur in persons of any age. In 80% of affected individuals, AR developed by the age of 20.

AR does not typically present itself as just a single disease. It it is often associated with numerous other pathologies. As it was proven by our results, 96.1% of positively tested patients had a coexisting morbidity. In a study by Zvezdin et al. [17], 74.1% of all patients had at least one concomitant disease. This data correlates with the results of our study, showing that the majority of patients have a comorbidity along with AR. The most common concomitant diseases were septal deviation, conjunctivitis, chronic rhinosinusitis with or without polyps, long lasting dry caught, gastroesophageal reflux disease (GERD), asthma and bronchial hyperactivity.

Analysis of the frequency and type of sensitization to standard inhalatory allergens is extremely significant since exposure to aeroallergens contributes to both the exacerbation of the symptoms and the formation of the disease itself. The standard inhalatory allergens that were used in the skin prick test can be categorized into three groups: indoor, outdoor and combined allergens. Indoor allergens include house dust, *Dermatophagoides pteronyssinus*, linen, animal hair, dog hair, cat hair, cockroaches, feathers, cigarette smoke, fungus (mould) and bacteria. Outdoor allergens are weed pollen, grass pollen and tree pollen, while combined allergens include both type of allergens. As far as our results are concerned, indoor allergens alone comprised 18.8% of patients, while combined indoor allergens made up 66.4% of the patients. Outdoor allergens make up 33.6% alone, although combined outdoor allergens make up 81.2% of the patients. Combined allergens comprised 47.6% of a total number of the patients. In a similar study, participants were hypersensitive to combined indoor allergens in 77.5% of cases, while 67.6% were positive to combined outdoor allergens. Hypersensitivity to both allergen types (combined allergens) was verified in 48.4% of patients. When interpreting the results of both studies, it was established that indoor allergens were more frequent in the other study while outdoor allergens were predominant in ours. The results of combined allergens were approximately the same [17, 18]. An international study done by the European Community Respiratory Health Survey (ECRHS) noted that different external factors which influence the prevalence of rhinitis and atopy were determined by the geographical features of a particular environment. For instance, our study confirmed that the most common pollen allergen in the region of Vojvodina was weed pollen. However, in the northern European countries, tree pollen was pointed out to be the most common allergen. Similarly, hypersensitivity to grass pollen was most frequent in the majority of other European countries. Thus, it can be said that sensitization to pollens is different in regions all over Europe depending on characteristics of that region such as vegetation and climate. Social factors within certain environment should also be taken into account when comparing the incidence of specific allergens among regions. Hypersensitivity to cat hair, for example, affected a relatively insignificant number of patients contributing to only 4% of all allergens, while some studies show that cat hair is the most common allergen in the adult population and in children with rhinitis and/or asthma, ranging from 15%–50% in western countries. The reasoning behind this information may be attributed to the cat being the most common pet in these environments [17, 18].

Our research showed that 72% of the patients were sensitized to weed pollen, making it the most common allergen among all pollens, outdoor allergens as well as all standard inhalatory allergens. Grass pollen is the second most common allergen, comprising 61% of total allergens. *Dermatophagoides pteronyssinus* is the third most common allergen when taking into account all allergens in total with a result of 46%; however, it is by far the most common indoor allergen. Our results are in accordance with the results of another studies that confirm that weed pollen is the most common outdoor allergen and that *Dermatophagoides pteronyssinus* is the most common indoor allergen. It is also important to mention that pollens, when calculated together, compose 34% of all standard inhalatory allergens [17, 18].

When observing hypersensitivity of each pateient to the number of allergens, it was established that 22% of individuals were allergic to only one allergen. Interestingly enough, the same result was observed in individuals who were allergic to two allergens, whereas slightly fewer patients (20%) were allergic to three allergens. In those hypersensitive to more allergens, the frequency and percentage of the participants decreased.

Conclusion

The majority of the patients tested via the skin prick method had a positive allergic reaction to standard inhalator allergens. Those in their third decade of life were the most commonly affected, with the female population being slightly predominant. Outdoor allergens were the prevalent group of allergens, with weed pollen as the most frequently found type of allergen within the population.

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Hypogonadism in chronic obstructive pulmonary disease (COPD) – risk factors

Hipogonadizam u hroničnoj opstruktivnoj bolesti pluća (HOBP) – faktori rizika

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Abstract

Bacground/Aim. Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality in pulmonary pathology. However, apart from its own pulmonary manifestations, this disease is also characterized by systemic effects, including hypogonadism which is described especially in the group of men with COPD. The aim of this study was to evaluate risk factors for hypogonadism in men with COPD. **Methods.** The study included 96 male patients with COPD in stable phase of the disease. All patients were checked for concentration of free testosterone in serum, markers of systemic inflammation, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and C reactive protein (CRP), pulmonary function test, gas exchange parameters, a 6-minute walk test (6MWT), nutritional status and condition of skeletal muscle (midthigh muscle cross-sectional area – MTCSA using computed tomography). **Results.** Decreased value of free testosterone was found in 37.5% of the patients. In the group with hypogonadism (free testosterone < 4.5 pg/mL), we found significantly increased serum concentration of TNF-α (5.88 ± 3.21 vs. 3.16 ± 2.53 pg/mL; $p < 0.05$), significantly lower MTSCA (68.2 ± 18.72 vs. 91.1 ± 21.4 cm^2; $p < 0.05$) and the 6MWT (268.33 ± 32.35 vs. 334.25 ± 43.25 m; $p < 0.05$). Lung function, gas exchange markers and body mass index (BMI) were similar in both groups. The multivariate regression analysis singled out serum value of TNF-α as an independent predictor of serum concentrations of free testosterone (B = -0.157; 95% confidence interval: -0.262–0.053). **Conclusion.** In our analysis we found that TNF-α as a marker of systemic inflammation is an independent predictor of the presence of hypogonadism in the patients with COPD. Our results indicate that hypogonadism predisposes to skeletal muscle wasting and exercise intolerance in male COPD patients.

Key words:
hypogonadism; pulmonary disease, chronic obstructive; risk factors.

Apstrakt

Uvod/Cilj. Hronična opstruktivna bolest pluća (HOBP) je vodeći uzrok morbiditeta i mortaliteta u plućnoj patologiji. Osim plućnih manifestacija, HOBP karakterišu brojni sistemski efekti, među kojima je opisan i hipogonadizam posebno u grupi muškaraca sa ovom bolešću. Cilj studije bio je procena faktora rizika za pojavu hipogonadizama kod muškaraca sa HOBP. **Metode.** Istraživanjem je obuhvaćeno 96 bolesnika muškog pola sa HOBP u stabilnoj fazi bolesti. Kod svih bolesnika određena je koncentracija: slobodnog testosterona u serumu, markera sistemske inflamacije, faktora nekroze tumora-alfa (TNF-α), interleukin 1-beta (IL-1β) i C-reaktivnog proteina (CRP), izvršeno je ispitivanje plućne funkcije, parametara gasne razmene, 6-minutni test hoda (6MWT), stanje uhranjenosti i stanje skeletnih mišića (*midthigh muscle cross-sectional area* – MTCSA), pomoću kompjuterizovane tomografije). **Rezultati.** Zastupljenost ispitanika sa hipogonadizmom je bila 37.5%. Ispitanici sa hipogonadizmom (slobodan testosteron < 4,5 pg/mL) su imali značajno povećanu koncentraciju TNF-α u serumu (5,88 ± 3,21 vs. 3,16 ± 2,53 pg/mL; $p < 0,05$), značajno manji MTSCA (68,2 ± 18,72 vs. 91,1 ± 21,4 cm^2; $p < 0,05$) i 6MWT (268,33 ± 32,35 vs. 334,25 ± 43,25 m; $p < 0,05$). Nije ustanovljena statistički značajna razlika između ove dve grupe ispitanika u pogledu starosti, parametara plućne funkcije i gasne razmene, kao i indeksa telesne mase. Pomoću multivarijantne resgresione analize kao nezavisni prediktor koncentracije slobodnog testosterona izdvojila se serumska vrednost TNF-α (B= -0.157; 95% interval poverenja: -0.262–0.053). **Zaključak.** Analizom je ustanovljeno da TNF-α, kao sistemski marker inflamacije, predstavlja nezavisni prediktor za postojanje hipogonadizma kod bolesnika sa HOBP. Hipogonadizam je značajno povezan sa gubitkom mišićne mase i lošijim tolerisanjem napora kod ovih bolesnika.

Ključne reči:
hipogonadizam; pluća, opstruktivna bolest, hronična; faktori rizika.

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Introduction

Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality in pulmonary pathology. However, apart from its own pulmonary manifestations, this disease is also characterized by systemic effects which are reflected in other tissue damage [1]. The COPD patients with progressive disease develop hypoxaemia and hypercapnia and systemic inflammation which can, along with the use of chronic glucocorticoid therapy, result in hypogonadism [2]. Previous investigations showed that male patients with COPD could develop hypogonadism and there was evidence that these patients had significant atrophy of Leydig cells. It was observed that many patients with COPD, most of whom are middle-aged or elderly, fit the profile of late-onset hypogonadism manifested by diminished energy level, libido and loss of skeletal muscle mass [3, 4]. One study showed that 75% of male COPD patients with low level of serum testosterone also had a low level of gonadotropine (secundary hypogonadism), while at the remaining 25% increased gonadotropine level (primary hypogonadism) was noticed [5].

Recent studies on male COPD patients have implied that hypogonadism could contribute to development of skeletal muscle dysfunction. Physical inactivity – sedentary lifestyle in patients with advanced chronic obstructive pulmonary disease (COPD) leads to weakening of muscles of lower extremities, especially quadriceps which is closely related to atrophy of muscles of thigh region [6].

The primary aim of this study is to assess the potential risk factors for hypogonadism in male COPD patients in stable state of the disease.

Methods

This clinical, cross-sectional study was conducted at the Clinic for Pulmonology, Clinical Centre Kragujevac, from January 2015 to June 2016. The protocol study was approved by the local Ethics Committee and written informed consent was obtained from each patient.

Subjects

The study included 96 male COPD patients in stable phase of the disease. All included patients fulfilled criteria for the COPD diagnosis according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) and they were in stable phase of the disease (without systemic corticosteroid therapy in last 4 weeks).

Exclusion criteria were: patients unable to perform lung function testing and a 6-minute walking test, patients with myocardial infarction within last 4 months, patients with unstable angina pectoris or heart failure NYHA III and IV as well as patients with history of primary or secondary hypogonadism, alcohol consumers and those with chronic kidney disease.

Laboratory assessments

Blood samples were taken by cubital venipuncture in the morning. Then, sex hormone was measured.

To measure the concentration of free serum testosterone for hypogonadism estimation, immunohistochemistry method (enzyme-linked immunosorbent assay – ELISA technology) was used (Nova Tec Immunodiagnostica Gmbh, Dietzenhbach, Germany). Cut off value for normal free serum testosterone was ≥ 4.5 pg/mL. Based on that value, the patients were divided into 2 groups: one with the value of free testosterone ≥ 4.5 pg/mL (normal value) and one with serum free testosterone below 4.5 pg/mL (decreased value). Systemic inflammation markers were serum concentration of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) which were measured by immunochemistry method (ELISA technology) (Orgenium, Helsinki, Finland) and C reactive protein (CRP).

Pulmonary function tests

All patients underwent standard spirometry testing before and after bronchodilator inhalation. The lung function testing was done by spirometer (Master Screen Pneumo Jaeger, Germany). Forced vital capacity (FVC), forced expirium volume in the first second (FEV1) and FEV1/FVC ratio were measured. The subjects who had postbronchodilatatory FEV1/FVC < 0.70 were classified into 4 COPD severity groups based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: FEV1 ≥80% of predicted (GOLD 1: mild stage), 50% ≤ FEV1 < 80% of predicted (GOLD 2: moderate stage), 30% ≤ FEV1 < 50% of predicted (GOLD 3: severe stage), FEV_1 < 30% of predicted (GOLD 4; very severe stage).

Body plethysmography (Master Screen Body Jaeger, Germany) was used to measure the total pulmonary capacity (TLC), thoracic gas volume at the end of calm expirium (TGV), residual volume (RV) and RV/TLC ratio.

Nutritional status

Nutritional status was determined according to the body mass index (BMI) calculated as body mass expressed in kilograms divided with squared body height expressed in meters. Undernutrition is defined as BMI < 18.5kg/m², normal nutrition is defined as BMI = 18.5–24.9 kg/m², overnutrition is defined as BMI = 25–29.9 kg/m² and obesity is defined as BMI > 30 kg/m².

Six-minute walking distance

Six-minute walking test (6MWT) was performed for exercise tolerance estimation. The test was performed on 30 meters distance and the total distance passed was expressed in meters (m).

Skeletal muscle condition

Area of cross-section of right femur muscles (*midthigh muscle cross-sectional area* – MTCSA) in the middle of the distance between pubic symphysis and femur condyle was measured by computed tomography (CT) in all patients (CT-Toshiba Scanner TSX101A). MTCSA density within values of 40–100 HU was determined by measuring this tissue area. MTCSA less than 70 cm² was considered to be a decreased value of cross-sectional area of the right femur muscle. All pictures were analyzed by one (blinded) investigator.

Statistical analysis

Descriptive statistic methods of middle values (arithmetic average, mediana), variability values (standard deviation, interval of variation, minimal and maximal value) and structure indicator (presented as percentage) were used. Significance of difference of continual data was tested with the *t*-test for 2 independent samples and with the Mann-Whitney U test and Wilcoxon signed rank test. Significance of difference frequency of categorical data was tested with the Fisher accurate probability test. The linear regression analysis was used to examine the relationship between free testosterone and the test scores, lung function, and 6 MWD. Using multivariate regression analysis, we examined the influence of the individual variables as independent predictors for observed parameters. Data were worked out in the SPSS (Statistical Package for Social Sciences)19.0 program.

Results

In this study, 96 male patients with stable COPD were investigated. The average age was 68.8 ± 9.64 years (range 57 to 79 years). Twenty-eight (29.2%) patients were current smokers. Thirty-six (37.5%) patients had mild and moderate COPD, 36 (37.5%) severe and 24 (25.0%) patients suffered from very severe COPD (Table 1).

Table 1

Demographics characteristics, GOLD study, inflammatory markers, MTCSA and 6MWT in the study group (n = 96)

Characteristics	Values
Age (years), mean ± SD	68.82 ± 9.64
BMI (kg/m²), mean ± SD	21.7 ± 2.35
Smoking habits, n (%)	
current smoker	28 (29.2)
ex-smoker	68 (70.8)
COPD stage, n (%)	
GOLD 1 and 2	36 (37.5)
GOLD 3	36 (37.5)
GOLD 4	24 (25.0)
Inflammatory markers, mean ± SD	
CRP (mg/L)	6.81 ± 8.61
TNF-α (pg/mL)	4.45 ± 2.55
IL-1β (pg/mL)	184.49 ±56.54
MTCSA (cm²)	86.92 ± 14.5
6MWT (m)	302.2 ± 24.23

BMI – body mass index; COPD – chronic obstructive pulmonary disease; GOLD – global initiative for chronic obstructive lung disease; CRP – C reactive protein; TNF-α – tumor necrosis factor-α; IL-1β – interleukin-1β; MTCSA – midthigh muscle cross-sectional area; 6MWT – six-minute walking test; SD – standard deviation.

Tabele 2

Characteristics of the patients in the groups with low and normal value of free testosterone

Variable	Free testosterone		*p*
	< 4.5pg/mL	≥ 4.5pg/mL	
COPD patients, n (%)	36 (37.5)	60 (62.5)	
Age (years), mean ± SD	68.50 ± 7.69	67.83 ± 9.42	0.315
BMI (kg/m²), mean ± SD	20.7 ± 3.8	23.7 ± 6.4	0.138
Smoking habits, n (%)			
current smokers	10 (27.8)	18 (30.0)	0.871
ex-smokers	26 (72.2)	42 (70.0)	0.753
Lung function parameters, mean ± SD			
FVC (%)	56.65 ± 37.71	61.06 ± 32.80	0.362
FEV1 (%)	37.60 ± 17.91	37.88 ± 20.29	0.438
FEV1/FVC	45.52 ± 8.13	42.72 ± 16.98	0.713
TLC (%)	123.25 ± 23.82	117.15 ± 43.09	0.227
TGV (%)	191.48 ± 50.34	170.93 ± 80.87	0.093
RV (%)	237.38 ± 72.71	198.75 ± 110.53	0.068
RV/TLC	69.19 ± 15.46	60.83 ± 21.97	0.348
Parameters of gas exchange (mmHg), mean ± SD			
PaO2	8.99 ± 2.02	8.05 ± 1.52	0.440
PaCO2	6.15 ± 1.52	6.58 ± 1.81	0.287
COPD stage, n (%)			
GOLD 1 and 2	12 (33.3)	24 (40.0)	
GOLD 3	14 (38.9)	22 (36.7)	
GOLD stage 4	10 (27.8)	14 (23.3)	
Inflammatory markers, mean ± SD			
CRP (mg/L)	7.2 ± 6.21	7.71 ± 9.71	0.322
TNF-α (pg/mL)	5.88 ± 3.21	3.16 ± 2.53	0.021*
IL-1β (pg/mL)	195.9 ± 87.73	195.56 ± 62.70	0.452
MTCSA (cm²)	68.2 ± 18.72	91.1 ± 21.4	0.014*
6MWT (m)	268.33 ± 32.35	334.25 ± 43.25	0.023*

χ^2 test; * statistically significant.

BMI – body mass index; FVC – forced vital capacity; FEV1 – forced expirium volume in the first second; FEV1/FVC – forced expirium volume in the first second/forced vital capacity ratio; TLC – total pulmonary capacity; TGV – thoracic gas volume at the end of calm expirium; RV – residual volume; RV/TLC – residual volume/total pulmonary capacity ratio; PaO2 – partial pressure of oxygen; PaCO2 – partial pressure of carbon dioxide; COPD – chronic obstructive pulmonary disease; GOLD – global initiative for chronic obstructive lung disease; CRP – C reactive protein; TNF-α – tumor necrosis factor-α; IL-1β – interleukin-1β; MTCSA – midthigh muscle cross-sectional area; 6MWT – six-minute walking test; SD – standard deviation.

The average free testosterone value in the study group was 13.99 ± 20.89 pg/mL (range 0.45 to 96.45 pg/mL). We found a low value of free testosterone (< 4.5 pg/mL) in 36 (37.5%) patients. According to the value of free testosterone, the patients were divided into 2 age matched groups (Table 2).

There was not statistically significant difference between parameters of lung function. We found that the value of free serum testosterone and a stage of COPD were independent (χ^2; $p = 0.177$).

Analysis of systemic inflammatory markers between groups showed significant difference only for serum values of TNF-α (Table 2). The patients with the low value of serum free testosterone had significantly lower mean value of MTCSA and distance traveled during the 6MWT.

Using the univariate and multivariate linear regression analysis, we examined the influence of individual variables as independent predictors of the free testosterone value (Table 3 and 4). The multivariate regression analysis singled out the serum value of TNF-α as an independent predictor of free testosterone concentration in serum in the male COPD patients.

Table 3

Univariate Analysis of Risk Factors Related to plasma level of free testosterone

The observed risk factors	Univariate regression analysis	
	#B (95% CI)	*p*
Age (years)	0.089 (0.021–0.199)	0.109
BMI (kg/m²)	3.988 (-0.02–7.995)	0.047*
FEV1 (%)	0.033 (-0.019–0.084)	0.220
TLC (%)	-0.025 (-0.115–0.065)	0.703
RV/TLC	-0.002 (-0.045–0.042)	0.839
PaO2 (mmHg)	0.131 (-0.021–0.284)	0.042*
CRP (mg/L)	-0.184 (-0.386–0.018)	0.303
TNF-α (pg/mL)	-0.192 (-0.284–0.10)	0.01*
Il-1 (pg/mL)	-0.076 (-0.239–0.086)	0.208

#Unstandardized coefficient B; *statistically significant. BMI – body mass index; FEV1 – forced expirium volume in the first second; TLC – total pulmonary capacity; RV/TLC – residual volume/total pulmonary capacity ratio; PaO2 – partial pressure of oxygen; CRP – C reactive protein; TNF-α – tumor necrosis factor-α; IL-1β - interleukin-1β; CI – confidence interval.

Table 4

Multivariate regression analysis of risk factors related to plasma level of free testosterone

The observed risk factors	Multivariate $R^2 = 0.929$	
	B (95% CI)	*p*
BMI (kg/m²)	0.024 (-0.036–0.085)	0.687
PaO2 (mmHg)	1.192 (-1.844–4.229)	0.198
TNF-α (pg/mL)	-0.157 (-0.262–0.053)	0.004

#Unstandardized coefficient B; *statistically significant. BMI – body mass index; PaO2 – partial pressure of oxygen; TNF-α - tumor necrosis factor-α.

Discussion

In our study, 96 men with stable COPD were investigated and subdivided into 2 groups according to the serum free testosterone level (< 4.5 or ≥ 4.5 pg/mL). In the group of patients with the low free testosterone level, a significantly higher value of TNF-α, along with the lower values of MTCSA and 6MWT were found. The level of free serum testosterone and the stage of COPD were found to be independent. TNF-α seems to be an independent predictor of the serum free testosterone level in the COPD patients.

Decreased levels of anabolic hormones have been described in various chronic illnesses, including chronic respiratory diseases. It was shown that many chronic illnesses, such as hypertension, diabetes and cerebrovascular illnesses, are associated with deficit of serum testosterone. Since COPD is also a chronic disease, it can be manifested through the decreased level of serum testosterone – hypogonadism [7].

In our study, we showed that hypogonadism was present in 37.5% of the COPD male patients. Our results are similar to results from Laghi et al. [8] who reported hypogonadism percentage of 38% in their study. Several recently published studies reported that prevalence of hypogonadism in males with COPD varies between 22% and 69% [5]. Significant variations in reported prevalence rates could be explained by the use of different criteria in patient selection, small sample size, the age of patients and their race.

COPD, as well as other chronic illnesses, is characterized by an increased concentration of inflammatory cytokines in circulation which results in a shift of balance towards catabolism with a decrease in anabolic effects [9, 10]. Apart from local inflammation in the airways, the low grade systemic inflammation, caused by the presence of numerous inflammatory cytokines within circulation and high concentration of certain inflammatory mediators on systemic level, was also noticed [11]. The low level of systemic inflammation is considered to be involved in patogenesis of various extrapulmonary disorders, systemic COPD manifestations, including skeletal muscle dysfunction and hypogonadism [12]. TNF-α and other inflammatory cytokines are partially responsible for muscle weight loss and cachexia [12].

The analysis of systemic inflammation markers in our study showed that a statistically significant difference between groups with normal and low values of free testosterone was found only for serum of the TNF-α value. Also, the serum value of TNF-α was found to be an independent predictor of free testosterone. However, Daabis et al. [13] did not find any significant correlation between the low testosterone and markers of systemic inflammation [high-sensitivity C reactive protein (hs-CRP) and interleukin-6 (IL-6)]. Similarly, in the study from Karadag et al. [9] , there was no correlation between sex hormones and TNF-α or IL-6.

Even though systemic inflammation is considered to be a possible cause of decreased level of free testosterone in the COPD male patients, currently, available literature data show no clear evidence to support this theory.

We found no correlation between the free serum testosterone levels and the COPD stages.

Also, no statistically significant lower average value of FEV1 and other parameters of lung function was measured in the group of the COPD patients with low value of free testosterone. Other studies did not show any association between free serum testosterone and the stage of COPD, either [8], [14, 15]. A recent study showed significantly positive correlation between serum free testosterone concentrations and FEV1 [13]. In the group of patients suffering from very severe COPD with the lowest FEV1 value, the testosterone level was lower than in other groups. As the severity of disease increased, testosterone decreased while luteinizing hormone (LH), follicle-stimulating hormone (FSH) increased in compensation. Shaker et al. [16] , who analysed the sex hormones level in the COPD patients during exacerbation and one month after the exacerbation, proved that the low levels of serum testosterone, found in these patients, were significantly correlated with severity of airway obstruction, measured by FEV1.

In the group of patients with the low value of free testosterone, we found the significantly lower values of peripheral muscle mass, evaluated by CT (MTCSA). Previous studies showed that low serum testosterone level could contribute to skeletal muscle dysfunction in the COPD male patients, that is to muscle wasting [14, 17], mainly due to high prevalence of hypogonadism in advanced stages of disease and also due to reduced anabolic effects of testosterone on muscles. However, it could not be claimed that the reduced level of serum testosterone is a key factor in muscle wasting. Muscle wasting with significant protein decomposition is associated with systemic inflammation which is also present in COPD [11]. Increased concentration of inflammatory cytokines in some COPD patients with muscle wasting [11], could be attributed to decreased testosterone secretion and influence on the Leydig cell function [18]. On the other side, anabolic hormones have the tendence to „down regulate“ cytokine expression, so that the reduced testosterone could induce an increase of the inflammatory cytokine IL-6 level, which potentiates its pro-catabolic effect [10, 13, 18]. It seems that there is a regulatory loop in-between the inflammatory cytokines and anabolic steroids [10, 18].

Muscular wasting is frequently encountered in the COPD patients and is related to a decrease in exercise tolerance [19]. Our results showed significant reduction of the exercise tolerance, measured by 6MWT in the COPD patients with hypogonadism. Regarding the fact that significantly lower MTSCA was found in the group of patients with hypogonadism, possible explanation is that hypogonadism contributes to low exercise tolerance in these patients through its influence on muscle wasting. Other studies have not confirmed that there is a relation between reduced exercise tolerance and the level of testosterone [4, 10, 13].

Conclusion

In our analysis we found that TNF-α as a marker of systemic inflammation is an independent predictor of the presence of hypogonadism in the patients with COPD. Our results indicate that hypogonadism predisposes to skeletal muscle wasting and exercise intolerance in the COPD male patients.

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The prevalence of peg-shaped and missing lateral incisors with maxillary impacted canines

Učestalost hipodoncije i atipičnih lateralnih sekutića udruženih sa impaktiranim maksilarnim očnjacima

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Abstract

Background/Aim. Many authors find that impacted maxillary canines is associated with missing and peg-shaped lateral incisor. The aim of this study was to examine the prevalence of peg-shaped and missing lateral incisor in subjects with impacted maxillary canines, and compare the size of maxillary lateral incisor on the side with palatally impacted canines and on the opposite side of the jaw where there is no impaction. **Methods**. The study included 64 patients with 80 impacted maxillary canines (23 males and 41 females, mean age 16.3). For each maxillary unerupted canine, precisely correct localization and classification into groups was done. We analyzed the morphology of the lateral incisor (normal, atypical) and frequency of missing of lateral maxillary incisors with canine impaction. Then, from the mentioned examinees sample with the maxillary canine teeth, a subgroup was formed. The criteria for selection were those with unilateral palatally impacted canines (33 subjects, 22 females and 11 males, mean age 17.8 years). The linear variables of the maxillary lateral incisor were measured by using digital measurements tools. The *t*-test was used to test the differences between the groups. Results. Normal morphology of the lateral incisors was found in 72% of the subjects with the impacted canines, 11.2% of the subjects had the peg-shaped lateral incisors, 6% had a bilateral and 4% had unilateral deficiency of lateral incisors. In the subgroup of the patients with unilateral palatal impaction, the middle value of the length of the lateral incisors was 1.9 mm shorter and the middle value of the width of the lateral incisors was smaller by 0.9 mm when comparing to the control group. **Conclusion**. The frequency of the deficiency of lateral incisors was statistically significantly higher in the group with palatal canine impaction. The maxillary lateral incisors on the side with palatally impacted canines were smaller than those on the side where there was no impaction.

Key words:
cuspid; tooth, impacted; incisor; cone-beam computed tomography.

Apstrakt

Uvod/Cilj. Mnogi autori pronalazili su da su atipični lateralni sekutići, kao i njihov nedostatak, udruženi sa impakcijama maksilarnih očnjaka. Cilj ovog rada bio je da se ispita učestalost atipičnih lateralnih sekutića i njihov nedostatak kod pacijenata sa impaktiranim maksilarnim očnjacima kao i da se uporede veličine maksilarnih lateralnih sekutića na strani gde postoji palatinalno impaktiran očnjak i na suprotnoj strani vilice, gde ne postoji impakcija. Dužina i širina lateralnih sekutića merene su na trodimentzionalnim snimcima. **Metode.** Istraživanjem je bilo obuhvaćeno 64 ispitanika (23 muškog pola i 41 ženskog pola, prosečne starosti 16,3 godine) sa 80 impaktiranih maksilarnih očnjaka. Za svaki impaktirani očnjak precizno je određena njegova lokalizacija (bukalan, palatinalan ili sredina alveole) pomoću trodimenzionalnog snimka maksile na osnovu čega su podeljeni u grupe po mestu impakcije. Analizirana je morfologija lateralnih sekutića (normalni, atipični) i učestalost nedostatka lateralnih sekutića u grupi sa bukalnim i palatinalnim impakcijama, a zatim je iz te grupe ispitanika izdvojena podgrupa. Kriterijum za odabir bile su unilateralne palatinalne impakcije očnjaka (33 ispitanika, 22 ženskog pola i 11 muškog pola, prosečne starosti 17,8 godina). T-test je korišćen za testiranje razlika između grupa. **Rezultati.** Ukupno 72% ispitanika sa impaktiranim očnjacima imalo je lateralne sekutiće normalne morfologije, 11,2% konične lateralne sekutiće, 6% ispitanika imalo je bilateralni nedostatak lateralnih sekutića i 4% unilateralni nedostatak lateralnog sekutića. U podgrupi ispitanika sa unilateralnim palatinalnim

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impakcijama srednja vrednost dužine lateralnih sekutića bila je za 0,9 mm kraća, u poređenju sa kontrolnom grupom. **Zaključak.** Učestalost nedostatka lateranih sekutića bila je statistički značajno veća u grupi ispitanika sa palatinalnim impakcijama očnjaka nego u grupi sa bukalnim impakcijama očnjaka. Lateralni sekutići na strani palatinalno impaktiranih očnjaka bili su manji od onih na strani na kojoj nije bilo impakcije.

Ključne reči:
očnjaci; zub, impakcija; sekutići; tomografija, kompjuterizovana, konusna.

Introduction

The impaction of maxillary canines is associated with lateral incisor anomalies and the other orthodontics malocclusions, some of which can be a cause or consequence for canine impaction.

Broadbent [1] stated that the most common reason given for palatal displacement of the permanent maxillary canine was the fact that it had a long and tortuous eruption path, beginning close to the floor of orbit. It was considered that, compared with other permanent teeth, this tooth had much further to travel before it erupted into the mouth and, therefore, it had a great chance of "losing its way". This has been standard teaching for many decades. Hitchin [2] considered that crowding of the dentition was the reason for this condition, although he offered no evidence to support his contention. In a series of other studies Jacoby [3], Becker [4], Becker et al. [5] and Brin et al. [6] pointed out that the likelihood of palatal displacement was much reduced where crowding was present. They showed it to be a far more prevalent occurrence when there was excessive space in dental arch.

Miller [7] and Bass [8] recorded a high prevalence of congenitally anomalies of maxillary lateral incisors associated with the palatally impacted maxillary canines. The canines initially had a strong mesial developmental path, which altered early on with the canine being guided downwards, apparently along the distal aspect of the lateral incisor root. They concluded that, in the absence of this guiding influence, the canine continued its mesial and palatal path. The tooth then became impacted in palatal area, posterior to the central incisors, and failed to erupt in its due time, if at all. Miller [7] assumed that since a peg-shaped or otherwise abnormally small lateral incisor developed a root of more or less normal length, such a tooth would provide the required guidance for normal eruption of its adjacent canine. Therefore, he rationalized that these anomalous teeth could not be an aetiological factor in canine impaction.

A series of clinical studies that followed indicated a statistically significant number of normal, small and peg-shaped lateral incisors associated with impacted maxillary canines compared with the general population. In the general population, 93% of all lateral incisors have normal morphology, compared with only 52% of the subjects with impacted canines. The deficiency of lateral incisor was found in 1.8% of general population, compared with 5.5% in cases of impacted maxillary canines, which occur three times more often [9]. These results clearly support Bass's [8] and Miller's [7] theory that lateral incisor manage in normal eruption of the permanent canines. Without this guidance, normal eruption of permanent canines is compromised even five times.

It was reported that, in Israel population, the prevalence values of small lateral incisors were 4%, peg-shaped 1.8% and missing lateral incisor 1.3%. In one study, 42.6% of palatally displaced canines were found to be associated with lateral incisor anomalies, 25.3% of palatally displaced canines were adjacent to small lateral incisor, 13.3% had peg-shaped lateral incisor and 4% of the subjects had missing lateral incisor [10].

A meta-analysis showed that the prevalence values of congenital absence of maxillary lateral incisors were 1.55% for males and 1.78% for females and there was no statistically significant difference between the sexes [11].

Becker and Chaushu [12] found that approximately a half of their subjects with palatally displaced canines had delayed dental development. Chaushu et al. [13] subsequently stated that there might be two distinct palatally displaced canines subgroups among the male subjects but not among the female subjects. Nevertheless, Oliver [14] found that both sexes with palatally displaced canines had delayed dental development, with a familial trend of delayed dental development among their siblings.

The latest study [15] was to investigate the prevalence of peg-shaped maxillary lateral incisors and the incidence of associated dental anomalies in children. Among children with peg-shaped lateral incisors, the frequencies of associated dental anomalies were as follows: 31.8% of congenitally missing teeth, 19.7%, of dens *invaginatus*, 12.1% of palatally displaced canines, 7.6% of supernumerary teeth and 7.6% of transposition.

It has been reported that the mesiodistal width of the crown of the lateral incisors was smaller in a palatally displaced canines sample [16]. Palatally displaced canines were also showed to be associated with short lateral incisor roots, thus, it was suggested that there was a link between lateral incisor crown size and root length [17, 18].

The aim of this study was to analyze morphology of maxillary lateral incisors and examine the prevalence of peg-shaped and missing of maxillary lateral incisors which were associated with maxillary impacted canines as well as to compare the size of maxillary lateral incisors between the group of lateral incisors with palatally displaced canines and the control group (on the contralateral side of jaw where there is no canine impaction).

Methods

This study included 64 examinees with 80 impacted maxillary canines (23 males and 41 females, mean age 16.3 years). Each patient underwent clinical examination, intraoral and extraoral photographs and the cone beam computed tomography (CBCT) image of maxilla were done.

For each maxillary unerupted canine, precisely correct localization was determined by impaction (buccal, palatal or midalveolar) and thus divided the subjects into groups. We analyzed the morphology of the lateral incisor (normal, atypical) and frequency of missing of lateral maxillary incisors in subjects in the group with the buccal impaction and the group with palatal impaction canines.

Then, a subgroup was formed from the mentioned examinees sample with the maxillary displaced canines. The criteria for selection included those with unilateral palatally impacted canines (33 examinees, 22 female and 11 male, mean age 17.8 years). The subjects with buccally or midalveolarly impacted canines, transposed canines and premolars, transposed canines and lateral incisors and severely resorbed maxillary lateral incisors were excluded. Thirty palatally impacted canines fulfilled the inclusion criteria and were available.

We measured the length and the width of the lateral incisors on the side where palatally impacted canines were and compared with lateral incisors on the contralateral side, where there was no impaction of canines. In this study, the width and the length of the lateral incisor was measured using three-dimensional CBCT images.

The cone-beam volumetric tomography DICOM files were imported into the *OnDemond* software (Cybermed. Inc version 2011) and the volumetric images (voxel size 0.2 mm, field of volume 75*100 mm) were reoriented with the long axis of lateral incisor vertical and then reconstructed into images of sagittal slice through the maxillary lateral incisors. The linear variables of the maxillary lateral incisors were measured by using digital measurement tools. The length of lateral incisors was measured on the sagittal slice image. The width of crowns were measured on the axial slice image across the equator of the lateral incisor crowns.

The data primarily obtained were analyzed with descriptive methods and methods for testing statistical hypotheses. From descriptive methods, measures of central tendency (median), measures of variability [standard deviation (SD), variation interval] and the relative numbers (structure indicators) were used. For testing hypotheses, the methods used were the χ^2 test, Student´s *t*-test, Fisher´s test.

Results

In this study, a total of 64 patients with CBCT images were enrolled and 80 impacted maxillary canines were diagnosed and analyzed individually. The mean age of the patients was 16.3 years (SD ± 4.3 years, range: 12–33 years). Of 64 examinees in research, 41 (64.1%) were females which was significantly more important than the representation of 23 (35.9%) male examinees. Of 80 impacted maxillary canines, 19 (23.75%) were buccally impacted, 3 (3.75%) in the middle of alveolus and 58 (72.5%) palatally impacted canines.

The side and the frequency of impacted maxillary canines on the cach side are presented in Table 1.

There were 48 subjects with unilaterally impacted maxillary canines. The female subjects prevailed – 32 (50%) in comparison to the male subjects – 16 (25%), which was statistically significant difference ($\chi^2 = 8.46$; $p < 0.01$) (Figure 1).

Table 1

Descriptive data regarding morphology and location of impacted canines in 64 patients

Variable	n (%)
Canines (n = 80)	
unilateral	48 (75)
bilateral	16 (25)
Age (year of patients), mean ± SD (range)	16.3 ± 4.3 (12–33)
Gender	
male	23 (35.9)
female	41 (64.1)
Canine type	
right	39 (48.8)
left	41 (51.2)
Canine localization sagittal	
labial	19 (24)
palatal	57 (72)
midalveolar	3 (4)

All values are given as n (%) of canines or patients, except for age [mean ± standard deviation (SD) (range)].

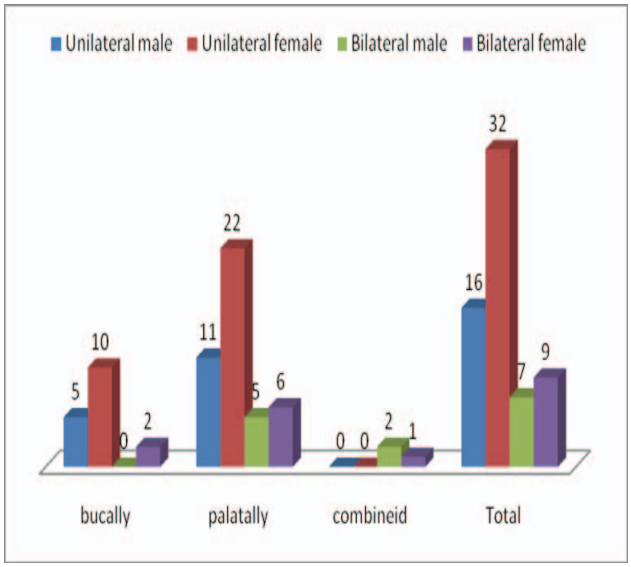

Fig. 1 – Distribution of unilateral and bilateral impacted maxillary canines according to the gender of subjects.

There was no statistically significant difference between the buccal and palatal impaction groups with missing lateral incisors (Fisher's exact probability test, $p = 0.498$). The missing of lateral incisors was present in 13 (16.3%) examinees only within the group of palatal impactions of maxillary canines. Atypical lateral incisors which were present within both groups, in the case with palatally impacted canines (7.5%) and with bucally impacted canines (3.7%). There was no statistically significant differences between gender regarding frequency of missing lateral incisors (the Fisher's exact probability test, $p = 0.757$) (Table 2).

Table 2

Distribution of missing and peg-shaped lateral maxillary incisors with impacted maxillary canines

Variable	Number (%)	*p**
Morphology of lateral incisors		
missing	13 (16.3)	
normal	58 (72.5)	
peg shaped	9 (11.2)	
Missing lateral incisors by gender		
male	4 (13.3)	0.757*
female	9 (18)	
Missing lateral incisors by impacted canine side		
bucally impacted canine	0 (0)	0.498*
palatally impacted canine	13 (16.3)	
Peg-shaped lateral incisors		
with bucal impacted canine	3 (3.7)	0.638*
with palatally impacted canine	6 (7.5)	

*Fisher's exact probability test.

There was an interesting information in the study of the morphology of lateral incisors in the subjects with maxillary canine impaction. The results concerning our examinees with impacted maxillary canines were: 72% of all lateral maxillary incisors had normal morphology, 11.2% were peg-shaped, 4% of subjects had bilaterally missing lateral incisors and 6% had unilaterally missing lateral incisors (Figure 2).

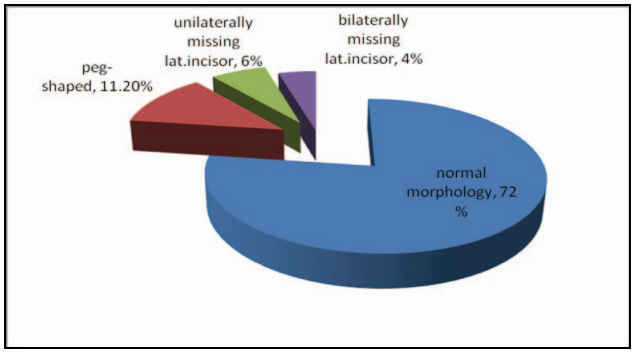

Fig. 2 – Morphology of lateral incisors with impacted maxillary canines.

In Table 3, the length of the lateral incisors and the width of lateral incisors in the subgroup with impacted canines and that with no conine impaction. The average value of the width of the tested lateral incisors was 5.9 ± 0.6 mm while the control lateral incisors was 6.1 ± 0.5 mm, which was a statistically significant difference (Student´s *t*-test, $t = 2.353$; $p = 0.022$).

The average value of the length of the tested lateral incisor was 19.7 ± 3.0 mm, while that of the control lateral incisors was 20.6 ± 1.7 mm, which was a statistically significant difference (Student´s *t*-test, $t = 2.362$; $p = 0.022$), i.e. lateral incisors on the side with canine impaction were shorter than those in the control group.

Palatally displaced canines were associated with shorter lateral incisor roots by 1.9 mm compared with lateral incisor roots in the control group (Table 3).

Also, there was a statistically significant difference regarding the mesiodistal width of the lateral incisors where tested lateral incisors were smaller than the lateral incisors in the control group for 0.9 mm (Table 3).

Discussion

Palatally displaced canines have been associated with missing lateral incisors and other animalies [19–22]. In another study, palatally displaced canines were reported to be associated with peg-shaped or missing lateral incisors, other impacted and missing teeth and deep bite with retroclined maxillary incisors [23].

Lai et al. [24] found that 70.9% of lateral incisors were normal within their subjects with impacted maxillary canines, 26.1% were peg-shaped and 2.99% missing lateral incisors. Garib et al. 25 found in a subgroup of patients with peg-shaped maxillary lateral incisors (aged 10 years and above) the prevalence of palatally displaced canines of 5.2%.

The similar results could be found in our subjects with impacted maxillary canines: 72% of all lateral maxillary incisors had normal morphology; 11.2% were peg-shaped, 45 of subjects have bilaterally missing lateral incisors and 6% had unilaterally missing lateral incisors.

In their researches, Liu et al. [26] and Scheied et al. [27] also found a statistically significant difference in length and width of lateral incisors in comparison with a control group of lateral incisors in the subjects where there was no canine impaction. However, the mean length of the lateral incisors reported in their study was much greater than that in our study because their measurements were mostly based on panoramic radiographs or periapical radiographs.

Table 3

Widths and lengths of lateral incisors in examined patients

Lateral incisor (mm)	mean ± SD	Med	Min	Max	*p**
Width					
tested	5.9 ± 0.6	6.0	4.0	7.0	0.022
control	6.1 ± 0.5	6.2	4.2	7.3	
Length					
tested	19.7 ± 3.0	20.3	12.5	22.3	0.022
control	20.6 ± 1.7	20.9	13.4	23.3	

SD – standard deviation; Med – median; Min-Max – minimal-maximal value; *Student's *t*-test.

Liuk et al. [28] used CBCT imaging and noted the difference in the length of lateral incisors by 2.1 mm, and in the width by 0.7 mm. Our study demonstrated that CBCT measurements were reliable and accurate, too [29]. In this study, the mean length of maxillary lateral incisors in the palatally displaced canine group was significantly shorter than the length in the control group by 1.9 mm, and the mean widths in dimension of the maxillary lateral incisors in the palatally displaced canine group were significantly smaller than those in the control group by 0.9 mm.

The authors conducted a comparison of the lateral dimensions of the maxillary incisors in subjects with palatally impacted canines and other subjects of the control group without impacted canines. The difference in lateral maxillary incisors was important because of the same subjects were involved of the maxilla different sides (therefore the appropriate subgroup with unilateral palatal impaction was isolated).

It was suggested that the smaller mesiodistal crown width of lateral incisors associated with palatally impacted canine might just reflect the shorter root length. In the patients with impacted maxillary incisors there was a higher incidence of peg-shaped or missing lateral maxillary incisors and other malocclusion. It is important to carefully plan the curing to the end of the treatment in order to satisfy aesthetic and functional criteria of occlusion.

The limitation of this study was that the palatally displaced canine group from the radiology practice could not represent the general population.

Conclusion

The missing lateral incisors was present in 16.3% of the cases, only among the subjects with palatally impacted canines. Atypical lateral incisors were present in 11.2% of cases, which explains that the palatally impacted canines associated with missing and atypical lateral incisors were one of the important hereditary phenomena. The prevalence of missing lateral incisors was higher but not statistically significant group with palatally impacted canines incomparison with the group with the bucally impacted maxillary canines. The differences of width and length of lateral incisors in the group of palatally impacted canines was statistically significant in comparison to those of lateral incisors in the control group, i.e. on the side where there is no impacted canine.

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S H O R T
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Efficacy of transrectal ultrasonography (TRUS) in preoperative staging of rectal cancer

Efikasnost transrektalne ultrasonografije (TRUS) u preoperativnoj proceni stadijuma rektalnog karcinoma

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Abstract

Background/Aim. The outcome of rectal cancer is dependant on the stage of the tumour. There are several classification systems used to describe the extent of the disease. The aim of this study was to compare the efficacy of transrectal ultrasonography (TRUS) in preoperative local staging of rectal cancer using endosonographic probes with different views (180° vs 360°), as well as an influence of experience of an endoscopist on the TRUS performance. **Methods.** TRUS was performed in 127 patients with rectal carcinoma by two endoscopists. Seventy-one patients were examined with a 180° endosonographic probe (group A) and 56 patients with a 360° rotating probe (group B). All findings were compared with a histopathology report. **Results**. TRUS had a diagnostic overall accuracy of 91.3% for the tumor (T) category (k = 0.866, SE (k) = 0.038, $p < 0.0001$) and 71.7% for the node (N) category ($\varkappa = 0.374$, SE (k) = 0.082, $p < 0.0001$). In the group A, TRUS had a diagnostic overall accuracy of 88.7% for the T category ($\varkappa = 0.805$, SE (k) = 0.063, $p < 0.0001$), and 70.4% for the N category ($\varkappa = 0.376$, SE (k) = 0.101, $P < 0.0001$). In the group B, TRUS had a diagnostic overall accuracy of 94.6% for the T category ($\varkappa = 0.920$, SE (k) = 0.044, $p < 0.0001$), and 73.2% for the N category ($\varkappa = 0.379$, SE (k) = 0.131, $p = 0.004$). Experience of the endoscopist had no significant influence on results of preoperative staging of rectal cancer by using TRUS. **Conclusion.** The accuracy rate of TRUS in the preoperative local staging of rectal cancer is high. Our results imply no significant difference in the overall accuracy rates when using endosonographic probes with different views (180° vs 360°). Also, there was no significant influence of endoscopist experience on results obtained.

Key words:
rectal neoplasms; carcinoma; neoplasm staging; preoperative period; ultrasonography; diagnosis, differential.

Apstrakt

Uvod/Cilj: Ishod lečenja rektalnog karcinoma zavisi od stadijuma u kome je otkriven. Postoji više klasifikacionih sistema koji se primenjuju u cilju određivanja proširenosti karcinoma. Cilj ovog istraživanja bio je upoređivanje efikasnosti transrektalne ultrasonografije (TRUS) u preoperativnoj lokalnoj proceni stadijuma rektalnog karcinoma uz pomoć različitih endosonografskih sondi (180° vs. 360°), kao i uticaj iskustva endoskopiste na izvođenje TRUS. **Metode.** Istraživanje je sprovedeno na 127 bolesnika tokom perioda od šest godina. Pregledan je 71 bolesnik uz pomoć 180° endosonografske sonde (grupa A) i 56 bolesnika uz pomoć 360° rotirajuće sonde (grupa B). Svi nalazi su komparirani sa patohistološkim izveštajima. **Rezultati.** TRUS je pokazao ukupnu dijagnostičku senzitivnost od 91,3% za tumor (T) kategoriju (k = 0.866, SE (k) = 0.038, $p < 0.0001$), i 71,7% za nodus (N) kategoriju ($\varkappa = 0.374$, SE (k) = 0.082, $p < 0.0001$). U grupi A, TRUS je pokazao senzitivnost od 88,7% za T kategoriju ($\varkappa = 0.805$, SE (k) = 0.063, $p < 0.0001$), i 70,4% za N kategoriju ($\varkappa = 0.376$, SE (k) = 0.101, $p < 0.0001$). U grupi B, TRUS je pokazao senzitivnost od 94.6% za T kategoriju ($\varkappa = 0.920$, SE (k) = 0.044, $p < 0.0001$), i 73,2% za N kategoriju ($\varkappa = 0.379$, SE (k) = 0.131, $p = 0.004$). Iskustvo endoskopiste u izvođenju TRUS nije imalo značajniji uticaj na preoperativnu procenu stadijuma rektalnog karcinoma. **Zaključak.** Efikasnost i tačnost TRUS u preoperativnoj lokalnoj proceni stadijuma rektalnog karcinoma je visoka. Naši rezultati ukazuju da ne postoji značajna razlika u dijagnostici rektalnog karcinoma uz pomoć različitih endosonografskih sondi (180° vs. 360°). Takođe, pokazano je da iskustvo endoskopiste u izvođenju TRUS ne utiče značano na procenu stadijuma rektalnog karcinoma.

Ključne reči:
rektum, neoplazme; karcinomi; neoplazme, određivanje stadijuma; preoperativni period; ultrasonografija; dijagnoza, diferencijalna

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Introduction

Colorectal cancer is the third most common cancer in Europe and the USA, and the third most common cause of cancer related deaths. Over 50% of patients have locally advanced disease that has spread to the lymph nodes and/or the liver at the time of diagnosis [1, 2]. The outcome of rectal cancer is dependant on the stage of the tumour. There are several classification systems used to describe the extent of disease. In this study, transrectal ultrasonography (TRUS) tumor stage was assessed by the Tumor-Node-Metastasis (TNM) classification as described by Hildebrandt and Pfeifel [3].

The managment of rectal cancer has evolved to become multidisciplinary because it offers the best clinical outcome, although surgery remains the most important treatment [4, 5]. This greatly increased the importance of the accurate preoperative staging in providing information about tumor infiltration and lymph node metastasis in order to make the right decision regarding rectal cancer treatment.

TRUS introduced by Wild and Reid in 1956, is very accurate imaging modality for the assessment of tumour growth in the bowel wall with the reported overall accuracies for the T and N staging between 69%–97% and 58%–83%, respectively [6–9]. Moreover, TRUS is inexpensive and quick diagnostic procedure associated with minimal discomfort to the patient.

The TRUS probes exist as radial and curved linear array depending on the orientation of the ultrasound transducer. The radial probes produce a 360° picture in a plane vertical to the long axis of the endoscope insertion tube, while a linear array create sector-shaped images horizontal to the long axis of the insertion tube [10]. Assessment of the wall of rectum and nearby structures is best achieved with radial probes with a frequency ranging from 6–16 MHz. Within these probes, two crystals are attached back to back, and can rotate inside the transducer [11].

The aim of the present study was to determine the accuracy of TRUS in rectal cancer staging compared with a histopathologic examination using the rotating endosonographic probes with different views (180° vs. 360°), and to evaluate the influence of experience of an endoscopist on the TRUS performance.

Methods

Preoperative TRUS was performed in all patients presented to the Clinic of Gastroenterology, Clinical Centre of Serbia, Belgrade with newly diagnosed rectal cancer who had no previous tumor staging evaluation. Patients with previously performed staging (MRI of the pelvis) were excluded. During 6-year period, 127 TRUS examinations were performed for the staging of rectal cancer by two endoscopists. Seventy-one TRUS examinations were conducted using a biplane endorectal probe with a field of view of 180° (Hitachi EUB 6500 U533), while 56 TRUS examinations were performed using the endorectal probe with a full 360° field of view (BK medical 1850). As the operator physically move the 1850 probe while the transducer moves along the entire length of the tumor and provides an image in the axial direction, the U533 biplane probe provides information both axial and sagittal.

The patient selection regarding the technique of TRUS was performed according to the department where they presented first. Informed consents were obtained from all of the patients prior to the examination. Before the probe was inserted into the rectum, a digital rectal examination was carried-out to identify the size, fixation, morphology and location of the tumor and to exclude clinically important stenosis to determine whether the anal canal and lower rectum are passable. All patients were evaluated to determine the diagnostic accuracy of depth of transmural tumor invasion and lymph node metastases. The TRUS results were correlated with the histopathological reports regarded as the gold standard in local staging of rectal carcinoma.

The TRUS T stage was assessed by visualising the depth of the tumour penetration through five defined layers of echogenicity in the rectal wall as described by Hildebrandt et al. [12]. All identified lymph nodes were measured and nodes greater than 5 mm in the maximum diameter were classified as positive (N+). The nodes smaller than this were assumed to be normal or inflammatory and were defined as N0. Comparison was made between the ultrasound staging and histopathologic findings after surgery.

Statistical analysis was performed using the Measure of Agreement-Kappa test for accuracy rates of T and N staging. Comparison of the accuracies within both the T and N staging results was made using the Fishers Exact Test or χ^2-test, with a p value of < 0.05 considered to be significant.

In order to determine the influence of experience of the endoscopist on the TRUS performance, TRUS performed during this period was divided into two time periods. The first time period was taken as the first half of practice, and the second period was taken as the second half of practice. Accuracy of T- and N- staging was calculated and compared in each time period.

Results

The total of 127 patients were examined by TRUS (90 males and 37 females, median age 63 years, range 26–85 years), and all of them underwent surgery. After surgery, preoperative findings were compared with histopathology findings of the surgical specimen.

Comparing TRUS and histopathologic findings the following correlations were found: the TRUS examination correctly staged 24 (88.9%) of 27 patients with T1 tumors, 34 (91.9%) of 37 patients with T2 tumors, 56 (93.3%) of 60 patients with T3 tumors, and 2 (66.7%) of 3 patients with T4 tumors. Overall accuracy rate was 91.3% (116 of 127 patients) ($k = 0.866$, SE (k) = 0.038, $p < 0.0001$) (Table 1). Using TRUS, overstaging was found in 6 (4.7%) and understaging in 5 (3.9%) of 127 patients.

The lymph node status was correctly assessed in 91 of 127 patients, with an accuracy rate of 71.7% ($\kappa = 0.374$, SE (k) = 0.082, $p < 0.0001$) (Table 1). Understaging was found in 9 (7.1%) and overstaging in 27 (21.3%) of the 127 patients.

Table 1

Comparison of transrectal ultrasonography versus histopathologic findings

Transrectal ultrasonography	T1 stage n (%)	T2 stage n (%)	T3 stage n (%)	T4 stage n (%)	Overall n (%)	N stage n (%)
Group A: 180°	5/8 (62.5)	23/25 (92)	35/37 (94.6)	0/1	63/71 (88.7)	50/71 (70.4)
Group B: 360°	19/19 (100)	11/12 (91.7)	21/23 (91.3)	2/2 (100)	53/56 (94.6)	41/56 (73.2)
Group A + B	24/27 (88.9)	34/37 (91.9)	56/60 (93.3)	2/3 (66.7)	116/127 (91.3)	91/127 (71.7)

T – tumor; N – node.

For the purpose of our analysis, the patients were divided into two groups. First group was examined with a 180° rotating endosonographic probe (group A, 71 patients) and the second group was examined with a 360° rotating endosonographic probe (Group B, 56 patients).

In the group A, the overall accuracy rate of the depth of tumor invasion was 88.7% (63 of 71 patients) ($\kappa = 0.805$, SE (k) = 0.063, $p < 0.0001$). TRUS correctly staged 5 (62.5%) of 8 patients with T1 tumors, 23 (92%) of 25 patients with T2 tumors, 35 (94.6%) of 37 patients with T3 tumors, and 0 (0%) of 1 patient with T4 tumors (Table 1). Overstaging was found in 6 (8.4%) and understaging in 2 (2.8%) of the 71 patients. In the group group B, the overall accuracy rate of the depth of tumor invasion was 94.6% (53 of 56 patients) ($\kappa = 0.920$, SE (k) = 0.044, $p < 0.0001$). TRUS correctly staged all 19 (100%) patients with T1 tumors, 11 (91.7%) of 12 patients with T2 tumors, 21 (91.3%) of 23 patients with T3 tumors and both (100%) patients with T4 tumors (Table 1). Understaging was found in 3 (5.3%) of 56 patients. There was no statistically significant difference in the overall accuracy rate of the depth of tumor invasion between groups ($\chi^2 = 0.736$, $p = 0.391$). No correlation was found between the groups in accuracy of the T2, T3 and T4 staging, respectively (Fisher's test, $p = 1.00$, $p = 0.634$, $p = 0.333$). There was a statistically significant difference in accuracy of the T1 staging between the groups (Fisher's test, $p = 0.019$).

In the group A, the lymph node status was correctly assessed in 50 of 71 patients, with the accuracy rate of 70.4% ($\kappa = 0.376$, SE (k) = 0.101, $p < 0.0001$) (Table 1). Understaging was found in 3 (4.2%) and overstaging in 18 (25.3%) of 71 patients. In the group B, the lymph node status was correctly assessed in 41 of 56 patients, with the accuracy rate of 73.2% ($\kappa = 0.379$, SE (k) = 0.131, $p = 0.004$) (Table 1). Understaging was found in 6 (7.1%) and overstaging in 9 (21.3%) of 56 patients. There was no statistically significant difference in the overall accuracy rate of assessing lymph node status between the groups ($\chi^2 = 0.022$, $p = 0.882$).

A high accuracy rate was maintained throughout the study period for the T staging in both groups. There was a slight improvement in the accuracy rate of the T staging in the group A from 83.3% in the first half of practice to 97.1% in the second half of practice, although the difference was not statistically significant. In the group B, a high level of accuracy in the T staging were maintained throughout the study - from 92.9% in the first half of practice to 100% in the second half of practice. There was a decrease in the accuracy rate of the N staging in the group A from 81% in the first half of practice to 60% in the second half of practice, although the difference was not statistically significant. In the group B, a high level of accuracy in the N staging was maintained throughout the study – from 68% in the first half of practice to 79% in the second half of practice.

Discussion

At present, a combination of computed tomography (CT), magnetic resonance imaging (MRI) and TRUS, is used for the preoperative staging of rectal cancer. A choice of modality depends on local expertise and availability.

For assessing the depth of tumour growth in the bowel wall, TRUS is very accurate with reported overall accuracies for the T staging varying between 69% and 97% [9]. On the other hand, CT is the current standard for staging of distant metastasis and cannot be considered appropriate for the local tumor staging [13]. MRI seems to be superior for more locally advanced disease with reported sensitivity between 66% and 92% [14]. Two meta-analyses showed that sensitivity was affected by the T stage [15, 16]. TRUS seems to be more accurate for staging of superficial rectal T1 and T2 tumours, with reported sensitivity of 94%. A report of a large endosonography study in 1,184 patients with rectal tumors confirmed these findings with the overall staging accuracy of 69% that is lower than previously reported because of less accurate assessment of the local tumor extent in advanced rectal cancer [17]. On the other hand, study conducted in Israel reported that the accuracy of TRUS in the local tumor staging was more accurate for T1 (81.2%) and T3 (94.1%) in comparison with T2 (63.6%) [18].

In our study, the overall accuracy rate in determining the depth of tumor invasion was 91.3%. Accuracy rates for T1 and T2 tumours were 88.9% and 91.9%, respectively. The highest accuracy rate was for T3 (93.3%). Overstaging was found in 4.7%, and understaging in 3.9% of 127 patients. Thus, our results are comparable to those reported in relevant literature [19]. A reason for good results of this study is the level of experience of the endoscopists. Both operators were highly experienced endosonographers that demonstrated superior performance, underscoring the existing learning curve for mastering endoscopic ultrasonography. The improvement with experience was shown by Orrom et al. [20], who found that the staging accuracy of rectal cancer increased from 58% in the initial 12 examinations to 88% for the subsequent 24 procedures. In our study, a high levels of accuracy in the T staging were maintained throughout the study in both groups – from 83.3% in the first half of practice to

97.1% in the second half of practice, and from 92.9% to 100%, respectively.

Assessment of pararectal lymph node involvement is essential for a selection of a high risk patients which are candidates for preoperative chemoradiotherapy, and still represents a diagnostic problem. Meta-analysis of 6 included studies showed that TRUS was only slightly superior to non-contrast enhanced MRI and CT in identifying lymph node metastasis with reported accuracy rate from 58%–83% [8, 21]. CT cannot accurately distinguish between malignant and benign lymph nodes with nodal staging accuracy between 54% and 70%. The MRI accuracy was found to range from 60% to 90% for lymph node metastases [14, 22–25]. In our study, the overall accuracy rate of assessing a lymph node status was 71.7% which was similar to the previously reported results. There was no significant difference between the groups in the overall accuracy rates of assessing the lymph node status. It seems that 360° view is not superior to 180° view in better visualization of perirectal lymph nodes.

A high accuracy rate for the N staging in this study (with a cut-off of 5 mm for positive nodes) was somewhat surprising as we were aware that almost 30–40% of the involved nodes were of 4 mm diameter or less. However, this should be viewed through the prism of a high level of false negative and false positive rates reported in the study. There was a tendency for overstaging nodes in both groups.

We are aware that this study has potential drawbacks. Only the patients without previous staging were included in the study, so this could be a source of selection bias. A lack of randomization is the most important drawback, since patients were not randomized for the technique of TRUS. Although it may be a potential source of error, we believe that this issue could not significantly influence results since the patients were not deliberately selected, as the type of TRUS was determined according to the unit where a patient was first presented.

Conclusion

In conclusion, the accuracy rate of TRUS in the preoperative local staging of the rectal carcinoma and regional lymph node involvement is high. Our results imply no significant difference in the overall accuracy rates of assessing local and lymph node status when using the endosonographic probes with different views (180° vs 360°) with an exception of accuracy in the T1 staging where 360° was superior to 180°.

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Spontaneus rupture of renal cell carcinoma in anuric patient on automated peritoneal dialysis

Spontana ruptura karcinoma bubrega kod anuričkog bolesnika na automatskoj peritoneumskoj dijalizi

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Abstract

Introduction. Spontaneous subcapsular or perirenal hematomas are relatively uncommon but often diagnostically challenging conditions. We present the first case described in the literature of successful continuation of the full regimen of peritoneal dialysis, that started immediately after urgent nephrectomy due to the spontaneous rupture of kidney cancer. **Case report.** A 55-year- old man had received continuous ambulatory peritoneal dialysis during 5 years for end-stage renal disease secondary to hypertensive nephropathy. He was switched to automated peritoneal dialysis two months before sudden worsening of his health condition, which was presented with strong left flank pain. Abdominal contrast enhanced computed tomography raised suspicion on retroperitoneal hematoma. The patient underwent radical left nephrectomy and restarted peritoneal dialysis immediately after surgery. The patient was discharged 5 days after the operation without any complications. The pathology report showed papillary renal cell carcinoma. **Conclusion.** Although renal cell carcinoma is the most common malignant tumor of the kidney, it has been rarely presented with spontaneous subcapsular or perirenal hematomas. However, radical nephrectomy with retroperitoneal approach is a requirement for minimising damage as well as keeping peritoneum integrity, allowing the continuation of automated peritoneal dialysis immediately after surgery without complications.

Key words:
peritoneal dialysis; rupture, spontaneous; kidney neoplasms; nephrectomy.

Apstrakt

Uvod. Spontano nastali supkapsularni ili perirenali hematomi su retki, ali se veoma teško dijagnostikuju. Dat je prikaz prvog slučaja, opisanog u literature, uspešnog nastavka lečenja punim režimom peritoneumske dijalize, koja je bila započeta neposredno nakon urgentne nefrektomije urađene zbog spontane rupture karcinoma bubrega. **Prikaz bolesnika.** Muškarac, star 55 godina, lečen je kontinuiranom ambulatornom peritoneumskom dijalizom u trajanju od pet godina zbog terminalnog stadijuma bubrežne slabosti u čijoj je osnovi bila hipertenzivna nefropatija. Bolesnik je preveden na automatsku peritoneumsku dijalizu dva meseca pre iznenadnog pogoršanja koje se manifestovalo intenzivnim bolom u levoj lumbalnoj loži. Na osnovu nalaza kompjuterizovane tomografije abdomena sa kontrastom posumnjalo se na retroperitonealni hematom. Bolesnik je urgentno podvrgnut levoj radikalnoj nefrektomiji i u neposrednom postoperativnom toku lečenje je nastavljeno peritoneumskom dijalizom. Otpušten je petog dana nakon operacije, bez komplikacija. Patohistološki nalaz bioptata ukazao je na karcinom bubrežnih ćelija. **Zaključak.** Iako je karcinom bubrežnih ćelija najčešći maligni tumor bubrega, retko se prezentuje spontanim supkapsularnim ili perirenalnim hematomom. Radikalna nefrektomija sa retroperitonealnim pristupom uslov je za minimalno oštećenje i očuvanje integriteta peritoneuma, čime se omogućava nastavak automatske peritoneumske dijalize neposredno nakon operacije.

Ključne reči:
dijaliza, peritoneumska; ruptura, spontana; bubreg, neoplazme; nefrektomija.

Introduction

Spontaneous subcapsular or perirenal hematomas are relatively uncommon but often diagnostically challenging conditions. The appropriate treatment of such patients is based firstly on the diagnosis that a subcapsular or perirenal hemorrhage has occurred, and secondly, on the determination of its cause. An accurate diagnosis of the cause requires

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a combination of clinical information and radiologic imaging [1]. It is especially difficult when the patient is anuric and receive some renal replacement modality.

Case report

A 55-year-old male patient had received continuous ambulatory peritoneal dialysis (CAPD) for 5 years for end-stage renal disease (ESRD) secondary to hypertensive nephropathy. Patient was anuric for the longer period and his peritoneal dialysis (PD) prescription was adjusted to that condition. He was switched to automated peritoneal dialysis (APD) 2 months before sudden worsening of his health condition which was presented with left flank pain without other subjective symptoms. On the admission, the patient had normal body temperature, with mild atrial tachyarrhythmia and hypertension (150/90 mmHg) and had strong left flank pain with tenderness of the left renal lodge on the percussion, without any change in physical findings on other systems. On the admission, his laboratory findings revealed the following values: sedimentation (SE) – 80.0 mm/h, red blood cell (RBC) – 3.40 × 10^{12}/L, hemoglobin (HGB) – 100 g/L, white blood cell (WBC) – 15,96 × 10^{9}/L, granulocytes % (GRAN) – 89.8%, urea – 26.5 mmol/L, creatinine – 1396 umol/L, potassium (K) – 4.6 mmol/L, C-reactive protein (CRP) – 68.6 mg/L, procalcitonin (PCT) 0.36 ng/mL and leukocytes (Le) in the peritoneal effluent 0.00 × 10^{9}/L. Abdominal ultrasonografy showed right kidney of normal size, wavy contoured with reduced parenchymal thickness with a larger number of cortical cysts and enlarged left kidney – 147 × 84 mm in diameter, thickened hypoechogenic and slightly inhomogenic parenchyma.

On the basis of clinical, laboratory and ultrasound diagnosis, the patient was treated for acute pyelonephritis, and began treatment with dual parenteral antibiotic therapy: quinolones (ciprofoxacin 200 mg twice a day) and cephalosporins of III generation (ceftriaxon 2 g – once a day). Patient was performing his APD program by himself every night, without any changing in monitored parameters – ultrafiltration (UF), body weight (BW), arterial blood pressure (ABP), and without changing in pulse rate with completely cleared dialysis effluent. The pain ceased after 24 hours and after that patient complained only about great weakness. After two days, a repeated laboratory findings revealed a slight fall in RBC: 3.07 × 10^{12}/L, and HGB: 95 g/L and unchanged leucocytes WBC 16.63 × 10^{9}/l, GRAN 81.7% despite the applied antibiotic therapy. Antibiotic therapy was changed due to the inadequate response to therapy and meropenem 500 mg i.v. qd / 24 h was introduced. On the third day, the RBC significantly fell to 2.55 × 10^{12}/L and HGB: 75 g/L, so it arose suspicion on intra-abdominal hematoma development. Urgent abdominal contrast enhanced computed tomography (CECT) was done, which confirmed enlarged left kidney with inhomogeneous parenchyma and completely disrupted structure (Figures 1 and 2). The patient underwent left open radical nephrectomy by retroperitoneal approach and restarted PD immediately after surgery. The patient was discharged 5 days after operation without any complications. The laboratory finding on the discharge day were as follows: RBC: 3.00 × 1012/L, HBG: 87 g/L, WBC: 12.48 × 109/L, CRP: 145.2 mg/L, urea: 19.9 mmol/L, creatinine: 1088 umol/L, K: 4.4 mmol/L. The pathology report showed papillary renal cell carcinoma (RCC) (Figure 3).

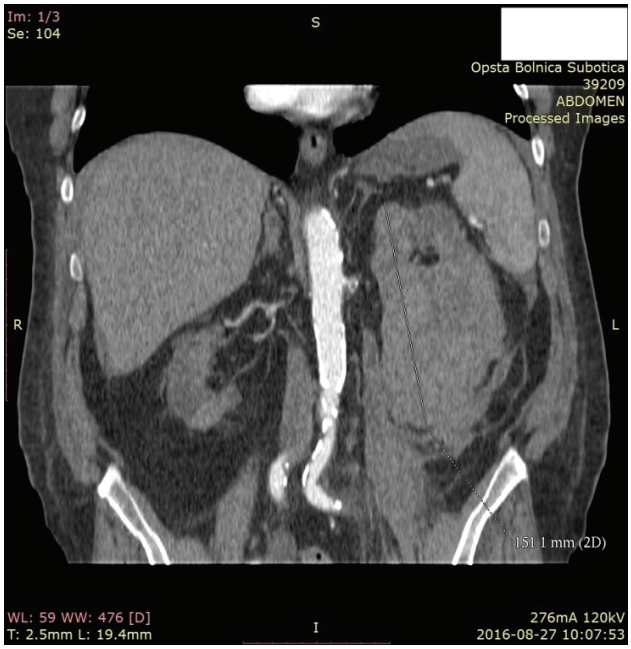

Fig. 1 – Abdominal computed tomography image (reconstruction): enlarged left kidney with longitudinal diameter 14 cm, erased cortico-medular line, completely disrupted structure, inhomogeneous density.

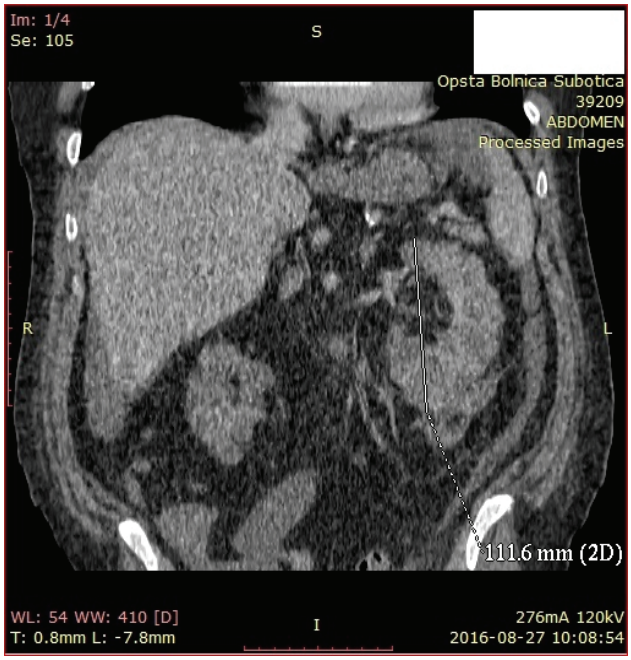

Fig. 2 – Abdominal computed tomography image: Retroperitoneal space on the left is entirely increased in density with hyperdense bands; the posterior part of the left pararenal space is fulfilled with inflammated-necrotic content of approximately 15 mm.

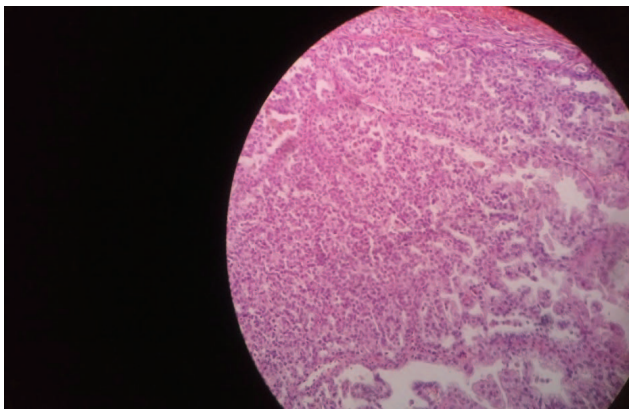

Fig. 3 – Microscopic view: papillary renal cell carcinoma, type 1 Fuhrman grade 2nd.

Discussion

Renal cell carcinoma is a rare, but serious complication in ESRD patients. The incidence of RCC is 20–40 times higher in these patients than in the general population [2]. Our patient had multiple risk factors for RCC: hypertension, tobacco smoking, obesity as well as pre-existing kidney disease and male gender [3]. RCC are usually discovered as 'incidentalomas' thanks to renal ultrasonography, which is responsible for 97% of the incidental diagnosis, in contrast to the classic presentation, as was the case with our patient [4]. Spontaneously ruptured RCC in ESRD patients is very rare and, to our knowledge, there are only 5 cases reported in the literature, all of which were in Japanese men [5, 6]. The spontaneous bleeding of the kidney (subcapsular and/or perinephritic space) was first described by Wunderlich. Wunderlich syndrome is described by the presence of Lenk's triad which manifests as acute flank/lumbar pain, palpable tender mass and features of active internal bleeding like hypotension, tachycardia and anemia. However, clinically, this triad is rarely seen and is commonly presented with abdominal pain (67%), hematuria (40%) and hypovolemic shock (26.5%) [7]. The clinical presentation in our patient was not so obvious, due to his having only abdominal pain from classical triad and the fact that the patient was anuric made the correct diagnosis more difficult. Most causes of Wunderlich syndrome are benign while neoplastic causes often accounted for in these cases, in different percentages to different authors. Moreover, the tumor size and rupture frequency were not correlated, and spontaneous renal rupture, even when tumor size was only 1 cm, was reported [8]. A possible mechanism underlying the spontaneous rupture of renal cell carcinoma was thought to be renal vein congestion due to tumor thrombosis, vessel rupture due to exponential tumor growth and direct invasion of the tumor into the renal vessels, but these are apparently not the major causes of ruptures [9]. Patohistological findings of renal biopsy verified the cause of spontaneous bleeding, which according to the available literature data is detected in 60% of all cases [10]. Therefore, the potential risk of an underlying renal tumor as a cause of spontaneous kidney rupture, should always be considered when making decision between a conservative and surgical therapy for these patients. Kendall et al. [11] proposed radical nephrectomy as the appropriate approach for treating these patients because there is a strong correlation between pararenal hemorrhage and small RCC.

Computed tomography (CT) is the most reliable modality in diagnosing retroperitoneal hemorrhage and RCC [12]. However, the efficiency of CT to diagnose RCC at the time of bleeding is an area of concern because of its inability to identify the RCC in 60% of cases, at the time of the initial CT [13]. In our case, tumor was not recognized as a cause of retroperitoneal hemorrhage before the operation. Nephrectomy can be performed by the transperitoneal or the retroperitoneal route [14]. The transperitoneal procedures can be troublesome for patients requiring PD. It is traditionally recommended that patients interrupt PD for at least 6 weeks after an open abdominal surgery to avoid complications and removal of the PD catheter, which may be required [15]. In that case temporary hemodialysis would be indicated with all risks of catheter related bacteriemia, infections and other complications [16]. Therefore**,** we made a decision to apply retroperitoneal approach which can minimize damage to the peritoneum and preserve its integrity [15].

Theoretically, a PD regimen can be restarted immediately after surgery, but there is little supporting evidence in the literature except for 3 patients who returned to PD after retroperitoneal radical nephrectomy, in a case report by Hsu et al. [15] with no negative effects on postoperative recovery. They referred that during postoperative care, the dialysate volume was reduced to about one half or two-thirds, and was titrated slowly upward according to patient's clinical condition. In the case of our patient, we applied the full CAPD regimen for the first postoperative day (Exreaneal® 2L during night started immediately after operation, followed with 2 exchanges with Dianeal® 2L 2.24% glucose, and with 2 exchanges with Dianeal® 2L 3.61% glucose, alternately), until evening of the first postoperative day when the patient himself started the whole previously prescribed APD regime on the second postoperative day (2 × 5 L + Extraneal 2 L, with filling volume of 1,700 mL). With intensive dialysis exchanges we achieved a satisfying depuration and ultrafiltration and we also enabled adequate volume loads for fluids and blood transfusion. The patient did not experience peritoneal leakage, poor wound healing, incisional hernia or impaired ultrafiltration after surgery. To our knowledge, our case report is the first one which describes open retroperitoneal radical nephrectomy in a patient with spontaneous kidney rupture, where the full CAPD and APD regime was started immediately after surgery.

Conclusion

There is a high risk of complications in immunocompromised patients such as patients treated with PD. Prompt selection of appropriate diagnostic procedures and surgical approach allows maintaining of the PD treatment modalities in these patients. We want to emphasize that in such patients RCC has more frequent occurrence and therefore they need

to have ultrasonography or CECT/nuclear magnetic resonance (NMR) control more often, indicated by their nephrologist. The aim of repeated controls is to discover this type of tumor on time, but not to wait for its spontaneous rupture on the background of previously undiagnosed and unrecognized RCC which has been developing over time.

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CASE REPORT

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Can troponin-I be used as an independent predictor of cardiac dysfunction after supraventricular tachycardia in children with structurally normal heart?

Da li se troponin-I može koristiti kao nezavisan prediktor srčane disfunkcije posle supraventrikulske tahikardije kod dece sa strukturno zdravim srcem?

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Abstract

Introduction. Elevated cardiac troponin gives excellent accuracy in the identification of myocardial damage in children, but it can also be elevated in a series of other diseases. **Case report.** We presented two children thirteen years of age with a high serum level of troponin-I after an acute episode of supraventricular tachycardia. We analyzed troponin-I levels in correlation with the maximum heart rate, duration of tachycardia and systolic left ventricular function (ejection fraction and fractional shortening). **Conclusion.** Abnormal troponin level can be seen in children with sustained supraventricular tachycardia and normal heart. Caution is advised in diagnosing cardiac dysfunction in children with supraventricular tachycardia and elevated troponin levels.

Key words:
tachycardia, supraventricular; arrhytmias, cardiac; troponin I; child; prognosis; ventricular dysfunction, left.

Apstrakt

Uvod. Povišen nivo srčanog troponina daje izuzetnu preciznost u identifikaciji oštećenja miokarda dece, ali može biti povišen i u nizu drugih bolesti. **Prikaz bolesnika.** Prikazano je dvoje dece uzrasta 13 godina sa visokim serumskim nivoom troponina-I nakon akutne epizode supraventrikulske tahikardije. Analiziran je nivo troponina-I u korelaciji sa maksimalnom srčanom frekvencijom, trajanjem tahikardije i sistolnom funkcijom leve komore (ejekciona frakcija i frakciono skraćenje). **Zaključak.** Izmenjen nivo troponina može se videti kod dece sa dugotrajnom supraventrikulskom tahikardijom i zdravim srcem. Savetuje se oprez u dijagnozi srčane disfunkcije kod dece sa supraventrikulaskom tahikardijom i povišenim nivoom troponina.

Ključne reči:
tahikardija, supraventrikulska; aritmija; troponin I; deca; prognoza; srce, disfunkcija leve komore.

Introduction

Cardiac troponin as a marker of myocardial necrosis is now commonly used in clinical practice in adults with coronary artery diseases. In children, it is a sensitive and specific biomarker consistent with cardiac damage (within severe acute and chronic heart failure, congenital heart disease and myocarditis, cardioversion, cateter ablation or trauma of myocardium, endomyocardial biopsy, drug- and toxin-induced cardiac toxicity) [1–3].

On the other hand, high level of cardiac troponin-I (cTnI) can be seen in sepsis, acute renal or respiratory dysfunction, "overtraining syndrome", pulmonary arterial hypertension or pulmonary embolism, amyloidosis or other infiltrative diseases, burns, as well after noncardiac surgery [4–9]. In neonatology, cTnI is analyzed as an early indicator of critically ill newborns with severe respiratory distress, hypoxic-ischemic encephalopathy, hemodynamically significant patent ductus arteriosus, or mortality risk. The reasons why the

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poor prognosis is associated with increased cardiac troponin are still not fully understood [10–13].

Up to now, supraventricular tachycardia (SVT)-induced elevations in cTnI in children with normal heart was not investigated. The aim of this study was to determine the prognostic value of troponin assays in children presenting to the emergency department with tachycardia. We assessed the test characteristics for positive cTnI (defined as > 0.04 μg/L, the manufacturer's upper limit of normal) in correctly identifying children who had SVT.

Case report

Case 1

A 13 and a half years old female child was admitted to our hospital because of the chest pain and palpitation after a heavy meal. The symptoms lasted for at least 8 hours and were relieved when she arrived to the hospital. She had no personal or family history about congenital heart anomaly, or other diseases (complete blood count, sedimentation, C-reactive protein, procalcitonin, glycaemia, electrolytes, transaminase, urea, creatinine, thyroid hormones and native chest X-ray were within normal ranges).

The results of physical examination showed a maximum heart rate (maxHR) 224 per minute, without symptoms and signs of low cardiac output: symmetrical palpable pulses, well-filled, blood pressure (BP) = 100/70 mmHg, respiration (R) 23 per minute, percutaneous oxygen saturation (SaO_2) 90%–91%. Gas analysis showed mild respiratory acidosis (partial pressure of carbon dioxide (pCO_2) 6.3 kPa, partial pressure of oxygen (pO_2) 4.9 kPa).

The patient's electrocardiogram (ECG) at the admission to the intensive care unit (ICU) showed atrioventricular reentry tachycardia (AVRT); ST segment depression 1.5–2 mm in leads V5–6 and max HR = 217 per minute. Figure 1 shows intermittent preexcitation in the Wolff-Parkinson-White syndrome that was determined later.

The echocardiogram showed no abnormal changes [ejection fraction (EF) and fractional shortening (FS) showed in Table 1]. After attempting vagal maneuvers, she was treated with adenosine and then continued with oral therapy – tablets of metoprolol (2 × 25 mg, 5 days and then 50 mg + 25 mg to control).

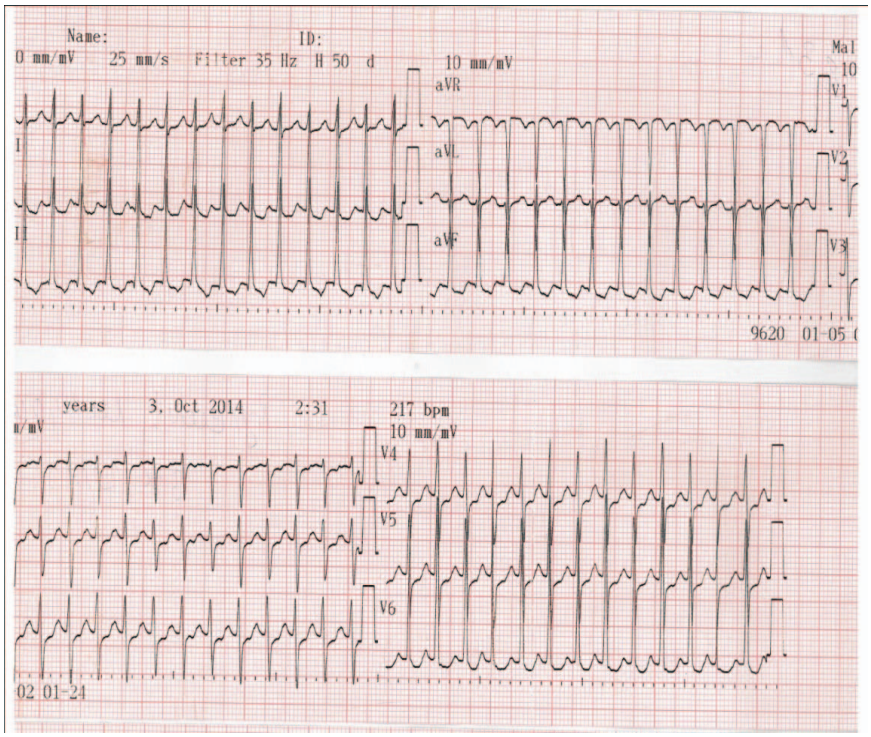

Fig. 1 – Electrocardiogram at admission **to the intensive care unit (ICU) showed atrioventricular reentry tachycardia (AVRT) in the patient.**

Table 1

Basic clinical characteristics of children presented to the emergency department with supraventricular tachycardia (SVT)

Patients	Duration of SVT (hours)	Max. HR (beats per minute)	EF (%)	FS (%)	Max. level of troponin-I (μg/L)
Case 1	8 h	217	66	37	0.115
Case 2	12 h	219	83	51	0.377

MaxHR – maximum heart rate; EF – ejection fraction; FS – fractional shortening.

A cardiac troponin I was determined at admission. The level of cTnI was 0.115 μg/L. On the fourth day, the value was lowered to normal (0.021 μg/L). In contrast, other cardiac markers simultaneously determined from the same blood sample were within normal ranges (creatine kinase 60 U/L, normal range 60–174 U/L; CK-MB fraction 10.3 U/L; lactate dehydrogenase 361 U/L, normal range 140–280 U/L), except for slightly elevated NT-Pro B-type natriuretic peptide (ProBNP): 391 pg/mL (normal range < 125 pg/mL, certain heart failure > 450 pg/mL).

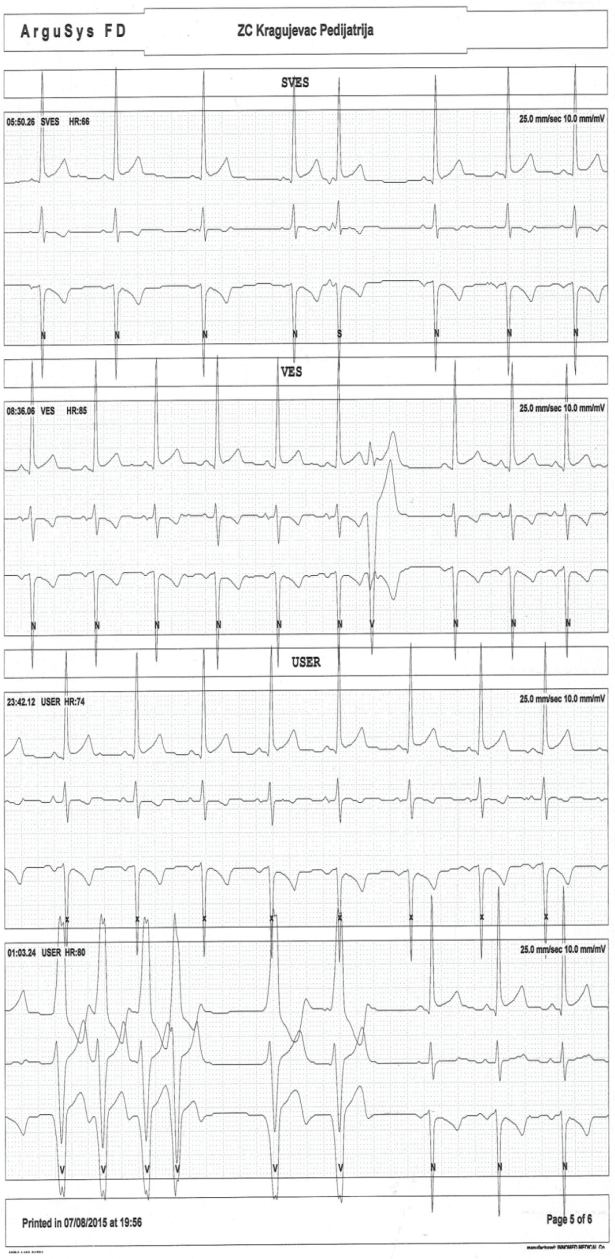

Fig. 2 – Accelerated idioventricular rhythm and supraventricular extrasystoles (SVES) after atrioventricular reentry tachycardia (AVRT) attacks.

Accelerated idioventricular rhythm [6 beats; 80 beat per minuta (bpm); 01:03.24h)], 25 supraventricular and 12 ventricular extrasystoles [or aberrantly conducted supraventricular extrasystoles (SVES)] were found during the 24-hour ambulatory ECG monitoring (Figure 2). ECG (without attack of SVT) and the test load were normal (MaxHR 139 per minute reached at the 5th to a degree; Blood pressure (BP) prior to the test load was 120/70 mmHg, at the maximum load BP was 140/50 mmHg, and after staying BP was 120/60 mmHg).

Case 2

A 13 years and 9 months old female child was hospitalized with complaint of the chest pain, palpitation and shortness of breath during the previous 12 hours, after emotional stress. A family history was as follows: her father suffers from high blood pressure, and grandfather had acute myocardial infarction. Physical examination showed maxHR 217 per minute, R 12 per minute, BP 91/51 mmHg, SaO_2 94%, (after SVT R 19 per minute, BP 108/50 mmHg, SaO_2 97%). Biochemistry and thyroid hormones showed normal values.

She was diagnosed as atrioventricular nodal reentry tachycardia (AVNRT): maxHR 219 per minute; ST segment depression 2 mm in leads V4–V6 in the surface ECG (Figure 3) and no abnormal changes in echocardiogram (Table 1). She received the same medicine as the first patient described.

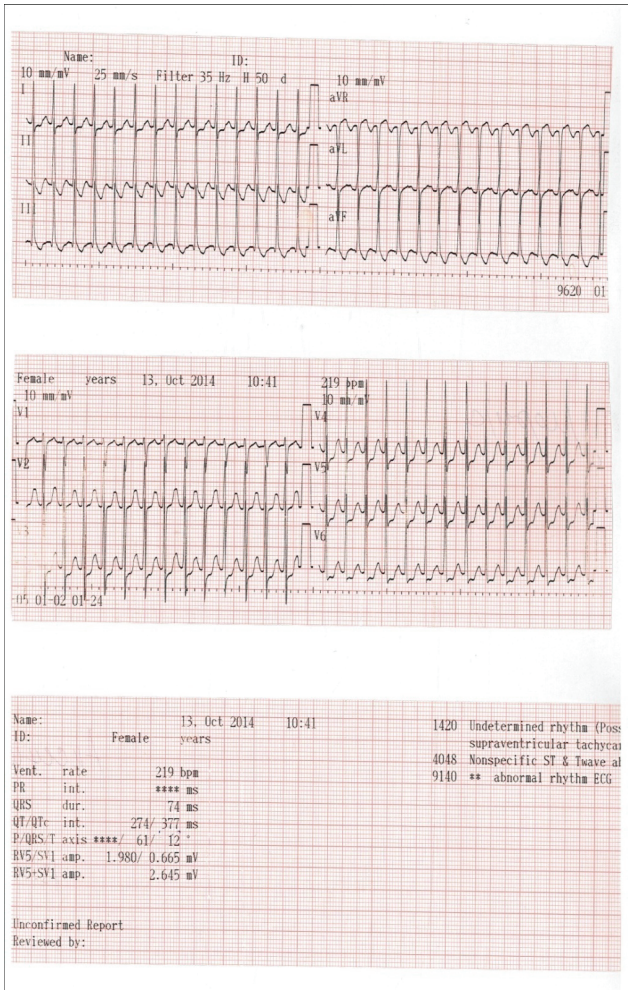

Fig. 3 – Electrocardiogram at admission to the intensive care unit (ICU) showed atrioventricular nodal reentry tachycardia (AVNR) in the case 2.

The level of cTnI was 0.377 μg/L at admission, and four days afterwards the value was up to 0.038 μg/L (Table 1, Figure 2). Also, ProBNP was clearly elevated in the serum (1,617 pg/mL) aut adission and after four days and the value was up to 286 pg/mL. During the 24-hour ambulatory ECG monitoring 6 SVES were found. Also, ECG (without attack of SVT) and the load test were normal.

Discussion

Cardiac troponin T (cTnT) and cTnI in serum are commonly used as standard biomarkers for the diagnosis of an acute coronary syndrome or myocardial infarction. In adult patients with SVT, most authors posed the question if troponin levels were useful for evaluating the presence of coronary artery disease [14–24]? Published reports (limited case series: 1–7 patients ages 18–72) presented that troponins could be released because of tachycardia alone in the absence of myodepressive factors, inflammatory mediators, or coronary artery disease [20–24]. The current literature on this topic shows that 12% to 48% of adult patients will have elevated troponins after SVT. Schmitz and Rezaic [14] in their research found troponin elevation in patients with SVT with normal coronary angiography and it was thought to be due to cardiac stretch, poor diastolic perfusion and/or coronary artery vasospasm.

In children, SVT is a common and generally benign arrhythmia. The causes of SVT include: lung disease, abnormal heart structure, or an abnormal extraelectrical pathway of the heart and use of certain medications (in the asthmatic status diastolic hypotension and tachycardia are dose-dependent side effects of high-dose albuterol) [25, 26]. The severity of SVT can vary greatly. It can last for < 30 s. (nonsustained SVT) and cause little or no symptoms or it can last for hours (sustained SVT) and cause palpitations, chest pain, shortness of breath and even fainting in rare cases.

Left ventricular dysfunction can show persisted symptoms or abnormal ECGs after conversion to normal sinus rhythm. While you treat the children's heart rate, you wonder if a troponin level would be useful in evaluating the presence of cardiac dysfunction. Our case report presented hemodynamically stable patients with various troponin elevation in proportion to the duration of tachycardia. Therefore, the troponin rise in our patients was a direct result of sustained SVT.

There has not been enough research to date to support the routine use of troponin in the evaluation of SVT in children. A routine testing can result in false positive findings (shortness of breath, persistent infection, chronic anemia, hemolysis and other reasons). Consequently, in children with various duration tachycardias, the use of troponin testing would be best performed selectively according to presented symptoms and risk factors for cardiac dysfunction.

Conclusion

Having the evidence, we do not recommend that troponin levels are determined in uncomplicated SVT in children. Future research in cardiology could be determination of the peak cardiac troponin levels that indicate a risk for left ventricular dysfunction after SVT. Moreover, it should be looked into whether these patients have increased cardiac rehospitalization over the next year.

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CASE REPORT

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Plasma cell gingivitis – an unusual case of simultaneus disease occurence in two siblings

Plazma ćelijski gingivitis – neuobičajen slučaj istovremene pojave oboljenja kod brata i sestre

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Abstract

Introduction. Plasma cell gingivitis (PCG) is a relatively rare disease that usually occurs on the anterior maxillary and mandibular gingiva. It manifests as extreme redness, swelling and gum tissue enlargement with propensity for bleeding, accompanied by extensive infiltration of plasma cells in the *lamina propria*. While the disease etiology remains unclear, its presentation is mostly attributed to nonspecific inflammatory reaction to certain foodstuffs or ingredients in oral hygiene products. **Case report.** A 9-year-old boy and 11-year-old girl were brought for exam by their mother because of fiery red lesions on the gingiva. The lesions had the same clinical features and identical localization and were concomitantly present in both siblings. After excluding other oral or systemic diseases with similar clinical manifestations, a diagnosis of PCG was established (most likely due to chewing gum). **Conclusion.** While beeing a purely benign, the PCG clinical appearance may mask much more detrimental conditions. Consequently, each such lesion requires due attention. To date, familial tendency for the development of such a condition has not been reported.

Key words:
gingivitis; plasma cells; diagnosis, differential; histological techniques.

Apstrakt

Uvod. Plazma-ćelijski gingivitis (PCG) je relativno retko oboljenje koje se najčešće javlja na gingivi frontalne regije gornje i donje vilice, a karakteriše se izrazitim crvenilom, otokom i uvećanjem desni sa izraženom tendencijom ka krvarenju, kao i masivnom infiltracijom plazma ćelija u rastresitom vezivnom tkivu (*lamina propria*). Bolest je do kraja nejasne etiologije mada se pretpostavlja da je u pitanju nespecifična inflamatorna reakcija na neki sastojak hrane ili sredstava za održavanje oralne higijene. **Prikaz bolesnika.** Brata i sestru, devetogodišnjeg dečaka i dve godine stariju devojčicu, majka je dovela na pregled zbog plamenocrvene promene na gingivi, istovremeno prisutne kod oba deteta, gotovo identičnog izgleda i lokalizacije. Nakon isključivanja drugih oralnih i sistemskih oboljenja sa sličnom prezentacijom, zaključeno je da se radilo o PCG (najverovatnije kao reakcija na žvakaće gume). **Zaključak.** Mada benigno, PCG je oboljenje koje svojom kliničkom slikom može maskirati postojanje znatno ozbiljnijih bolesti. Stoga svaka ovakva lezija zahteva odgovarajuću pažnju. Porodična sklonost ka oboljevanju nije opisana sve do sada.

Ključne reči:
gingivitis; plazma ćelije; dijagnoza, diferencijalna; histološke tehnike.

Introduction

Plasma cell gingivitis (PCG) is a relatively rare disease that can affect the gingiva only, or involve other parts of the mouth, usually lips and tongue. It typically manifests as pronounced redness of the anterior maxillary and mandibular gingiva, clearly demarcated towards the mucogingival junction and the surroundings, whereby the gingiva is edematous and enlarged with a pronounced tendency toward bleeding. The disease severity ranges from clearly delimited to diffuse lesions affecting the lateral gingiva as well. If lips and tongue are also affected, the disease is characterized by filiform and fungiform papillae atrophy and deepening grooves on the dorsal surface of the tongue, along with swolen and fisurated lips, mainly the lower one. The lesions are usually asymptomatic, although some patients may complain of pricking, burning sensation and even pain. Changes may occur in other parts of the oral cavity, and can extend to the en-

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tire upper aerodigestive tract. Similar cases involving other periorificial mucous membranes have been reported as well [1, 2].

PCG is also often referred to as gingival plasmacytosis, idiopathic gingivostomatitis, or plasma cell mucositis. Irrespective of the nomenclature, characteristic histological findings are the same, with marked plasmacellular infiltration in the *lamina propria*. While the disease etiology is presently unclear, available evidence is indicative of a nonspecific inflammatory reaction to some exogenous antigen. Various food additives and preservatives along with artificial sweeteners found in candy, chewing gum and oral hygiene products are commonly cited as the likely causative factors [3].

PCG is a benign condition and there is no evidence of association with the development of plasma cell neoplasm. But the clinical appearance of the disease may resemble leukemia infiltration, lichen planus, discoid lupus, pemphigoid and myeloma. Therefore, along with allergy testing, a diagnostic procedure requires hematological screening and histopathological examination [4]. The therapies offered vary and often fail to yield the desired therapeutic results. Even extensive allergen tests may not reveal the responsible allergen. Similarly, a drug treatment, in particular use of steroids, may prove ineffective [5]. Hence, for more severe cases surgical excision of the affected tissue is recommended.

Existing literature reports on the PCG cases with various potential etiologies and diverse clinical presentation. Familial propensity, to the best of our knowledge, has not been reported thus far. Searching the Medline database, we found 46 journal articles on PCG published between 1965 and 2015. No case described pertained to PCG diagnosed in family members. In this article, we presented a case of PCG characterized by nearly identical localization and clinical appearance, simultaneously present in two members of the same family – a brother and a sister.

Case report

Nine-year-old boy was brought to the clinic by his mother due to the gingival redness observed by her son's dentist during a routine checkup. As she was unaware of this condition, and the boy had no complaints, she could not indicate when the redness occurred. The mother was alarmed by the fact that she subsequently noted almost the same lesion at virtually the same spot in her 11-year-old daughter's mouth, who she also brought in for an exam. According to her, both children were healthy, they had no allergies and did not take any prescription medications. The children reported that they were unaware of the disease onset; they also confirmed lack of any subjective complaints and could not indicate any potential cause of redness.

Extraoral examination did not reveal any specificities in either sibling. Intraorally, on the gingiva surrounding the upper right central incisor, fiery-red lesion with brighter red pinpoints, clearly demarcated from the surrounding tissue, was noted in both children. In the boy's case, the lesion was about 1 cm in diameter, flat and almost macular, affecting the attached gingiva only, while the one observed in his sister was larger, slightly elevated, and affected both attached and marginal gingiva (Figure 1). Based on the clinical appearance, age and general good health of both siblings, a preliminary diagnosis of PCG was established. It was explained to the mother that, in order to reach a final diagnosis, further tests would be needed. Also, it was stressed that it would be advisable to attempt to relate the gum redness with potential modifications in dietary or oral hygiene patterns because the condition like this could be a reaction to some food, especially candy, chewing gum or a toothpaste ingredient. Mother pointed out that the entire family had been using the herbal toothpaste for some time, while children regularly chew gum ("the stronger the better", in the words of her son). Based on these assertions, the patients were advised to discontinue the use of the herbal toothpaste as well as chewing gum consumption and were invited for a checkup in one week's time when blood work results and microbiology findings would be reviewed. At the subsequent visit, clinical picture remained unchanged. The swabs were negative for bacteria and fungi in both children while complete blood count and differential were normal. The children were scheduled for the next control visit after completing allergy and immunology testing.

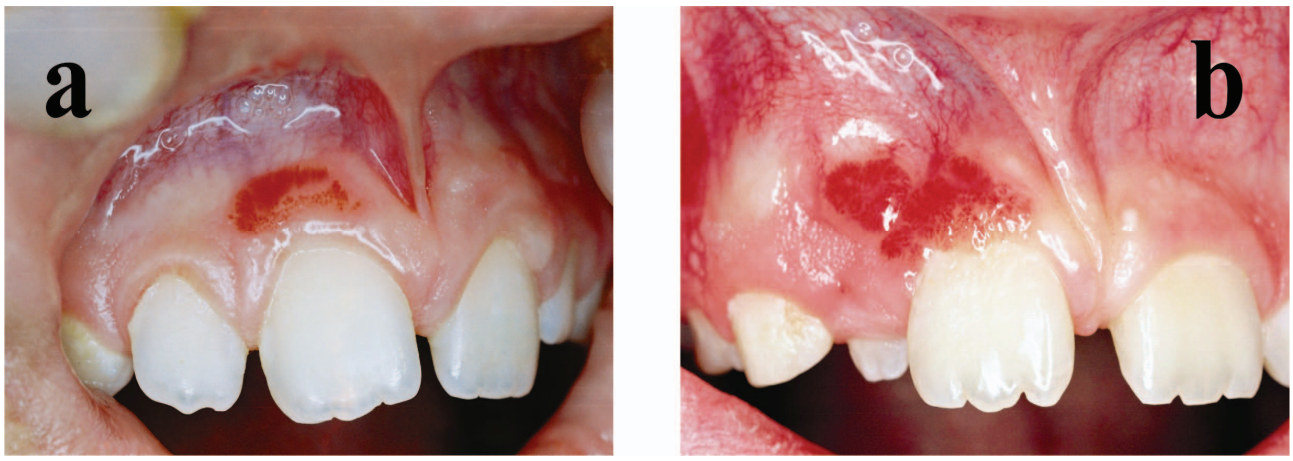

Fig. 1 – a) A flaming-red sharply demarcated lesion on the anterior gingiva in two siblings: a 9-year-old boy, and b) 11-year-old girl.

After three weeks, at the next appointment, although the mother confirmed that the entire family no longer used herbal toothpaste and the children were adamant that they stopped chewing gum, clinical presentation was virtually unchanged, without visible signs of lesion regression. The allergy testing for the most common inhaled allergens (house dust, animal hair, feathers, tobacco, mould, bacteria, grass pollen, weed pollen and tree pollen) and the most frequent food allergens (chicken eggs, wheat flour, soya bean, peanut, fish-based products, carrot, cow's milk) were negative, with the normal total serum immunoglobulin E (IgE) levels. Other immunoglobins (IgG, IgM, IgA), complement (C3, C4), C-reactive protein (CRP), rheumatoid factor (RF), transfferin, ferritin, haptoglobin and serum protein electroforesis were also within the normal range. Similarly, auto-antibodies antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), antiparietal cell antibodies (APCA), antineutrophic cytoplasmic antibodies (ANCA), antismooth muscle antibodies (ASMA), and ANA on Hep2 cells) were negative for both siblings.

After the two-week treatment with topical 0.1% triamcinolone in orabase, which failed to yield any improvements, the excision biopsy was performed. The lesions were excided completely and specimens were sent for pathohistiological analysis. Pathohistiological findings revealed that excised portions of the mucous lining had the same morphological characteristics in both children and were comprised of mucous membrane fragments covered with stratified squamous epithelium with mild parakeratosis, with moderately elongated epithelial ridges. In both cases, the keratinocyte distribution and maturation was normal. The entire *lamina propria* was edematous and occupied with diffuse, heavy infiltrate of mature, well-formed plasma cells, with eccentric nuclei and homogeneous eosinophilic cytoplasm. In addition, moderate dilation of capillary blood vessels was noted (Figures 2 and 3). These pathohistiological results supported the plasma cell gingivitis diagnosis.

At the assessments following surgery, both siblings were asymptomatic and free of lesions, including their last appointment six months after surgery. Unfortunately, they failed to attend subsequent follow-ups.

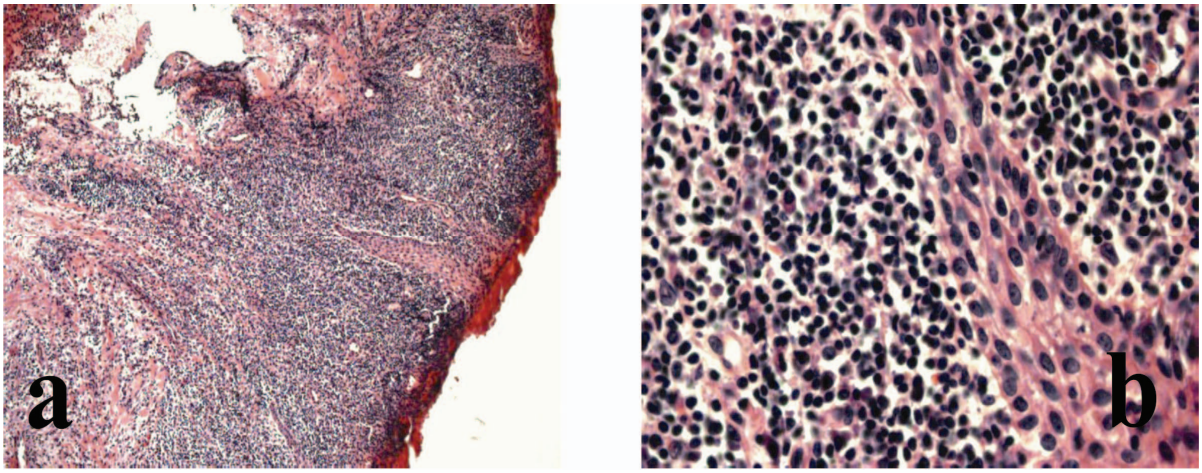

Fig. 2 – Histological findings in the boy: a) stratified epithelium with dense inflammatory infiltrate in the lamina propria hematoxyllin and eosin [(HE) ×50]; b) Inflammatory infiltrate is composed mainly of mature plasma cells (HE ×400).

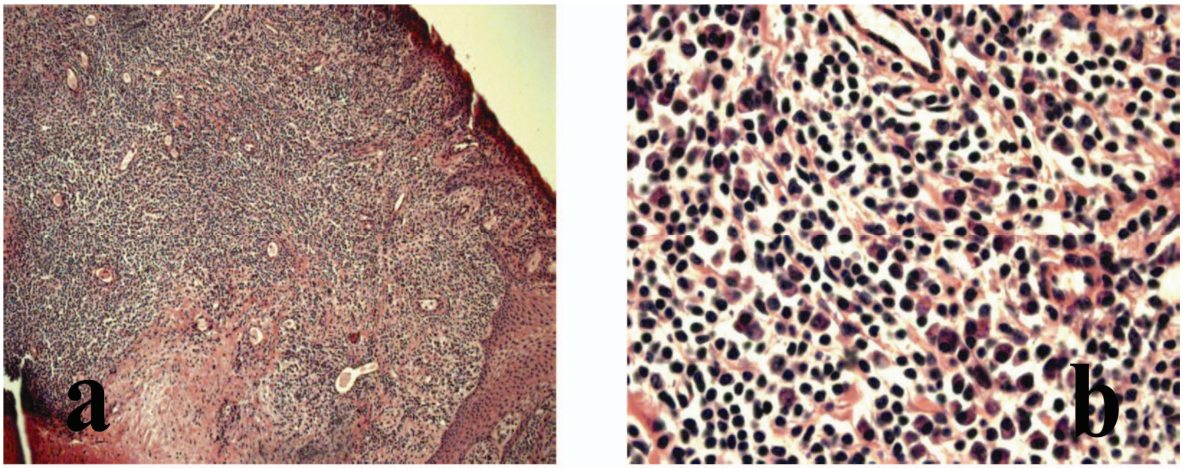

Fig. 3 – The same histological findings in the girl: a) stratified epithelium with dense inflammatory infiltrate in the lamina propria (hematoxyllin and eosin [(HE) ×100]; b) Inflammatory infiltrate is composed mainly of mature plasma cells (HE ×630).

Discussion

PCG has been reported in relevant literature since the 1960s. However, the disease etiology remains unclear. Early publications suggested allergic nature of this condition. In 1969, Owings speculated that the lesions were caused by an autoimmune response to certain anaerobic bacteria from gingival crevice [6]. Other causes like fungal infection, undetectable hormonal inbalance or decresed vitamin intake were also postulated. In 1971, Kerr et al. [7] described eight PCG cases concomitant with cheilitis and glossitis, ascribing these to hypersensitive reaction to certain chewing gum ingredients. These authors noted that all patients were habitual gum chewers and all experienced marked improvements in the symptoms two weeks after abstaining from gum use, with complete lesion absence within one month from gum chewing cessation. In addition, the same authors reported that, in some patients, lesions reappeared after chewing gum for 15 minutes. Since then, other authors also reported similar cases, leading to the conclusion that PCG is likely an allergic reaction to various artificial sweeteners and preservatives, typically found in candy or chewing gum, but also present in toothpaste and mouthwash. Even though the allergen typically remains unidentified, many researchers cite cinnamon, clove, chili peppers and essential oils such as peppermint, spearmint and wintergreen as likely allergens [8].

The case described here is noteworthy due to the fact that PCG in this case had familial occurrence, which is, to the best of our knowledge, the first case of its kind described in literature. Moreover it is unique due to the fact that the disease had almost the same appearance and affected the same gingival region simultaneously in two siblings. According to Sollecito and Greenberg [9], three types of PCG are presently recognized; PCG caused by known allergens, neoplastic PCG, and PCG of unknown etiology. We postulate that, in our case, PCG is an allergic reaction to some chewing gum ingredient, even though we failed to establish that with certainty. Our hypothesis is based on the children self-reported penchant for chewing gum. Also, according to their mother, both siblings not only chewed gum at home, but they were also often reprimanded by their teachers for chewing gum during class. It is thus likely, even though refuted by the children, that they deposited the gum during the class in the fornix, rather than throwing it away, and resumed chewing in the intermission. While these are merely suppositions, they fit the clinical picture, given that the lesions had particular localization, were well-demarcated and indicative of contact-induced allergy. In adition, the habit of keeping chewing matter between the cheek or lip and gum is not unknown. It is particulary familiar with tobacco chewers who usually place tobacco in the sulkus where it is retained for several hours. In the existing literature, a PCG case was reported in an individual with propensity for chewing khat leaves which were frequently deposited in the sulcus resulting in mandibular gingiva and buccal mucosa reddening and swelling [10]. Our supposition is, however, countered by the fact that, in contact-induced allergy, similar changes would be expected in the alveolar and upper lip mucosa as well. These regions were clinically healthy in both children examined in this work. Similarly, we would expect the lesions to disappear or at least regress once the children stopped chewing gum which did not occur. While it was noted that PCG may persist despite the elimination of the suspected allergens, it is also reasonable to question whether the siblings did indeed stop chewing gum as they so adamantly claim.

Burkhart [8] emphasize that the term PCG is currently utilized when the histological picture is dominated by a mass of plasma cells, suggesting that this is indicative of a Type IV hypersensitive reaction that is not life threatening, but rather a delayed, cell mediated response. As PCG is a benign lesion, it is essential to exclude in the differential diagnosis other oral or systemic diseases with similar clinical manifestations and localisation. Comprehensive medical history, hematological analyses and immunological assays should be performed in order to exclude acute leukemia, multiple myeloma and lupus. Further diagnostic assessments should include diet history and allergen testing, as their findings can be indicative of causative factors. Elimination of other inflammatory conditions like desquamative gingivitis, lichen, or other dermatological disorders with oral presentation is often impossible without examining the tissue under the microscope [2, 10].

Disease treatment varies, and there is presently no standardized protocol that clinicians should follow. Although allergen remains elusive in most cases, the first line therapy should commence with exclusion of all known potential allergens, as this may result in improvements in some cases. However, as with other recommended therapy modes, such measures often fail to yield satisfactory results. Also, oral hygiene improvements and professional periodontal care usually result in the reduction of the marginal gingivitis, without any beneficial effects on the attached gingiva. Moreover, antifungal therapy, even with the positive *Candida albicans* diagnosis as well as corticosteroid application, whether topical, intralesional or systemic, does not always produce improvements [5, 11]. Consequently, excision biopsy of the lesion, wherever applicable, including the case presented here, followed by histological analysis might be not only the best diagnostic approach, but also the most beneficial therapeutic option.

Conclusion

PCG is a rare condition, most likely allergic in nature. While being a purely benign, the clinical appearance and localization may mask much more detrimental conditions. Consequently, each such lesion requires due attention.

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DiMaio VJ. Forensic Pathology. 2nd ed. Boca Raton: CRC Press; 2001.

Blinder MA. Anemia and Transfusion Therapy. In: Ahya NS, Flood K, Paranjothi S, editors. The Washington Manual of Medical Therapeutics, 30th edition. Boston: Lippincot, Williams and Wilkins; 2001. p. 413-28.

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

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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Balint B. From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

Mladenović T, Kandolf L, Mijušković ŽP. Lasers in dermatology. In: *Karadaglić Đ*, editor. Dermatology. Beograd: Vojnoizdavački zavod & Verzal Press; 2000. p. 1437–49. (Serbian)

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

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